

## Therapeutic modification of arterial stiffness: An update and comprehensive review

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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  $\omega$ -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 3-hydroxy-3-methyl-glutaryl-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<sup>[1-4]</sup>. 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<sup>[4]</sup>. 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<sup>[5]</sup>. 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

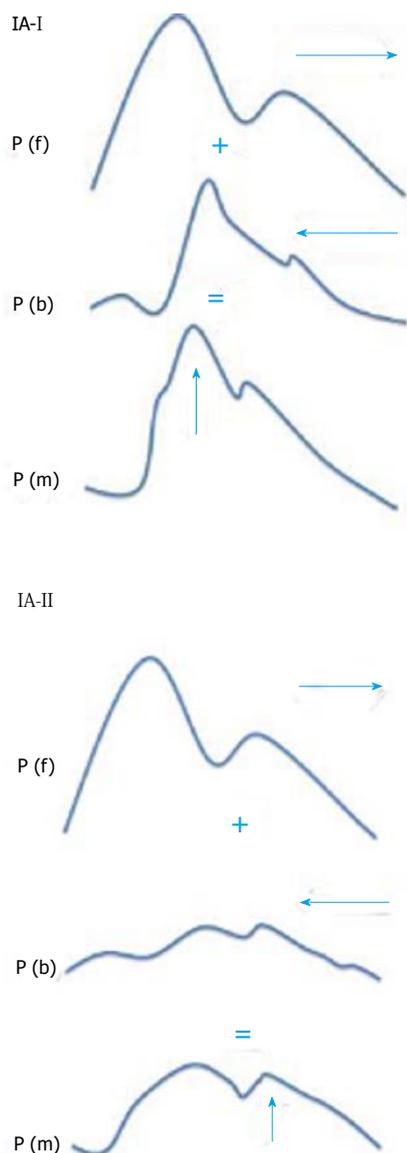
central in the case of hypertension, atheromatous arteries or increased sympathetic activity<sup>[6]</sup>.

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<sup>[7]</sup>. 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<sup>[7]</sup> (Figure 1). The added part on systolic pressure and cardiac afterload was named aortic augmentation index [Aix, (second/first systolic peak) × 100%]<sup>[8]</sup>. 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<sup>[9]</sup> (Figure 2).

### **Factors affecting arterial stiffness**

Age is a main determinant of stiffness in large elastic arteries<sup>[7,10]</sup>. 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<sup>[10]</sup>.

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<sup>[11,12]</sup>. Distending pressure as estimated by 24-h pulse pressure was another major factor additionally to older age contributing to the occurrence of arterial stiffness<sup>[13]</sup>. In patients with diabetes or metabolic syndrome, arterial stiffening is consistently observed across all age groups, even in childhood<sup>[14]</sup>. Insulin resistance is dose-dependent and positively correlated with arterial stiffness<sup>[15-17]</sup>. 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



**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 IA-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).

and fibrosis<sup>[18,19]</sup>.

In addition hyperinsulinemia has proliferative effects, *via* unbalanced activities on growth-promoting mitogen activated kinase pathways and PI3-kinase-dependent signaling<sup>[20]</sup>. 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<sup>[21,22]</sup>.

Chronic kidney disease (CKD) is a well-known risk factor of arterial stiffness<sup>[23]</sup>. Several mechanisms have been proposed to explain the effect of CKD. For

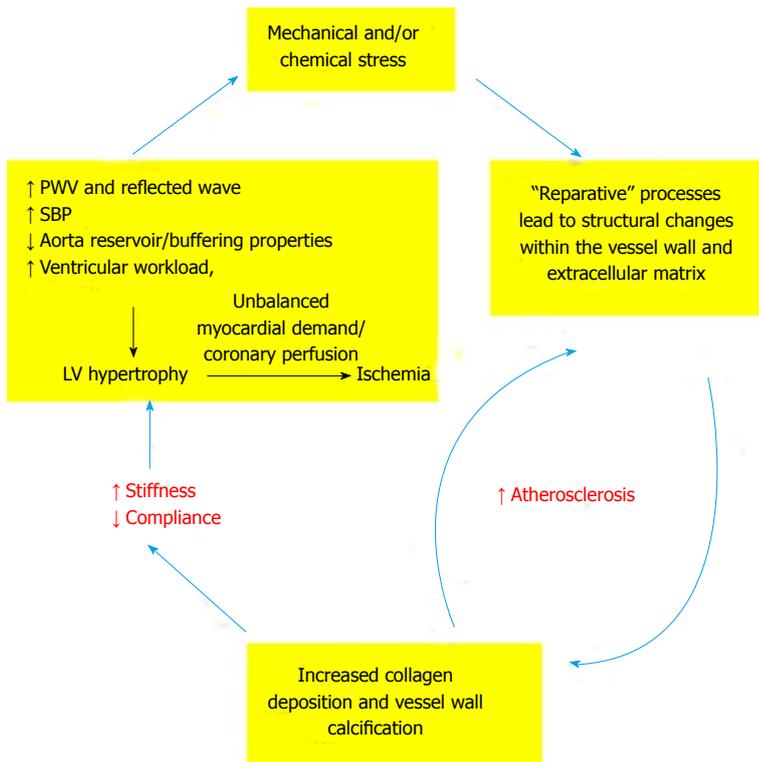
instance, upregulation of matrix metalloproteinases enhances collagen and elastin turnover through enzymatic cross-link degradation<sup>[24]</sup>, causing weakening of the extracellular matrix<sup>[25]</sup>. Accumulation of advanced glycation end-products makes collagen stiffer as well<sup>[26]</sup>. 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<sup>[27]</sup>. Chronic inflammation and RAAS activation are also involved in the process of arterial stiffening in CKD<sup>[28,29]</sup>. 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 Gla protein, and fetuin A levels<sup>[30]</sup>.

Arterial elastic properties are impaired in young people with a family history of hypertension, diabetes or myocardial infarction<sup>[31]</sup>. 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<sup>[32]</sup>. Potential candidate genes in these regions included the insulin-like growth factor-1 receptor, myocyte-specific enhancer factor 2A, chondroitin synthase (CHSY1), proprotein convertases (PACE4 and FURIN), b-adducin (ADD2), neurokinin-1 receptor (TACR1),  $\alpha$ -2B adrenergic receptor (ADRA2B), and interleukin-6 (IL-6). 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<sup>[33]</sup>.

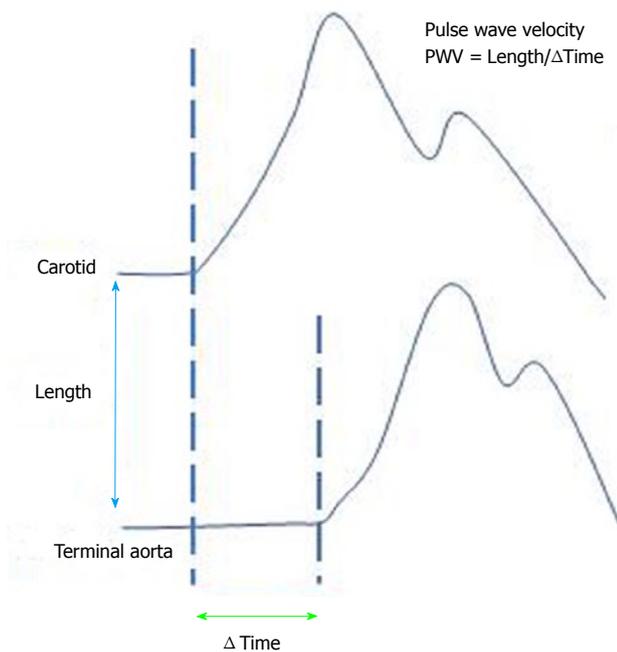
Lifestyle characteristics are important determinants of arterial stiffness. Cigarette smoking, including passive smoking and current smoking has an adverse impact on the arterial stiffness<sup>[34-36]</sup>. Elevated arterial stiffness has been found among patients with chronic obstructive pulmonary 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<sup>[37-40]</sup>. Intake of caffeine, a neurotoxin has also been acknowledged of an unfavorable effect on arterial compliance<sup>[40]</sup>. Other risk factors such as chronic cytomegalovirus infection, has been known as a novel potential contributor to arterial stiffening<sup>[41]</sup>. 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



**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 ΔTime represents the time delay between the feet of the 2 waves, pulse wave velocity.

**Table 1** Demographic, clinical, and lifestyle factors associated with arterial stiffness

Age <sup>[7]</sup>
Sex <sup>[110]</sup>
Established cardiovascular disease <sup>[3]</sup>
Potential risk factors for atherosclerosis
Hypertension <sup>[11]</sup>
Dyslipidemia <sup>[2]</sup>
Cigarette smoking <sup>[63]</sup>
Chronic obstructive pulmonary disease <sup>[111]</sup>
Diabetes <sup>[14]</sup>
Obesity <sup>[3]</sup>
Obstructive sleep apnea <sup>[106]</sup>
Menopause <sup>[110]</sup>
Polycystic ovarian syndrome <sup>[112]</sup>
Hypothyroidism <sup>[113]</sup>
Chronic kidney disease <sup>[23]</sup>
Endothelial dysfunction <sup>[27]</sup>
Systemic inflammation <sup>[99]</sup>
Cytomegalovirus infection <sup>[114]</sup>
Nutritional and lifestyle aspects
Caffeine <sup>[115]</sup>
Chronic alcohol consumption <sup>[116]</sup>
Sedentary lifestyle <sup>[58]</sup>
Resistance exercise training <sup>[61]</sup>
Genes variants
Genes of the Renin-Angiotensin-Aldosterone system <sup>[33]</sup>
Genes of the extracellular matrix proteins <sup>[33]</sup>

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 (ΔT) 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<sup>[42-44]</sup>. 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<sup>[5]</sup>. 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<sup>[42-44]</sup>. 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<sup>[45]</sup>. The two indexes were highly correlated and the predictive values of these two PWVs were comparable<sup>[46]</sup>. 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<sup>[47,48]</sup>. 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<sup>[49]</sup>. 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<sup>[50]</sup>. 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<sup>[51]</sup>. 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<sup>[52]</sup>.

The stiffness parameter  $\beta$  is another measure of arterial stiffness. The equation for stiffness parameter  $\beta$  is  $\ln(P_s/P_d) \times D/\Delta D$ , where  $P_s$  is the systolic blood pressure,  $P_d$  is the diastolic blood pressure,  $D$  is the diameter of the artery, and  $\Delta D$  is the change in arterial diameter between  $P_s$  and  $P_d$ <sup>[53]</sup>. The stiffness parameter  $\beta$  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<sup>[53]</sup>. Therefore, the cardio-ankle vascular index, CAVI, was developed to incorporate the stiffness parameter  $\beta$ <sup>[54]</sup>. The equation for CAVI is  $a [(2\rho/\Delta P) \times \ln(P_s/P_d) \times PWV^2] + b$ , where  $\rho$  is the blood viscosity,  $\Delta P$  is  $P_s - P_d$ , 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<sup>[55]</sup>. Theoretically, the CAVI is essentially intrinsic to the stiffness parameter  $\beta$  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<sup>[56]</sup>. In addition, weight reduction was found in association with decreased CAVI values in a cohort of 47 obese individuals in Japan<sup>[57]</sup>. 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<sup>[58]</sup>. Almost 60% of the benefits are contributed by the reduction of body weight, blood pressure and serum lipids<sup>[59]</sup>, and the other 40% may be explained by the improvement of vascular hemodynamics including endothelial function, arterial compliance and remodeling<sup>[60]</sup>. Whether mode and dose of exercise affecting arterial stiffness had been recently reviewed in a meta-analysis<sup>[61]</sup>. 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 to -0.35, and AIx (WMD: -2.63%; 95%CI: -5.25 to -0.02). The benefits for improving arterial stiffness were greater in the peripheral index, baPWV (WMD: -1.01 m/s; 95%CI: -1.57 to -0.44) than in central index, cfPWV (WMD: -0.39 m/s; 95%CI: -0.52 to -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<sup>[61]</sup>. In individuals with stiffer arteries (PWV  $\geq$  8 m/s), aerobic exercise had a larger effect in reducing PWV. 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,  $-7.1 \pm 1.4$  mmHg vs  $1.2 \pm 2.7$  mmHg,  $P < 0.01$ ; baPWV,  $-204 \pm 64$  cm/s vs  $-43 \pm 72$  cm/s,  $P < 0.01$ ; reduced radial AIx,  $-6.4 \pm 2.8\%$  vs  $-1.0 \pm 3.9\%$ ,  $P < 0.01$ )<sup>[62]</sup>. Another observational study also showed that smoking cessation was associated with improved arterial stiffness as evaluated by CAVI values<sup>[63]</sup>. Moreover, avoidance of second-hand smoke, such as workplace smoking bans,

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

	Advantage	Disadvantage
cfPWV <sup>[42-44]</sup>	Reflects the stiffness of the descending aorta The gold standard measure for arterial stiffness	Largely affected by the change of BP Overestimated for the inaccurate measurement in the distance between the carotid and the femoral arteries
baPWV <sup>[116]</sup>	Reflects the stiffness of both the descending aorta and the leg artery High association with CV risk factors Ease of use for large-scale population studies	Largely affected by the change of BP Underestimates arterial stiffness in hypertensive patients with a history of cardiovascular events
hfPWV <sup>[117]</sup>	Strongly correlated with cfPWV Moderately correlated with baPWV	Require a high level of proficiency in order to obtain accurate results
faPWV <sup>[117]</sup>	Moderately correlated with baPWV	The predictive value to incident vascular events remains unknown
pAIx <sup>[110]</sup>	Assessed non-invasively and peripherally, <i>e.g.</i> , carotid, and radial arteries Correlated well with the central AIx	Largely affected by the change of BP Not a valid surrogate of arterial compliance in the elderly and diabetic populations
The stiffness parameter $\beta$ <sup>[53,54]</sup>	Independent of the change of BP	Assessing only a local segment of the artery Loss of the independence of BP for those with moderate to severe hypertension or hypotension
CAVI <sup>[118]</sup>	Independent of the change of BP A novel atherosclerotic index that incorporates PWV and BP measurements The 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.

has been reported to improve PWV after introducing smoke-free workplaces<sup>[64]</sup>.

**Dietary and nutrient interventions:** Several dietary modifications had been reported with beneficial effects on arterial stiffness. Among them, omega ( $\omega$ )-3 fatty acids (fish oil) supplementation was mostly studied. In most of clinical trials,  $\omega$ -3 fatty acids supplementation improved arterial stiffness, especially in the population with overweight, metabolic syndrome, diabetes or hypertension<sup>[65]</sup>. Aside from a study with acute  $\omega$ -3 fatty acids administration in healthy participants, almost all  $\omega$ -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<sup>[66]</sup>. 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<sup>[67]</sup>. Sjöberg *et al.*<sup>[68]</sup> 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.*<sup>[69]</sup> reported a significant improvement in PWV and AIx immediately after a long chain  $\omega$ -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<sup>[70]</sup>. 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<sup>[71,72]</sup>. Accordingly, the benefits from  $\omega$ -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 studied frequently. Among five soy isoflavone interventional studies, four interventional studies showed an improvement in PWV or systemic arterial compliance in subjects taking soy isoflavone relative to their placebos<sup>[73-76]</sup>, whereas one study reported no effect<sup>[77]</sup>. 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<sup>[78]</sup>, and a study showed that consumption of black tea flavonoids could reduce the digital volume pulse-stiffness index but not PWV<sup>[79]</sup>. Other dietary and nutritional interventions, nonetheless, reported no definite effect on arterial stiffness, such as garlic<sup>[80]</sup>, conjugated linoleic acid<sup>[81]</sup>, vitamins or folic acid<sup>[82-86]</sup> 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<sup>[87,88]</sup>. 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<sup>[87]</sup>.

In addition, Gates *et al.*<sup>[89]</sup> revealed that large elastic artery compliance was much improved in the older adults with systolic hypertension following only one-week of dietary sodium restriction.

**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<sup>[90,91]</sup>. Among all classes of anti-hypertensive medications, RAAS system antagonists have shown the best clinical results, probably due to their anti-fibrotic properties<sup>[91]</sup>. 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<sup>[92,93]</sup>. In patients with diabetes, glycemic control with oral anti-diabetic agents with metformin and glitazone were reported to improve arterial stiffness<sup>[94,95]</sup>. Using high dose of RAAS antagonists was extremely effective in attenuating the severity of arterial stiffness in diabetic patients with hypertension<sup>[96]</sup>. Notably, pharmacological modifications to these traditional vascular risk factors have been confirmed to improve arterial stiffness evaluated by PWV or CAVI<sup>[97]</sup>. 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<sup>[98,99]</sup>. 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<sup>[100]</sup>. The phosphate binder, sevelamer was found to improve arterial stiffening in patients with end-stage renal disease<sup>[101]</sup>. 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<sup>[102,103]</sup>. 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<sup>[104,105]</sup>.

**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<sup>[106]</sup>.

Enhanced external counterpulsation (EECP), using pneumatic 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<sup>[107]</sup>.

Since autonomic nervous system is involved in the pathogenesis of hypertension, its modification such as renal sympathetic denervation, and baroreflex activation therapy could attenuate arterial stiffness by improving arterial stiffness indices and central hemodynamics in patients with resistant hypertension<sup>[108,109]</sup>. 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.

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## 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  $\omega$ -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.

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