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Therapeutic modification of arterial stiffness: An update and comprehensive review

Wu CF *et al*. A comprehensive review of arterial stiffness

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**Abstract**

Arterial stiffness has been recognized as a marker of cardiovascular disease and associated with long-term worse clinical outcomes in several populations. Age, hypertension, smoking, and dyslipidemia, known as traditional vascular risk factors, as well as diabetes, obesity, and systemic inflammation lead to both atherosclerosis and arterial stiffness. Targeting multiple modifiable risk factors has become the main therapeutic strategy to improve arterial stiffness in patients at high cardiovascular risk. Additionally to life style modifications, long-term ω-3 fatty acids (fish oil) supplementation in diet may improve arterial stiffness in the population with hypertension or metabolic syndrome. Pharmacological treatment such as renin-angiotensin-aldosterone system antagonists, metformin, and HMG-CoA reductase inhibitors were useful in individuals with hypertension and diabetes. In obese population with obstructive sleep apnea, weight reduction, aerobic exercise, and continuous positive airway pressure treatment may also improve arterial stiffness. In the populations with chronic inflammatory disease such as rheumatoid arthritis, a use of antibodies against tumor necrosis factor-alpha could work effectively. Other therapeutic options such as renal sympathetic nerve denervation for patients with resistant hypertension are investigated in many ongoing clinical trials. Therefore our comprehensive review provides knowledge in detail regarding many aspects of pathogenesis, measurement, and management of arterial stiffness in several populations, which would be helpful for physicians to make clinical decision.

**Key words:** Arterial stiffness; Cardio-ankle vascular index; Pulse-wave velocity; Renin-angiotensin-aldosterone system antagonist

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**Core tip:** Arterial stiffness has been recognized as a marker of cardiovascular disease and associated with long-term worse clinical outcomes in several populations. Age, hypertension, smoking, and dyslipidemia, known as traditional vascular risk factors, as well as diabetes, obesity, and systemic inflammation lead to both atherosclerosis and arterial stiffness. Targeting multiple modifiable risk factors has become the main therapeutic strategy to improve arterial stiffness in patients at high cardiovascular risk.

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**INTRODUCTION**

Arteries provide not only blood flow conduits from the heart to peripheral organs, but also play a major role in hemodynamic cushioning, buffering the forward propagating flow from the heart, and the backward resistance by the peripheral arterioles, which maximize cardiovascular efficiency. Arterial stiffness characterized by higher intravascular distending pressure has been recognized as a marker of cardiovascular disease (CVD) and associated with long-term prognosis in several populations[1-4]. A recent meta-analysis including 17 longitudinal studies demonstrated that aortic stiffness was an independent predictor of incident CVD and all-cause mortality in the general population[4]. Therefore, evidence-based approaches for improving arterial stiffness are of clinical importance to reduce the hazards of subsequent CVD. This review article will discuss the latest knowledge of the pathological backgrounds, the measurements, and the effects of pharmacological and non-pharmacological interventions for arterial stiffness.

***The pathophysiology of arterial stiffness***

As a major component of the circulatory system, the arterial system can be functionally and structurally divided into two sub-systems: (1) the large elastic, conducting arteries (*e.g.*, the aorta, the carotid arteries, and the iliac arteries), which store blood ejected from the heart during systole, and expel blood to the peripheral tissues during diastole, thereby ensuring a steady blood flow irrespective of cardiac cycles or concurrent blood pressure; (2) Resistance muscular arteries, especially those of the lower limb (*e.g.*, femoral, popliteal, and posterior tibial arteries), which are capable of altering vascular smooth muscle tone, allowing them to modulate the velocity of pressure wave that is conducted to the resistance muscular arteries from the central aorta[5]. The sites of aortic flow reflection are not simply anatomically determined, but also subjected to systemically structural and functional control. For example, the site of reflection is more central in the case of hypertension, atheromatous arteries or increased sympathetic activity[6].

The pressure waveform recorded at any site of aorta is the summation of the forward-traveling waveform generated by cardiac pumping force and the backward traveling wave, the ‘‘echo’’ wave reflected at peripheral sites. The summation result determines the cardiac afterload during systolic phase and the augmented backward coronary perfusion pressure during diastolic phase. When the arteries are compliant and elastic, the reflected wave merges with the incident propagating wave during diastole, thus augmenting the diastolic blood pressure and enhancing coronary perfusion[7]. On the contrary, when arteries are stiffer, pulse wave velocity increases, and both the incident and the reflected wave travel faster; therefore, the reflected wave merges with the incident wave at systole and increase systolic pressure and cardiac afterload, while, concomitantly, losing the augmented diastolic perfusion pressure[7] (Figure 1). The added part on systolic pressure and cardiac afterload was named aortic augmentation index [AIx, (second/first systolic peak) ×100%][8]. In the long term, increasing pulsatility causes stretching of load-bearing elastic lamellae and mechanical stress on the wall leading to vascular structural changes and stiffening. Hence, the harm of arterial stiffness is two-sided, negatively affecting the heart and blood vessels[9] (Figure 2).

***Factors affecting arterial stiffness***

Age is a main determinant of stiffness in large elastic arteries[7,10].The stiffness of these arteries increases significantly after the age of 55 years. Aging causes the degeneration and remodeling of elastic components of arterial wall. At the cellular–molecular level, an age-related decrease in intra- cellular magnesium concentration is associated with increases in stiffness[10].

Most traditional cardiovascular risk factors and CVD have an adverse effect on arterial stiffness, via endothelial dysfunction and adverse vascular remodeling. Hypertension, diabetes, dyslipidemia, and insulin resistance, which contribute to atherosclerosis, have been involved in the process of arterial stiffening. In essential hypertension, the elastic properties of large arteries are impaired, although it is not clear whether the disease itself alters the intrinsic elastic properties or this is the ultimate final effect of increase in distending pressure[11,12]. Distending pressure as estimated by 24-hour pulse pressure was another major factor additionally to older age contributing to the occurrence of arterial stiffness[13]. In patients with diabetes or metabolic syndrome, arterial stiffening is consistently observed across all age groups, even in childhood[14].Insulin resistance is dose-dependent and positively correlated with arterial stiffness[15-17]. Chronic hyperglycemia and hyper- insulinemia may increase local activity of renin-angiotensin-aldosterone system (RAAS) and expression of angiotensin type I receptor in vascular tissue and thus promote the development of arterial wall hypertrophy and fibrosis[18,19].

In addition hyperinsulinemia has proliferative effects, via unbalanced activities on growth-promoting mitogen activated kinase pathways and PI3-kinase-dependent signaling[20]. In pre-diabetic stage, impaired glucose tolerance enhances nonenzymatic glycation of proteins with covalent cross- linking of collagen and alters the mechanical properties of interstitial tissue of arterial wall[21,22].

Chronic kidney disease (CKD) is a well-known risk factor of arterial stiffness[23]. Several mechanisms have been proposed to explain the effect of CKD. For instance, upregulation of matrix metalloproteinases enhances collagen and elastin turnover through enzymatic cross-link degradation[24], causing weakening of the extracellular matrix[25]. Accumulation of advanced glycation end-products makes collagen stiffer as well[26]. In addition, CKD may cause endothelial dysfunction, which attributes to high oxidative stress, increased endothelin-1 concentrations and impairment of endothelial nitric oxide synthase and arterial relaxation[27]. Chronic inflammation and RAAS activation are also involved in the process of arterial stiffening in CKD[28,29]. CKD alters bone metabolism to promote vascular calcification by increasing osteoclast activity, fibroblast growth factor 23, osteoprotegerin which inhibit bone morphogenic proteins, and reducing pyrophosphate, Matrix G1a protein, and fetuin A levels[30].

Arterial elastic properties are impaired in young people with a family history of hypertension, diabetes or myocardial infarction[31].It has been recognized that genetic factors may contribute to arterial stiffening as well. The latest advances in genome-wide association study have identified that some genetic variants and specific polymorphisms may affect arterial stiffness. The Framingham Heart Study showed that four regions of suggestive linkage were found in chromosomes 2, 7, 13, and 15 (LOD scores 2.0) for higher risk of arterial stiffness[32]. Potential candidate genes in these regions included the insulin-like growth factor-1 receptor (IGF1R), myocyte-specific enhancer factor 2A (MEF2A), chondroitin synthase (CHSY1), proprotein convertases (PACE4 and FURIN), b-adducin (ADD2), neurokinin-1 receptor (TACR1), a-2B adrenergic receptor (ADRA2B), and interleukin-6 (IL6). Other candidate gene polymorphism, such as the renin–angiotensin–aldosterone genes, the Matrix and metalloproteinase genes, the endothelial cell-related genes, and the inflammatory genes, are all in undergoing investigations[33].

Lifestyle characteristics are important determinants of arterial stiffness. Cigarette smoking, including passive smoking and current smoking has an adverse impact on the arterial stiffness[34-36].Elevated arterial stiffness has been found among patients with chronic obstructive pulmonary disease and inflammation, which are highly related to the adverse effect of smoking. Obesity, weight gain, lack of physical activity and high dietary intake of sodium chloride, which is associated with blood pressure elevation, can aggravate arterial stiffness[37-40]. Intake of caffeine, a neurotoxin has also been acknowledged of an unfavorable effect on arterial compliance[40, 41]. Other risk factors such as chronic cytomegalovirus infection, has been known as a novel potential contributor to arterial stiffening[42]. Table 1 lists the main demographic, clinical and lifestyle characteristics that may influence arterial stiffness.

***Measurement of arterial stiffness***

A stiffer vessel will conduct the pulse wave faster than a more distensible and compliant vessel. Arterial stiffness can be noninvasively evaluated by measuring pulse-wave velocity (PWV). The PWV is calculated by the distance (L) between the 2 vascular sites divided by the wave foot-to-foot time (△T) it takes for that forward wave to reach the end measuring point (Figure 3) Currently, PWV is the most validated measurement to noninvasively quantify arterial stiffness. It is considered the gold standard index to measure arterial stiffness, given its simplicity, reproducibility, accuracy, and strong prediction of adverse CVD events[43-45]. An increase in aortic PWV by 1 m/s corresponds to an age-, sex-, and risk factor–adjusted risk increase of 14%, 15% and 15% in total CVD events, CVD mortality, and all-cause mortality, respectively[5].Nowadays, two kinds of PWV were frequently used to evaluate arterial stiffness. Carotid-femoral PWV (cfPWV) measured by Doppler ultrasound is the most widely used measure of aortic stiffness and is regarded as the gold standard measure for evaluating arterial stiffness. Alternatively, brachial- ankle PWV (baPWV) measured by the Omron oscillometric/plethysmographic system has recently received attention because of its consistent association with CVD risk factors and its ease of use for large-scale population studies[43-45]. Based on the formula assumptions, cfPWV reflects the stiffness of descending aorta, while baPWV reflects the stiffness of both descending aorta and leg arteries. In a study conducted among healthy men aged 40-49, cfPWV strongly correlated with central PWV, and baPWV correlated with both central and peripheral PWVs[46]. The two indexes were highly correlated and the predictive values of these two PWVs were comparable[47]. Both cfPWV and baPWV have been reported to be independent predictors of subclinical coronary artery calcification, incident vascular events, incident heart failure, and all-cause mortality in the general population[48,49]. The main disadvantage of cfPWV is inevitably affected by blood pressure, which is an important confounder for CVD. In addition, cfPWV is often overestimated for the inaccurate measurement in the distance between the carotid and the femoral to measure the pulse wave[50]. Other methods for the PWV measurements include single-point, carotid–radial or femoral–tibial arterial segments. The predictive values of these more peripheral PWV measurements to incident vascular events remain unknown[51]. Aortic characteristic impedance standing for the minimal impedance for higher frequencies of pressure-and-flow harmonics and being proportional to PWV is an indirect technique, but this is rarely used alone now[52]. AIx, arterial wave reflection magnitude [(reflected/forward wave amplitude) × 100%], and pulse pressure amplification [(radial/aortic pulse pressure) × 100%], the analysis of pulse waveforms parameters of central arteries, have been associated with the development of end organ damage as well[53].

The stiffness parameter β is another measure of arterial stiffness. The equation for stiffness parameter β is ln(Ps/Pd)×D/ΔD, where Ps is the systolic blood pressure, Pd is the diastolic blood pressure, D is the diameter of the artery, and ΔD is the change in arterial diameter between Ps and Pd[54]. The stiffness parameter β is less affected by blood pressure; however it is limited by assessing a local segment of the artery, and becoming dependent on blood pressure for those with hypotension or moderate and severe hypertension[54]. Therefore, the cardio-ankle vascular index, CAVI, was developed to incorporate the stiffness parameter β[55]. The equation for CAVI is a [(2ρ/ΔP) × ln(Ps/Pd) × PWV2]+ b, where ρ is the blood viscosity, ΔP is Ps – Pd, PWV is the pulse wave velocity from the aortic origin to the ankle region via the femoral artery, and a and b are constants for converting a CAVI value to a value obtained by Hasegawa’s method[56]. Theoretically, the CAVI is essentially intrinsic to the stiffness parameter β and thus less dependent of blood pressure than PWV. Table 2 summarizes the merits and disadvantages of different measurements of arterial stiffness.

***Therapeutic modification of arterial stiffness***

**Lifestyle modification:** Obesity is related to insulin resistance, hypertension, obstructive sleep apnea (OSA), and eventually arterial stiffness. A meta-analysis involving 20 studies (including 3 randomized controlled trials) revealed that modest weight loss (mean 8% of initial body weight) could improve PWV values by 32% in the collected 1259 participants[57]. In addition, weight reduction was found in association with decreased CAVI values in a cohort of 47 obese individuals in Japan[58]. Effects of exercise on arterial stiffness were extensively investigated. Physical activity was associated with 35% reduction in cardiovascular mortality and 33% reduction in all-cause mortality[59]. Almost 60% of the benefits are contributed by the reduction of body weight, blood pressure and serum lipids[60], and the other 40% may be explained by the improvement of vascular hemodynamics including endothelial function, arterial compliance and remodeling[61]. Whether mode and dose of exercise affecting arterial stiffness had been recently reviewed in a meta-analysis[62]. In total, forty-two studies and 1627 participants were included in the study, which concluded aerobic exercise, but not resistant exercise or combined aerobic and resistant exercise, improved PWV weighted mean difference (WMD): -0.63 m/s, 95%CI -0.90, -0.35, and AIx (WMD: -2.63%; 95%CI: -5.25, -0.02). The benefits for improving arterial stiffness were greater in the peripheral index, baPWV (WMD: -1.01 m/s; 95%CI: -1.57,-0.44) than in central index, cfPWV (WMD: -0.39m/s; 95%CI: -0.52, -0.27). There was dose-dependent relationship between exercise intensity (frequency of exercise sessions and absolute exercise intensity) and the improvement of AIx. Nevertheless, the exercise session duration was not significantly associated with the reduction of AIx[62]. In individuals with stiffer arteries (PWV≧8 m/s), aerobic exercise had a larger effect in reducing PWW. In addition, the benefits of aerobic exercise were documented in subpopulations with normal health, overweight/obese, pre-hypertension, hypertension, or CKD.

Smoking cessation has been proven to decrease aortic stiffness. In one 60 wk follow-up observational study, smoking cessation group had better arterial stiffness indices (central blood pressure, -7.1 ± 1.4 mmHg *vs* 1.2 ± 2.7 mmHg, *P* < 0.01; baPWV, -204 ± 64 cm/s *vs* −43 ± 72 cm/s, *P* < 0.01; reduced radial AIx, −6.4 ± 2.8% *vs* -1.0 ± 3.9%, *P* < 0.01)[63]. Another observational study also showed that smoking cessation was associated with improved arterial stiffness as evaluated by CAVI values[64]. Moreover, avoidance of second-hand smoke, such as workplace smoking bans, has been reported to improve PWV after introducing smoke-free workplaces[65].

**Dietary and nutrient interventions:** Several dietary modifications had been reported with beneficial effects on arterial stiffness. Among them, omega (ω)-3 fatty acids (fish oil) supplementation was mostly studied. In most of clinical trials, ω-3 fatty acids supplementation improved arterial stiffness, especially in the population with overweight, metabolic syndrome, diabetes or hypertension[66]. Aside from a study with acute ω-3 fatty acids administration in healthy participants, almost all ω-3 trials were long-term prescribed varying from 1.5 to 25 mo. In this acute fish-oil supplementation study, there were no immediate reductions in parameters of arterial stiffness[67]. The lowest daily dosage of long-chain polyunsaturated fatty acids (PUFAs) that documented an effect on arterial stiffness was 540 mg eicosapentaenoic acid (EPA) along with 360 mg docosahexaenoic acid (DHA) in overweight patients with hypertension[68]. Sjoberg *et al*[69] introduced 2 , 4 , and 6 g of fish oil supplementation per day into the diets of overweight or obese adults for 12 wk. Only the highest dose group (6 g of fish oil per day) revealed significant improvement in arterial distensibility, as measured by PWV.Among healthy subjects, Chong *et al*[70] reported a significant improvement in PWV and AIx immediately after a long chain ω-3 PUFA-rich meal containing 4.7 g of DHA and EPA. In a randomized controlled trial in Japan, highly purified EPA administration (1.8 g/d for 3 mo) significantly reduced both PWV and CAVI values in individuals with metabolic syndrome[71]. However, other two studies using smaller amount (1.7 g of EPA/DHA per day for 12 wk and 1.8 g of EPA/ DHA per day for 12 mo) did not improve arterial stiffness among slightly overweight but relatively healthy subjects[72,73]. Accordingly, the benefits from ω-3 supplementation could be more evident using a comparable dose over a greater duration within an older age, more diseased populations.

Soy isoflavones was another nutrient, which has been **s**tudied frequently. Among five soy isoflavone interventional studies, four interventional studies showed an improvement in PWVor systemic arterial compliance in subjects taking soy isoflavone relative to their placebos[74-77], whereas one study reported no effect[78]. Notably, the majority of the soy interventions were conducted in postmenopausal women. In other studies with positive results, one study reported that consumption of alcoholic red wine might decrease AIx acutely relative to that after consumption of dealcoholized red wine[79], andastudy showed that consumption of black tea flavonoidscouldreduce the digital volume pulse-stiffness index but not PWV[80].Other dietary and nutritional interventions, nonetheless, reported no definite effect on arterial stiffness, such as garlic[81], conjugated linoleic acid[82], vitamins or folic acid[83-87] on PWV.

Among the minerals, salt plays a detrimental role. Consistent evidence suggest that 10-140 mmol sodium chloride supplementation per day would increase arterial stiffness in individuals with hypertension[88,89]. In a randomized clinical trial, salt reduction was associated with decreased pulse pressure across all ethnic groups including white, black and Asians, whereas PWV decreased only in blacks in response to salt reduction[88]. In addition, Gates et al. revealed that large elastic artery compliance was much improved in the older adults with systolic hypertension following only one-week of dietary sodium restriction[90].

**Pharmacological therapy:** Since blood pressure is the strongest modifiable factor directly leading to arterial stiffness, a number of clinical trials have been conducted to investigate the effect of antihypertensive medications on the change of arterial stiffness. Notably almost all classes of anti-hypertensive medications except diuretics and non-vasodilating beta-blockers such as atenolol could decrease arterial stiffness effectively[91,92]. Among all classes of anti-hypertensive medications, RAAS system antagonists have shown the best clinical results, probably due to their anti-fibrotic properties[92]. With regard to other modifiable risk factors, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) could decrease arterial stiffness by lowering low-density lipoprotein cholesterol concentrations, the effect of anti-inflammation, and stabilizing the atheroma plaques[93,94]. In patients with diabetes, glycemic control with oral anti-diabetic agents with metformin and glitazone were reported to improve arterial stiffness[95,96]. Using high dose of RAAS antagonists was extremely effective in attenuating the severity of arterial stiffness in diabetic patients with hypertension[97]. Notably, pharmacological modifications to these traditional vascular risk factors have been confirmed to improve arterial stiffness evaluated by PWV or CAVI[98]. In patients with chronic inflammatory disease such as rheumatoid arthritis, several anti-inflammatory agents have been tested, but until now, only antibodies against tumor necrosis factor-alpha have been shown to improve arterial stiffness, independently of adequate blood pressure control[99,100]. In menopausal women, although the effect of sex hormone replacement therapy on arterial stiffness is uncertain, one study showed that using raloxifene, a potent selective estrogen receptor modulator may lead to positive result[101]. The phosphate binder, sevelamer was found to improve arterial stiffening in patients with end-stage renal disease[102]. Alagebrium, an advanced glycation end-products crosslink breaker, has shown to improve arterial stiffness in animal studies despite the effect was missing in a small group of older individuals[103,104]. However, further clinical trials were not conducted because of financial problems of the developing company. Currently, some ongoing trials are conducted to evaluate the effect of antidiabetic pharmacological therapy including metformin and alogliptin, the dipeptidyl peptidase 4, on the improvement of arterial stiffness in obese children and adolescents, and in adult individuals with type 2 diabetes, respectively[105,106].

**Device and interventional therapy:** It is well known that OSA is related to obesity and correlated with several CVD risk factors, such as hypertension and metabolic syndrome, which contributes to adverse clinical outcomes. A meta-analysis involving 15 articles, investigated the effect of continuous positive airway pressure (CPAP) on arterial stiffness in 615 patients with OSA. A significant improvement of all indices of arterial stiffness was observed after CPAP treatment (SMD = -0.74; 95%CI: -1.08 to -0.41). Neither the proportion of compliance nor the duration of CPAP use altered the outcomes after CPAP treatment[107].

Enhanced external counterpulsation (EECP), using pneumonic cuffs over the legs to inflate and deflate according to the cardiac cycle, is a non-invasive modality for treatment of symptomatic patients with coronary artery disease not amenable to revascularization procedures. In a randomized clinical trials conducted in 42 patients with coronary artery disease, central arterial stiffness and AIx were reduced following 17- and 35-sessions respectively, as well as peripheral arterial stiffness was reduced following 35 sessions in the EECP treatment group as compared with the placebo[108].

Since autonomic nervous system is involved in the pathogenesis of hypertension, its modification such as renal sympathetic denervation, and baroreflex activation therapycould attenuate arterial stiffness by improving arterial stiffness indices and central hemodynamics in patients with resistant hypertension[109,110]. However, these studies were conducted in patients with resistant hypertension, and the result may not be simply extrapolated to all the patients with arterial stiffness.

**CONCLUSION**

Arterial stiffness has been recognized as a marker of CVD and associated with long-term prognosis in several populations. Older age, hypertension, cigarette smoking, and dyslipidemia, known as traditional vascular risk factors, as well as diabetes, obesity, and systemic inflammation contribute to arterial stiffness. Targeting multiple modifiable risk factors has become the main therapeutic strategy to improve arterial stiffness in patients at high cardiovascular risk. Additionally to life style modifications, long-term ω-3 fatty acids intake in diet may improve arterial stiffness in the population with hypertension or metabolic syndrome. Pharmacological treatment such as RAAS antagonists, metformin, and HMG-CoA reductase inhibitors were useful in individuals with hypertension or diabetes. In obese people with OSA, weight reduction, aerobic exercise, and CPAP treatment may improve arterial stiffness as well. In specific populations such as with chronic inflammatory disease, a use of antibodies against tumor necrosis factor-alpha could work effectively. Other therapeutic options such as renal sympathetic nerve denervation for patients with resistant hypertension remains under investigated clinically. Therefore this comprehensive review provides knowledge in detail regarding the aspect of pathogenesis, measurement, and management of arterial stiffness in several populations, which would be helpful for physicians to make clinical decision.

**REFERENCES**

1 **Eiken O**, Kölegård R. Repeated exposures to moderately increased intravascular pressure increases stiffness in human arteries and arterioles. *J Hypertens* 2011; **29**: 1963-1971 [PMID: 21873885 DOI: 10.1097/HJH]

2 **Satoh-Asahara N**, Kotani K, Yamakage H, Yamada T, Araki R, Okajima T, Adachi M, Oishi M, Shimatsu A, Japan Obesity and Metabolic Syndrome Study (JOMS) Group. Cardio-ankle vascular index predicts for the incidence of cardiovascular events in obese patients: A multicenter prospective cohort study (Japan Obesity and Metabolic Syndrome Study: JOMS). *Atherosclerosis* 2015; **242**: 461-468 [PMID: 26295798 DOI: 10.1016/j.atherosclerosis.2015.08.003]

3 **Shore AC**, Colhoun HM, Natali A, Palombo C, Östling G, Aizawa K, Kennbäck C, Casanova F, Persson M, Gooding K, Gates PE, Khan F, Looker HC, Adams F, Belch J, Pinnoli S, Venturi E, Morizzo C, Goncalves I, Ladenvall C, Nilsson J. Measures of atherosclerotic burden are associated with clinically manifest cardiovascular disease in type 2 diabetes: a European cross-sectional study. *J Intern Med* 2015; **278**: 291-302 [PMID: 25752315 DOI: 10.1111/joim.12359]

4 **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**: 1318-1327 [PMID: 20338492 DOI: 10.1016/j.jacc.2009.10.061]

5 **Gkaliagkousi E**, Douma S. The pathogenesis of arterial stiffness and its prognostic value in essential hypertension and cardiovascular diseases. *Hippokratia* 2009; **13**: 70-75 [PMID: 19561773]

6 **van der Heijden-Spek JJ**, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, van Bortel LM. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. *Hypertension* 2000; **35**: 637-642 [PMID: 10679510 DOI: 10.1161/01.HYP.35.2.637]

7 **Yaginuma T**, Avolio A, O'Rourke M, Nichols W, Morgan JJ, Roy P, Baron D, Branson J, Feneley M. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. *Cardiovasc Res* 1986; **20**: 153-160 [PMID: 3085950 DOI: 10.1093/cvr/20.2.153]

8 **Munir S**, Guilcher A, Kamalesh T, Clapp B, Redwood S, Marber M, Chowienczyk P. Peripheral augmentation index defines the relationship between central and peripheral pulse pressure. *Hypertension* 2008; **51**: 112-118 [PMID: 17998476 DOI: 10.1161/HYPERTENSIONAHA.107.096016]

9 **Cavalcante JL**, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol* 2011; **57**: 1511-1522 [PMID: 21453829 DOI: 10.1016/j.jacc.2010.12.017]

10 **Zieman SJ**, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; **25**: 932-943 [PMID: 15731494 DOI: 10.1161/01.ATV.0000160548.78317.29]

11 **Stefanadis C**, Dernellis J, Vlachopoulos C, Tsioufis C, Tsiamis E, Toutouzas K, Pitsavos C, Toutouzas P. Aortic function in arterial hypertension determined by pressure-diameter relation: effects of diltiazem. *Circulation* 1997; **96**: 1853-1858 [PMID: 9323072 DOI: 10.1161/01.CIR.96.6.1853]

12 **Laurent S**. Arterial wall hypertrophy and stiffness in essential hypertensive patients. *Hypertension* 1995; **26**: 355-362 [PMID: 7635546 DOI: 10.1161/01.HYP.26.2.355]

13 **Muxfeldt ES**, Fiszman R, Castelpoggi CH, Salles GF. Ambulatory arterial stiffness index or pulse pressure: which correlates better with arterial stiffness in resistant hypertension? *Hypertens Res* 2008; **31**: 607-613 [PMID: 18633171 DOI: 10.1291/hypres.31.607]

14 **Tounian P**, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, Girardet JP, Bonnet D. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet* 2001; **358**: 1400-1404 [PMID: 11705484 DOI: 10.1016/S0140-6736(01)06525-4]

15 **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**: 1432-1443 [PMID: 7867184 DOI: 10.1161/01.CIR.91.5.1432]

16 **Sutton-Tyrrell K**, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, Spurgeon H, Vaitkevicius P. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension* 2001; **38**: 429-433 [PMID: 11566917 DOI: 10.1161/01.HYP.38.3.429]

17 **Scuteri A**, Najjar SS, Muller DC, Andres R, Hougaku H, Metter EJ, Lakatta EG. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. *J Am Coll Cardiol* 2004; **43**: 1388-1395 [PMID: 15093872 DOI: 10.1016/j.jacc.2003.10.061]

18 **Nickenig G**, Röling J, Strehlow K, Schnabel P, Böhm M. Insulin induces upregulation of vascular AT1 receptor gene expression by posttranscriptional mechanisms. *Circulation* 1998; **98**: 2453-2460 [PMID: 9832492 DOI: 10.1161/01.CIR.98.22.2453]

19 **Jesmin S**, Sakuma I, Hattori Y, Kitabatake A. Role of angiotensin II in altered expression of molecules responsible for coronary matrix remodeling in insulin-resistant diabetic rats. *Arterioscler Thromb Vasc Biol* 2003; **23**: 2021-2026 [PMID: 12958045 DOI: 10.1161/01.ATV.0000094235.78783.D1]

20 **Cusi K**, Maezono K, Osman A, Pendergrass M, Patti ME, Pratipanawatr T, DeFronzo RA, Kahn CR, Mandarino LJ. Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. *J Clin Invest* 2000; **105**: 311-320 [PMID: 10675357 DOI: 10.1172/JCI7535]

21 **Schram MT**, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Westerhof N, Stehouwer CD. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. *Hypertension* 2004; **43**: 176-181 [PMID: 14698999 DOI: 10.1161/01.HYP.0000111829.46090.92]

22 **Brownlee M**, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N Engl J Med* 1988; **318**: 1315-1321 [PMID: 3283558 DOI: 10.1056/NEJM198805193182007]

23 **Wang MC**, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. *Am J Kidney Dis* 2005; **45**: 494-501 [PMID: 15754271 DOI: 10.1053/j.ajkd.2004.11.011]

24 **Chung AW**, Yang HH, Kim JM, Sigrist MK, Chum E, Gourlay WA, Levin A. Upregulation of matrix metalloproteinase-2 in the arterial vasculature contributes to stiffening and vasomotor dysfunction in patients with chronic kidney disease. *Circulation* 2009; **120**: 792-801 [PMID: 19687355 DOI: 10.1161/CIRCULATIONAHA.109.862565]

25 **Jacob MP**. Extracellular matrix remodeling and matrix metalloproteinases in the vascular wall during aging and in pathological conditions. *Biomed Pharmacother* 2003; **57**: 195-202 [PMID: 12888254 DOI: 10.1016/S0753-3322(03)00065-9]

26 **Bucala R**, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *J Clin Invest* 1991; **87**: 432-438 [PMID: 1991829 DOI: 10.1172/JCI115014]

27 **Farkas K**, Nemcsik J, Kolossváry E, Járai Z, Nádory E, Farsang C, Kiss I. Impairment of skin microvascular reactivity in hypertension and uraemia. *Nephrol Dial Transplant* 2005; **20**: 1821-1827 [PMID: 15985514 DOI: 10.1093/ndt/gfh944]

28 **Mäki-Petäjä KM**, Hall FC, Booth AD, Wallace SM, Yasmin PW, Harish S, Furlong A, McEniery CM, Brown J, Wilkinson IB. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. *Circulation* 2006; **114**: 1185-1192 [PMID: 16952987 DOI: 10.1161/CIRCULATIONAHA.105.601641]

29 **Kranzhöfer R**, Schmidt J, Pfeiffer CA, Hagl S, Libby P, Kübler W. Angiotensin induces inflammatory activation of human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 1999; **19**: 1623-1629 [PMID: 10397679 DOI: 10.1161/01.ATV.19.7.1623]

30 **Nemcsik J**, Kiss I, Tislér A. Arterial stiffness, vascular calcification and bone metabolism in chronic kidney disease. *World J Nephrol* 2012; **1**: 25-34 [PMID: 24175239 DOI: 10.5527/wjn.v1.i1.25]

31 **Laurent S**, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. *Hypertension* 2005; **45**:1050–1055. [PMID: 15851625 DOI: 10.1161/01.HYP.0000164580.39991.3d]

32 **Mitchell GF**, DeStefano AL, Larson MG, Benjamin EJ, Chen MH, Vasan RS, Vita JA, Levy D. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham Heart Study. *Circulation* 2005; **112**: 194-199 [PMID: 15998672 DOI: 10.1161/CIRCULATIONAHA.104.485326]

33 **Lacolley P**, Challande P, Osborne-Pellegrin M, Regnault V. Genetics and pathophysiology of arterial stiffness. *Cardiovasc Res* 2009; **81**: 637-648 [PMID: 19098299 DOI: 10.1093/cvr/cvn353]

34 **Benetos A**, Topouchian J, Ricard S, Gautier S, Bonnardeaux A, Asmar R, Poirier O, Soubrier F, Safar M, Cambien F. Influence of angiotensin II type 1 receptor polymorphism on aortic stiffness in never-treated hypertensive patients. *Hypertension* 1995; **26**: 44-47 [PMID: 7607731 DOI: 10.1161/01.HYP.26.1.44]

35 **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**: 31-38 [PMID: 8994413 DOI: 10.1161/01.CIR.95.1]

36 **Stefanadis C**, Vlachopoulos C, Tsiamis E, Diamantopoulos L, Toutouzas K, Giatrakos N, Vaina S, Tsekoura D, Toutouzas P. Unfavorable effects of passive smoking on aortic function in men. *Ann Intern Med* 1998; **128**: 426-434 [PMID: 9499325 DOI: 10.7326/0003-4819-128-6-199803150-00002]

37 **Vlachopoulos C**, Alexopoulos N, Panagiotakos D, O'Rourke MF, Stefanadis C. Cigar smoking has an acute detrimental effect on arterial stiffness. *Am J Hypertens* 2004; **17**: 299-303 [PMID: 15062882 DOI: 10.1016/j.amjhyper.2003.12.014]

38 **Zebekakis PE**, Nawrot T, Thijs L, Balkestein EJ, van der Heijden-Spek J, Van Bortel LM, Struijker-Boudier HA, Safar ME, Staessen JA. Obesity is associated with increased arterial stiffness from adolescence until old age. *J Hypertens* 2005; **23**: 1839-1846 [PMID: 16148607 DOI: 10.1097/01.hjh.0000179511.93889.e9]

39 **Wildman RP**, Farhat GN, Patel AS, Mackey RH, Brockwell S, Thompson T, Sutton-Tyrrell K. Weight change is associated with change in arterial stiffness among healthy young adults. *Hypertension* 2005; **45**: 187-192 [PMID: 15596570 DOI: 10.1161/01.HYP.0000152200.10578.5d]

40 **Vlachopoulos C**, Hirata K, O'Rourke MF. Pressure-altering agents affect central aortic pressures more than is apparent from upper limb measurements in hypertensive patients: the role of arterial wave reflections. *Hypertension* 2001; **38**: 1456-1460 [PMID: 11751735 DOI: 10.1161/hy1201.098767]

41 **Wall NA**, Chue CD, Edwards NC, Pankhurst T, Harper L, Steeds RP, Lauder S, Townend JN, Moss P, Ferro CJ. Cytomegalovirus seropositivity is associated with increased arterial stiffness in patients with chronic kidney disease. *PLoS One* 2013; **8**: e55686 [PMID: 23451030 DOI: 10.1371/journal.pone.0055686]

42 **Lehmann ED**, Parker JR, Hopkins KD, Taylor MG, Gosling RG. Validation and reproducibility of pressure-corrected aortic distensibility measurements using pulse-wave-velocity Doppler ultrasound. *J Biomed Eng* 1993; **15**: 221-228 [PMID: 8320981 DOI: 10.1016/0141-5425(93)90118-I]

43 **Asmar RG**, Topouchian JA, Benetos A, Sayegh FA, Mourad JJ, Safar ME. Non-invasive evaluation of arterial abnormalities in hypertensive patients. *J Hypertens Suppl* 1997; **15**: S99-107 [PMID: 9218206]

44 **Asmar R**, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995; **26**: 485-490 [PMID: 7649586 DOI: 10.1161/01.HYP.26.3]

45 **Yamashina A**, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359-364 [PMID: 12135313 DOI: 10.1291/hypres.25.359]

46 **Tomiyama H**, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, Hori S, Yamamoto Y, Doba N, Hinohara S. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement--a survey of 12517 subjects. *Atherosclerosis* 2003; **166**: 303-309 [PMID: 12535743 DOI: 10.1016/S0021-9150(02)00332-5]

47 **Turin TC**, Kita Y, Rumana N, Takashima N, Kadota A, Matsui K, Sugihara H, Morita Y, Nakamura Y, Miura K, Ueshima H. Brachial-ankle pulse wave velocity predicts all-cause mortality in the general population: findings from the Takashima study, Japan. *Hypertens Res* 2010; **33**: 922-925 [PMID: 20555327 DOI: 10.1038/hr.2010.103]

48 **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**: 664-670 [PMID: 16461839 DOI: 10.1161/CIRCULATIONAHA.105]

49 **Van Bortel LM**, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, Filipovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD, Schillaci G, Segers P, Vermeersch S, Weber T. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; **30**: 445-448 [PMID: 22278144]

50 **Boutouyrie P**, Fliser D, Goldsmith D, Covic A, Wiecek A, Ortiz A, Martinez-Castelao A, Lindholm B, Massy ZA, Suleymanlar G, Sicari R, Gargani L, Parati G, Mallamaci F, Zoccali C, London GM. Assessment of arterial stiffness for clinical and epidemiological studies: methodological considerations for validation and entry into the European Renal and Cardiovascular Medicine registry. *Nephrol Dial Transplant* 2014; **29**: 232-239 [PMID: 24084326 DOI: 10.1093/ndt/gft309]

51 **Westerhof BE**, van den Wijngaard JP, Murgo JP, Westerhof N. Location of a reflection site is elusive: consequences for the calculation of aortic pulse wave velocity. *Hypertension* 2008; **52**: 478-483 [PMID: 18695144 DOI: 10.1161/HYPERTENSIONAHA.108.116525]

52 **Lemogoum D**, Flores G, Van den Abeele W, Ciarka A, Leeman M, Degaute JP, van de Borne P, Van Bortel L. Validity of pulse pressure and augmentation index as surrogate measures of arterial stiffness during beta-adrenergic stimulation. *J Hypertens* 2004; **22**: 511-517 [PMID: 15076156 DOI: 10.1097/01.hjh.0000098265.58662.94]

53 **Hayashi K**, Handa H, Nagasawa S, Okumura A, Moritake K. Stiffness and elastic behavior of human intracranial and extracranial arteries. *J Biomech* 1980; **13**: 175-184 [PMID: 7364778 DOI: 10.1016/0021-9290(80)90191-8]

54 **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**: 101-107 [PMID: 16733298 DOI: 10.5551/jat.13.101]

55 **Hasegawa M**. Fundamental research on human aortic pulse wave velocity. *Jikei Med J* 1970; **85**:742–760

56 **Petersen KS**, Blanch N, Keogh JB, Clifton PM. Effect of weight loss on pulse wave velocity: systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol* 2015; **35**: 243-252 [PMID: 2541425]

57 **Nagayama D**, Endo K, Ohira M, Yamaguchi T, Ban N, Kawana H, Nagumo A, Saiki A, Oyama T, Miyashita Y, Shirai K. Effects of body weight reduction on cardio-ankle vascular index (CAVI). *Obes Res Clin Pract* 2013; **7**: e139-e145 [PMID: 24331775 DOI: 10.1016/j.orcp.2011.08.154]

58 **Nocon M**, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil* 2008; **15**: 239-246 [PMID: 18525377 DOI: 10.1097/HJR.0b013e3282f55e09]

59 **Mora S**, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 2007; **116**: 2110-2118 [PMID: 17967770 DOI: 10.1161/CIRCULATIONAHA.107.729939]

60 **Green DJ**, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol* 2004; **561**: 1-25 [PMID: 15375191 DOI: 10.1113/jphysiol.2004.068197]

61 **Ashor AW**, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2014; **9**: e110034 [PMID: 25333969 DOI: 10.1371/journal.pone.0110034]

62 **Takami T**, Saito Y. Effects of smoking cessation on central blood pressure and arterial stiffness. *Vasc Health Risk Manag* 2011; **7**: 633-638 [PMID: 22102787 DOI: 10.2147/VHRM.S25798]

63 **Noike H**, Nakamura K, Sugiyama Y, Iizuka T, Shimizu K, Takahashi M, Hirano K, Suzuki M, Mikamo H, Nakagami T, Shirai K. Changes in cardio-ankle vascular index in smoking cessation. *J Atheroscler Thromb* 2010; **17**: 517-525 [PMID: 20215706 DOI: 10.5551/jat.3707]

64 **Rajkumar S**, Schmidt-Trucksäss A, Wellenius GA, Bauer GF, Huynh CK, Moeller A, Röösli M. The effect of workplace smoking bans on heart rate variability and pulse wave velocity of non-smoking hospitality workers. *Int J Public Health* 2014; **59**: 577-585 [PMID: 24504155 DOI: 10.1007/s00038-014-0545-y]

65 **Pase MP**, Grima NA, Sarris J. The effects of dietary and nutrient interventions on arterial stiffness: a systematic review. *Am J Clin Nutr* 2011; **93**: 446-454 [PMID: 21147858 DOI: 10.3945/ajcn.110.002725]

66 **Fahs CA**, Yan H, Ranadive S, Rossow LM, Agiovlasitis S, Wilund KR, Fernhall B. The effect of acute fish-oil supplementation on endothelial function and arterial stiffness following a high-fat meal. *Appl Physiol Nutr Metab* 2010; **35**: 294-302 [PMID: 20555373 DOI: 10.1139/H10-020]

67 **Wang S**, Ma AQ, Song SW, Quan QH, Zhao XF, Zheng XH. Fish oil supplementation improves large arterial elasticity in overweight hypertensive patients. *Eur J Clin Nutr* 2008; **62**: 1426-1431 [PMID: 17805229 DOI: 10.1038/sj.ejcn.1602886]

68 **Sjoberg NJ**, Milte CM, Buckley JD, Howe PR, Coates AM, Saint DA. Dose-dependent increases in heart rate variability and arterial compliance in overweight and obese adults with DHA-rich fish oil supplementation. *Br J Nutr* 2010; **103**: 243-248 [PMID: 19664302 DOI: 10.1017/]

69 **Chong MF**, Lockyer S, Saunders CJ, Lovegrove JA. Long chain n-3 PUFA-rich meal reduced postprandial measures of arterial stiffness. *Clin Nutr* 2010; **29**: 678-681 [PMID: 20199827 DOI: 10.1016/j.clnu.2010.02.001]

70 **Satoh N**, Shimatsu A, Kotani K, Himeno A, Majima T, Yamada K, Suganami T, Ogawa Y. Highly purified eicosapentaenoic acid reduces cardio-ankle vascular index in association with decreased serum amyloid A-LDL in metabolic syndrome. *Hypertens Res* 2009; **32**: 1004-1008 [PMID: 19763135 DOI: 10.1038/hr.2009.145]

71 **Root M**, Collier SR, Zwetsloot KA, West KL, McGinn MC. A randomized trial of fish oil omega-3 fatty acids on arterial health, inflammation, and metabolic syndrome in a young healthy population. *Nutr J* 2013; **12**: 40 [PMID: 23565815 DOI: 10.1186/1475-2891-12-40]

72 **Sanders TA**, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. *Am J Clin Nutr* 2011; **94**: 973-980 [PMID: 21865334 DOI: 10.3945/ajcn.111.018036]

73 **Teede HJ**, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: a placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab* 2001; **86**: 3053-3060 [PMID: 11443167 DOI: 10.1210/jc.86.7.3053]

74 **Teede HJ**, McGrath BP, DeSilva L, Cehun M, Fassoulakis A, Nestel PJ. Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1066-1071 [PMID: 12714433 DOI: 10.1161/01.ATV.0000072967.97296.4A]

75 **Nestel P**, Fujii A, Zhang L. An isoflavone metabolite reduces arterial stiffness and blood pressure in overweight men and postmenopausal women. *Atherosclerosis* 2007; **192**: 184-189 [PMID: 16730732 DOI: 10.1016/j.atherosclerosis.2006.04.033]

76 **Nestel PJ**, Yamashita T, Sasahara T, Pomeroy S, Dart A, Komesaroff P, Owen A, Abbey M. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler Thromb Vasc Biol* 1997; **17**: 3392-3398 [PMID: 9437184 DOI: 10.1161/01.ATV.17.12.3392]

77 **Törmälä R**, Appt S, Clarkson TB, Groop PH, Rönnback M, Ylikorkala O, Mikkola TS. Equol production capability is associated with favorable vascular function in postmenopausal women using tibolone; no effect with soy supplementation. *Atherosclerosis* 2008; **198**: 174-178 [PMID: 17961576 DOI: 10.1016/j.atherosclerosis.2007.09.010]

78 **Karatzi KN**, Papamichael CM, Karatzis EN, Papaioannou TG, Aznaouridis KA, Katsichti PP, Stamatelopoulos KS, Zampelas A, Lekakis JP, Mavrikakis ME. Red wine acutely induces favorable effects on wave reflections and central pressures in coronary artery disease patients. *Am J Hypertens* 2005; **18**: 1161-1167 [PMID: 16182104 DOI: 10.1016/j.amjhyper]

79 **Grassi D**, Mulder TP, Draijer R, Desideri G, Molhuizen HO, Ferri C. Black tea consumption dose-dependently improves flow-mediated dilation in healthy males. *J Hypertens* 2009; **27**: 774-781 [PMID: 19516176 DOI: 10.1097/HJH.0b013e328326066c]

80 **Turner B**, Mølgaard C, Marckmann P. Effect of garlic (Allium sativum) powder tablets on serum lipids, blood pressure and arterial stiffness in normo-lipidaemic volunteers: a randomised, double-blind, placebo-controlled trial. *Br J Nutr* 2004; **92**: 701-706 [PMID: 15522140 DOI: 10.1079/BJN20041255]

81 **Sluijs I**, Plantinga Y, de Roos B, Mennen LI, Bots ML. Dietary supplementation with cis-9,trans-11 conjugated linoleic acid and aortic stiffness in overweight and obese adults. *Am J Clin Nutr* 2010; **91**: 175-183 [PMID: 19923377 DOI: 10.3945/ajcn.2009.28192]

82 **Kelly RP**, Poo Yeo K, Isaac HB, Lee CY, Huang SH, Teng L, Halliwell B, Wise SD. Lack of effect of acute oral ingestion of vitamin C on oxidative stress, arterial stiffness or blood pressure in healthy subjects. *Free Radic Res* 2008; **42**: 514-522 [PMID: 18484415 DOI: 10.1080/10715760802087431]

83 **Magliano D**, McNeil J, Branley P, Shiel L, Demos L, Wolfe R, Kotsopoulos D, McGrath B. The Melbourne Atherosclerosis Vitamin E Trial (MAVET): a study of high dose vitamin E in smokers. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 341-347 [PMID: 16926662 DOI: 10.1097/01.hjr.0000219108.10167]

84 **Rasool AH**, Rehman A, Wan Yusuf WN, Rahman AR. Vitamin E and its effect on arterial stiffness in postmenopausal women--a randomized controlled trial. *Int J Clin Pharmacol Ther* 2003; **41**: 587-592 [PMID: 14692708]

85 **Zoungas S**, McGrath BP, Branley P, Kerr PG, Muske C, Wolfe R, Atkins RC, Nicholls K, Fraenkel M, Hutchison BG, Walker R, McNeil JJ. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: a multicenter, randomized, controlled trial. *J Am Coll Cardiol* 2006; **47**: 1108-1116 [PMID: 16545638 DOI: 10.1016/j.jacc.2005.10.064]

86 **Khandanpour N**, Armon MP, Jennings B, Finglas PM, Willis G, Clark A, Meyer FJ. Randomized clinical trial of folate supplementation in patients with peripheral arterial disease. *Br J Surg* 2009; **96**: 990-998 [PMID: 19672935 DOI: 10.1002/bjs.6670]

87 **He FJ**, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, MacGregor GA. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. *Hypertension* 2009; **54**: 482-488 [PMID: 19620514 DOI: 10.1161/HYPERTENSIONAHA.109.133223]

88 **Todd AS**, Macginley RJ, Schollum JB, Johnson RJ, Williams SM, Sutherland WH, Mann JI, Walker RJ. Dietary salt loading impairs arterial vascular reactivity. *Am J Clin Nutr* 2010; **91**: 557-564 [PMID: 20107199 DOI: 10.3945/ajcn.2009.28645]

89 **Gates PE**, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension* 2004; **44**: 35-41 [PMID: 15173128 DOI: 10.1161/01.HYP.0000132767.74476.64]

90 **Williams B**, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; **113**: 1213-1225 [PMID: 16476843 DOI: 10.1161/CIRCULATIONAHA.105.595496]

91 **Boutouyrie P**, Lacolley P, Briet M, Regnault V, Stanton A, Laurent S, Mahmud A. Pharmacological modulation of arterial stiffness. *Drugs* 2011; **71**: 1689-1701 [PMID: 21902292 DOI: 10.2165/11593790-000000000-00000]

92 **Van Doornum S**, McColl G, Wicks IP. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. *Ann Rheum Dis* 2004; **63**: 1571-1575 [PMID: 15547080 DOI: 10.1136/ard.2003.018333]

93 **Monte AA**, Chuang R, Bodmer M. Dextromethorphan, chlorphenamine and serotonin toxicity: case report and systematic literature review. *Br J Clin Pharmacol* 2010; **70**: 794-798 [PMID: 21175434 DOI: 10.1111/j.1365-2125.2010.03745.x]

94 **Agarwal N**, Rice SP, Bolusani H, Luzio SD, Dunseath G, Ludgate M, Rees DA. Metformin reduces arterial stiffness and improves endothelial function in young women with polycystic ovary syndrome: a randomized, placebo-controlled, crossover trial. *J Clin Endocrinol Metab* 2010; **95**: 722-730 [PMID: 19996308 DOI: 10.1210/jc.2009-1985]

95 **Yu J**, Jin N, Wang G, Zhang F, Mao J, Wang X. Peroxisome proliferator-activated receptor gamma agonist improves arterial stiffness in patients with type 2 diabetes mellitus and coronary artery disease. *Metabolism* 2007; **56**: 1396-1401 [PMID: 17884451]

96 **Karalliedde J**, Smith A, DeAngelis L, Mirenda V, Kandra A, Botha J, Ferber P, Viberti G. Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension* 2008; **51**: 1617-1623 [PMID: 18426991]

97 **Shirai K**, Utino J, Saiki A, Endo K, Ohira M, Nagayama D, Tatsuno I, Shimizu K, Takahashi M, Takahara A. Evaluation of blood pressure control using a new arterial stiffness parameter, cardio-ankle vascular index (CAVI). *Curr Hypertens Rev* 2013; **9**: 66-75 [PMID: 23807874 DOI: 10.2174/1573402111309010010]

98 **Wong M**, Oakley SP, Young L, Jiang BY, Wierzbicki A, Panayi G, Chowienczyk P, Kirkham B. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. *Ann Rheum Dis* 2009; **68**: 1277-1284 [PMID: 18930987 DOI: 10.1136/ard.2007.086157]

99 **Angel K**, Provan SA, Gulseth HL, Mowinckel P, Kvien TK, Atar D. Tumor necrosis factor-alpha antagonists improve aortic stiffness in patients with inflammatory arthropathies: a controlled study. *Hypertension* 2010; **55**: 333-338 [PMID: 20038753 DOI: 10.1161/HYPERTENSIONAHA.109]

100 **da Costa LS**, de Oliveira MA, Rubim VS, Wajngarten M, Aldrighi JM, Rosano GM, Neto CD, Gebara OC. Effects of hormone replacement therapy or raloxifene on ambulatory blood pressure and arterial stiffness in treated hypertensive postmenopausal women. *Am J Cardiol* 2004; **94**: 1453-1456 [PMID: 15566926]

101 **Othmane Tel H**, Bakonyi G, Egresits J, Fekete BC, Fodor E, Jarai Z, Jekkel C, Nemcsik J, Szabo A, Szabo T, Kiss I, Tisler A. Effect of sevelamer on aortic pulse wave velocity in patients on hemodialysis: a prospective observational study. *Hemodial Int* 2007; **11** Suppl **3**: S13-S21 [PMID: 17897105 DOI: 10.1111/j.1542-4758.2007.00224.x]

102 **Steppan J**, Tran H, Benjo AM, Pellakuru L, Barodka V, Ryoo S, Nyhan SM, Lussman C, Gupta G, White AR, Daher JP, Shoukas AA, Levine BD, Berkowitz DE. Alagebrium in combination with exercise ameliorates age-associated ventricular and vascular stiffness. *Exp Gerontol* 2012; **47**: 565-572 [PMID: 22569357 DOI: 10.1016/j.exger.2012.04.006]

103 **Oudegeest-Sander MH**, Olde Rikkert MG, Smits P, Thijssen DH, van Dijk AP, Levine BD, Hopman MT. The effect of an advanced glycation end-product crosslink breaker and exercise training on vascular function in older individuals: a randomized factorial design trial. *Exp Gerontol* 2013; **48**: 1509-1517 [PMID: 24400341 DOI: 10.1016/j.exger.2013.10.009]

104 **van der Aa MP**, Elst MA, van Mil EG, Knibbe CA, van der Vorst MM. METFORMIN: an efficacy, safety and pharmacokinetic study on the short-term and long-term use in obese children and adolescents - study protocol of a randomized controlled study. *Trials* 2014; **15**: 207 [PMID: 24899137 DOI: 10.1186/1745-6215-15-207]

105 **Wang H**, Liu J, Zhao H. Emerging options for the treatment of type 2 diabetes in Chinese patients: focus on arterial function and alogliptin. *Drug Des Devel Ther* 2015; **9**: 683-686 [PMID: 25678772 DOI: 10.2147/DDDT.S53048]

106 **Vlachantoni IT**, Dikaiakou E, Antonopoulos CN, Stefanadis C, Daskalopoulou SS, Petridou ET. Effects of continuous positive airway pressure (CPAP) treatment for obstructive sleep apnea in arterial stiffness: a meta-analysis. *Sleep Med Rev* 2013; **17**: 19-28 [PMID: 22575367 DOI: 10.1016/j.smrv.2012.01.002]

107 **Casey DP**, Beck DT, Nichols WW, Conti CR, Choi CY, Khuddus MA, Braith RW. Effects of enhanced external counterpulsation on arterial stiffness and myocardial oxygen demand in patients with chronic angina pectoris. *Am J Cardiol* 2011; **107**: 1466-1472 [PMID: 21420062 DOI: 10.1016/j.amjcard.2011.01.021]

108 **Brandt MC**, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 2012; **59**: 901-909 [PMID: 22381425 DOI: 10.1016/j.jacc.2011.11.034]

109 **Wallbach M**, Lehnig LY, Schroer C, Helms HJ, Lüders S, Patschan D, Patschan S, Müller GA, Wachter R, Koziolek MJ. Effects of baroreflex activation therapy on arterial stiffness and central hemodynamics in patients with resistant hypertension. *J Hypertens* 2015; **33**: 181-186 [PMID: 25232758 DOI: 10.1097/HJH.0000000000000361]

110 **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**: 43-48 [PMID: 17114200 DOI: 10.1093/ageing/afl115]

111 **Vivodtzev I**, Tamisier R, Baguet JP, Borel JC, Levy P, Pépin JL. Arterial stiffness in COPD. *Chest* 2014; **145**: 861-875 [PMID: 24687708 DOI: 10.1378/chest]

112 **Armeni E**, Stamatelopoulos K, Rizos D, Georgiopoulos G, Kazani M, Kazani A, Kolyviras A, Stellos K, Panoulis K, Alexandrou A, Creatsa M, Papamichael C, Lambrinoudaki I. Arterial stiffness is increased in asymptomatic nondiabetic postmenopausal women with a polycystic ovary syndrome phenotype. *J Hypertens* 2013; **31**: 1998-2004 [PMID: 24107731 DOI: 10.1097/HJH.0b013e3283630362]

113 **Masaki M**, Komamura K, Goda A, Hirotani S, Otsuka M, Nakabo A, Fukui M, Fujiwara S, Sugahara M, Lee-Kawabata M, Tsujino T, Koshiba M, Masuyama T. Elevated arterial stiffness and diastolic dysfunction in subclinical hypothyroidism. *Circ J* 2014; **78**: 1494-1500 [PMID: 24694766 DOI: 10.1253/circj.CJ-13-1556]

114 **Vlachopoulos C**, Kosmopoulou F, Panagiotakos D, Ioakeimidis N, Alexopoulos N, Pitsavos C, Stefanadis C. Smoking and caffeine have a synergistic detrimental effect on aortic stiffness and wave reflections. *J Am Coll Cardiol* 2004; **44**: 1911-1917 [PMID: 15519028 DOI: 10.1016/j.jacc.2004]

115 **Sasaki S**, Yoshioka E, Saijo Y, Kita T, Okada E, Tamakoshi A, Kishi R. Relation between alcohol consumption and arterial stiffness: A cross-sectional study of middle-aged Japanese women and men. *Alcohol* 2013; **47**: 643-649 [PMID: 24239150 DOI: 10.1016/j.alcohol.2013.10.003]

116 **Ito N**, Ohishi M, Takagi T, Terai M, Shiota A, Hayashi N, Rakugi H, Ogihara T. Clinical usefulness and limitations of brachial-ankle pulse wave velocity in the evaluation of cardiovascular complications in hypertensive patients. *Hypertens Res* 2006; **29**: 989-995 [PMID: 17378371 DOI: 10.1291/hypres.29.989]

117 **Choo J**, Shin C, Barinas-Mitchell E, Masaki K, Willcox BJ, Seto TB, Ueshima H, Lee S, Miura K, Venkitachalam L, Mackey RH, Evans RW, Kuller LH, Sutton-Tyrrell K, Sekikawa A. Regional pulse wave velocities and their cardiovascular risk factors among healthy middle-aged men: a cross-sectional population-based study. *BMC Cardiovasc Disord* 2014; **14**: 5 [PMID: 24410766 DOI: 10.1186/1471-2261-14-5]

118 **Hayashi K**, Yamamoto T, Takahara A, Shirai K. Clinical assessment of arterial stiffness with cardio-ankle vascular index: theory and applications. *J Hypertens* 2015; **33**: 1742-1757 [PMID: 26114836 DOI: 10.1097/HJH.0000000000000651]

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| --- |
| **Table 1 Demographic, clinical, and Lifestyle factors associated with arterial stiffness** |
| **Age[7]****Sex[111]****Established cardiovascular disease**[3]**Potential risk factors for atherosclerosis**Hypertension[11]Dyslipidemia[2]Cigarette smoking[64]Chronic obstructive pulmonary disease**[112]**Diabetes[14]Obesity[3]Obstructive sleep apnea[107]Menopause[111]Polycystic ovarian syndrome[113]Hypothyroidism[114]Chronic kidney disease[23]Endothelial dysfunction[27]Systemic inflammation[100]Cytomegalovirus infection[115]**Nutritional and lifestyle aspects**Caffeine[116]Chronic alcohol consumption[117]Sedentary lifestyle[59]Resistance exercise training[62]**Genes variants**Genes of the Renin-Angiotensin-Aldosterone system[33] Genes of the extracellular matrix proteins[33] |

**Table 2 A summary of the advantages and disadvantages of different measurements for evaluating arterial stiffness**

|  |  |  |
| --- | --- | --- |
|  | **Advantage** | **Disadvantage** |
| **cfPWV**[43-45] | reflects the stiffness of the descending aortathe gold standard measure for arterial stiffness | largely affected by the change of BPoverestimated for the inaccurate measurement in the distance between the carotid and the femoral arteries |
| **baPWV**[118,119] | reflects the stiffness of both the descending aorta and the leg arteryhigh association with CV risk factors ease of use for large-scale population studies | largely affected by the change of BPunderestimates arterial stiffness in hypertensive patients with a history of cardiovascular events |
| **hfPWV**[120] | strongly correlated with cfPWVmoderately correlated with baPWV | require a high level of proficiency in order to obtain accurate results |
| **faPWV**[119,120] | moderately correlated with baPWV | the predictive value to incident vascular events remains unknown |
| **pAIx**[111,121] | assessed non-invasively and peripherally, *e.g.*,carotid, and radial arteriescorrelated well with the central AIx  | largely affected by the change of BPnot a valid surrogate of arterial compliance in the elderly and diabetic populations |
| **The stiffness parameter β**[54,55] | independent of the change of BP | assessing only a local segment of the arteryloss of the independence of BP for those with moderate to severe hypertension or hypotension |
| **CAVI**[122] | independent of the change of BPa novel atherosclerotic index that incorporates PWV and BP measurementsthe coefficients of variation are small (< 4%), and does not require significant training | CAVI, as a cardiovascular risk marker has not to be investigated definitively in large prospective clinical trials |

Ba: Brachial-ankle arteries; CAVI: Cardio-ankle vascular index; BP: Blood pressure; cf: Carotid-femoral arteries; fa: Femoral-ankle arteries; hf: Heart-femoral arteries; pAIx: Peripheral augmentation index; PWV: Pulse-wave velocity.



IA-II

IA-I

**Figure 1 The central aortic pressure waveform is the summation of forward travelling wave, P (f) and the reflected backward-travelling wave, P (b).** On the top graph IA-I, is an illustration of a stiff aorta or peripheral vasoconstriction, both P (f) and P (b) travel fast and the magnitude of the reflected wave is increased, thus augmenting the systolic pressure of summated central aortic pressure waveform, P (m). In graph 1A-II, is another illustration of a distensible aorta or with vasodilatation. Length and thickness of horizontal arrows correspond to the waveform velocity and the magnitude of the reflected wave, respectively. Vertical arrows indicate point of merging of P (f) and P (b).

Mechanical and/or chemical stress

“Reparative” processes lead to structural changes within the vessel wall and extracellular matrix

Increased collagen deposition and vessel wall calcification

PWV and reflected wave

SBP

Aorta reservoir/buffering properties

Ventricular workload,

LV hypertrophy ischemia

uu

Unbalanced myocardial demand/

coronary perfusion

uu

**Stiffness**

**Compliance**

**Atherosclerosis**

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**Figure 2 Aortic elastic properties may be altered by several processes, resulting in increased stiffness, decreased compliance, and encompassing the diseased ventricular-arterial coupling.** Mechanical and chemical stress factors include hypertension, inflammation, advanced glycation end products, *etc.* LV: Ventricular; PWV: Pulse wave velocity; SBP: Systolic blood pressure.



**Figure 3 For practical purpose, femoral artery is counted as the terminal aorta.** The measured distance is length. If ∆Time represents the time delay between the feet of the 2 waves, pulse wave velocity. PWV: Length/∆Time.