Large Artery Stiffness: A Companion to the 2015 AHA Science Statement on Arterial Stiffness

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Keywords

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Abstract

Large artery stiffness (LAS) has proven to be an independent risk factor for cardiovascular disease and mortality. Nevertheless, the position of current hypertension guidelines regarding the usefulness of assessing LAS differs across different continents. In general, European Guidelines recognize pulse wave velocity (PWV) as a marker of target organ damage but do not recommend its systematic use in general population. Asian guidelines consider PWV as a recommended test at diagnosis of hypertension, in contrast to North American guidelines that do not state any position about its usefulness. However, PWV predicts cardiovascular events, and several studies have shown that it improves risk classification adjusting for established risk factors especially for intermediate-risk patients. Finally, some advances have been made related to treatments affecting LAS. Dietary interventions such as sodium restriction and exercise-based interventions have a modest effect in reducing LAS. Pharmacological interventions, such as statins, or more recent advances with mineralocorticoid blocker seem to have a beneficial effect. Last, controversial effects of renal denervation on LAS have been found. Our goal here is to update the reader on LAS on these areas since the 2015 American Heart Association Scientific Statement.

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Introduction

This report is written to provide complementary material to the American Heart Association Science Statement on Arterial Stiffness published in 2015 [1]. We will provide the reader with an interval report on how various global guidelines on hypertension address the value of large artery stiffness measurements, how large artery stiffness measurements may help to improve cardiovascular (CV) outcome prediction through reclassification of risk status, and an update on clinical research investigating a range of treatments that could reduce large artery stiffness.

What Do Current Guidelines Recommend (or Not Recommend) about Using PWV?

Several guidelines about hypertension management and cardiovascular disease (CVD) prevention recognize pulse wave velocity (PWV), the gold standard for assessing large arterial stiffness, as a useful marker to improve CV risk prediction and as an indicator of target organ damage. However, recommendations and clinical application vary across different continents.

Since 2007, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) Guidelines for the Management of Hypertension have in-

Table 1. Current position of hypertension and CV disease guidelines about the clinical use of PWV

Guideline	Recommendation
2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice [3]	Arterial stiffness may serve as a useful biomarker to improve CV risk prediction for patients close to decisional thresholds, but its systematic use in the general population to improve risk assessment is not recommended
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [10]	Not mentioned
2018 ESC/ESH Guidelines for the Management of Arterial Hypertension [4]	Measurement of PWV may be considered for measuring arterial stiffness. However, routine use of PWV measurement is not practical and is not recommended for routine practice
2018 Chinese Guidelines for Prevention and Treatment of Hypertension [5]	PWV is a recommended test at diagnosis
2018 Korean Society of Hypertension Guidelines for the Management of Hypertension [6–8]	Subclinical organ damage marker can be considered as a carotid-femoral pulse wave velocity >10 m/s or a brachial-ankle pulse wave velocity >18 m/s PWV recommended test at diagnosis
2019 The Japanese Society of Hypertension Guidelines for the Management of Hypertension [9]	Indicators of organ damages, such as increased arterial stiffness (PWV >10 m/s), could also be evaluated as needed for further evaluation of risk assessment cfPWV may be useful when measured in cases at moderate or higher risk For indicators largely affected by blood pressure (e.g., PWV and pulse wave analysis), it seems essential to conduct evaluation upon stabilization of blood pressure after the start of antihypertensive treatment
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [12]	Not mentioned
2020 International Society of Hypertension Global Hypertension Practice Guidelines [13]	Although there is evidence to indicate that using PWV to assess large artery stiffening provide added value beyond traditional risk factors, its routine use is currently not recommended unless clinically indicated, such as in isolated systolic hypertension
Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children [11]	Not mentioned
PWV, pulse wave velocity; CV, cardiovascular.	

cluded carotid-femoral pulse wave velocity (cfPWV) as an indicator of subclinical organ damage [2]. The last published European Guidelines, from 2016, on Cardiovascular Disease Prevention on Clinical Practice have recognized that arterial stiffness may serve as a useful biomarker to improve CV risk prediction for patients close to decisional thresholds, but its systematic use in the general population to improve risk assessment is not recommended [3]. Two years later, the ESH/ESC Hypertension Guidelines reinforced the same message, maintaining that even though measuring PWV may be considered for assessing arterial stiffness, its systematic use in the general population is not practical and is not recommended [4].

Asian Hypertension Guidelines included recommendations about the use of PWV for assessing large arterial

stiffness. The 2018 Chinese Guidelines for Prevention and Treatment of Hypertension state that increased PWV is a strong predictor of CV events and all-cause mortality, that a cfPWV >12 m/s is an important prognostic factor for hypertensive patients, and that PWV is a recommended test at diagnosis of hypertension [5]. In the same line of thought, 2018 Korean Society Hypertension Guidelines recommend PWV as a recommended test at diagnosis and consider that a cfPWV >10 m/s or a brachial-ankle pulse wave velocity (baPWV) >18 m/s can be considered as a subclinical organ damage marker [6–8].

Moreover, the 2019 Japanese Society of Hypertension Guidelines for the Management of Hypertension states that PWV >10 m/s is an indicator of organ damage and could also be evaluated as needed for further evaluation

of risk assessment [9]. It is mentioned that cfPWV may be useful when measured in cases at moderate or higher risk [9]. However, for these indicators largely affected by blood pressure (e.g., PWV and pulse wave analysis), it seems essential to conduct evaluation upon stabilization of blood pressure after the start of antihypertensive treatment [9]. In contrast, North American Guidelines, from the USA and Canada, do not include any recommendation about using or not PWV nor any other method to assess arterial stiffness [10–12].

Finally, the recently published 2020 Hypertension Guidelines from the International Society of Hypertension mention that although there is evidence to indicate using PWV to assess large artery stiffening and that it provides added value beyond traditional risk factors, its routine use is currently not recommended unless clinically indicated, such as in isolated systolic hypertension [13]. Table 1 summarizes what is recommended (or not) about using PWV.

Section Summary

European and Asian Guidelines recognize PWV as an indicator of target organ damage in hypertensive patients. Asian Guidelines suggest PWV measurement as a recommended test at the time of diagnosis of hypertension; meanwhile, European Guidelines consider its systematic use in general population as not recommended. North American Guidelines do not state a position about its usefulness.

Using Measures of Large Artery Stiffness to Reclassify Cardiovascular Risk

A large body of evidence demonstrates the prognostic value of arterial stiffness for the prediction of CV events [14–16]. cfPWV and baPWV have been reported to be independent indicators of prognosis for future target organ damage in the meta-analyses based on individual participant data summarized from published data [15, 16]. Both cfPWV and baPWV have been shown to improve the evaluation results of existing risk prediction models, with the improvement of the prognostic ability larger when baPWV was used in the low-risk group [15]. cfPWV may be useful when considered in cases at moderate or higher CVD risk [16].

In 2014, Ben-Shlomo et al. [16] published a participant-level meta-analysis of prospective studies whose

aim was to determine whether cfPWV improves prediction of CVD events beyond conventional risk factors. Of the 17,635 participants included, 1,785 (10%) had a CV event. After adjusting for conventional risk factors, the hazard ratio (95% confidence interval [CI]) per standard deviation (SD) change in cfPWV was 1.23 (1.11, 1.35, $p < 0.001$) for coronary heart disease, 1.28 (1.16, 1.42, $p < 0.001$) for stroke, and 1.30 (1.18, 1.43, $p < 0.001$) for CV events. In this study, addition of cfPWV into risk prediction models also increased the number of participants correctly classified, particularly among younger individuals at intermediate risk, and improved the overall 10-year classification by 13% [16].

In 2017, Ohkuma et al. [15] conducted an individual participant data meta-analysis with data of 14,673 Japanese participants without a history of CVD to examine the association of the baPWV with the risk of development of CVD. During the 6.4-year follow-up, 687 participants died and 735 developed CV events. A higher baPWV was significantly associated with a higher risk of CVD, even after adjustments for conventional risk factors (p for trend < 0.001). Every 1-SD increase of the baPWV was associated with a 1.19-fold (1.10–1.29; $p < 0.001$) increase in the risk of CVD. Moreover, addition of baPWV to a model incorporating the Framingham Risk Score significantly increased the C statistics from 0.8026 to 0.8131 ($p < 0.001$) and also improved the category-free net reclassification (0.247; $p < 0.001$) [15].

Based on the present evidence presented, Chirinos et al. [17] in a recent review article suggested some clinical applications of measurement of arterial stiffness in primordial and primary prevention of CVD. They suggested that large artery stiffness can be useful in ACC/AHA stage 1 hypertension (130–139/80–89 mm Hg) with a calculated 10-year CVD risk of $\sim 10\%$ without diabetes or chronic kidney disease to redefine stratification for deciding initiation of pharmacologic antihypertensive treatment. Another application might be for stage 2 isolated systolic hypertension (> 140) in very young adults with paucity of other CVD to withhold of pharmacologic antihypertensive treatment. Other clinical scenarios were also suggested [17].

Section Summary

PWV predicts CV events and improves risk classification adjusting for established risk factors; specifically, cfPWV has proven to be useful for intermediate-risk patients. To the degree that measurements of large artery stiffness predict CVD risk independently of traditional risk factors, they can be used to enhance CV risk assess-

Table 2. Recent publications of intervention studies on large artery stiffness

Author	Subjects, <i>n</i>	Intervention	Control	Duration	Method of LAS	Hypertensive (Y/N/mixed)	Difference within group [#]	Difference between groups	Independent of blood pressure?
D'Elia et al. [18] ^m	431	↓ salt	↔ or ↑ salt	1–6 weeks	cPWV*	Y*	–	–2.8% (~0.3 m/s)	Yes
Lopes et al. [19] ^m	642	AerEx +/or ResEx	No exercise	4–26 weeks	cPWV or baPWV	Mixed	–	–0.7 to –1 m/s	Yes
Park et al. [20]	20	AerEx + ResEx	No exercise	12 weeks	baPWV	N	–10 cm/s	–16 cm/s	Not clear
Otsuki et al. [21]	27	AerEx + ResEx	No exercise	6 weeks	baPWV	N	–50 cm/s	–60 cm/s	Not tested
Upala et al. [22] ^m	303	Statin	No statin	2–26 weeks	cPWV*	Mixed	–	–2.3 m/s	Not tested
Ikeda et al. [23]	89	Rosuvastatin	–	18 months	cPWV	Mixed	–0.4 m/s	–	No
D'Elia et al. [24] ^m	573	Statin	No statin	2–144 weeks	cPWV	Mixed	7%	–	Yes
Sakima et al. [25] ^m	515	AldoAntag	Various	4–26 weeks	cPMV*	Y	–	–0.75 m/s	Not clear
Vlachopoulos et al. [26] ^m	208	Anti-TNF-α	DMARD*	6–56 weeks	cPWV*	Mixed	–0.53 m/s	–	Often
Solini et al. [27]	16	SGLT2	HCTZ	2 days	cPWV	N	–1.2 m/s	–	No (see text)
Katakami et al. [28]	154	SGLT2	No SGLT2	104 weeks	baPWV	Mixed	–53 cm/s	–105 cm/s	Yes
Berukstis et al. [29]	73	RDN	None	Up to 12 m	cPWV	Y	~1 m/s	–	Yes
Peters et al. [30]	53	RDN	Sham RDN	6 m	cPWV	Y	–0.6 m/s	–	No

cPWV, carotid-femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity; AerEx, aerobic exercise; ResEx, resistance exercise; AldoAntag, aldosterone antagonist; Anti-TNF, antitumor necrosis factor alpha; DMARD, (nonbiologic) disease-modifying antirheumatic drugs; SGLT2, sodium-glucose linked transport type 2; HCTZ, hydrochlorothiazide; RDN, renal denervation. [#] Within the intervention group. ^m Meta-analysis publication. * Most commonly.

ment. However, randomized clinical trials are needed to provide more conclusive evidence that these methods have clinical value.

Update on Treatments Affecting Large Artery Stiffness

We have divided this section into the following subsections:

- Dietary interventions
- Exercise
- Pharmacologic therapies
- Device therapies

Before beginning this section, several general comments are in order. This report is meant to be an update, so we have concentrated on publications from 2015 to the present time. Table 2 contains a more in-depth narrative listing of the interventions covered in the next sections, providing more details on study design and methodology used to assess large artery stiffness. Figure 1 presents a graphic summary of this section.

Dietary Interventions

Beginning with dietary interventions, interest persists in defining a role for sodium intake in the modulation of LAS. Abundant animal research confirms a role for sodium in regulating LAS [31]. The relationship between sodium intake and vascular outcomes in humans is not quite so clear. Recommendations are to keep oral sodium intake below 1,500 mg daily if there is a reason to lower blood pressure in a person [32]; otherwise, either a value of <2,000 mg daily [33] or a decrease in intake of 1,000 mg daily [10] is recommended for most others. There is growing concern that sodium intake needs to be considered in light of concurrent potassium intake, which seems to offset some of the deleterious in that for any level of sodium intake, increasing potassium intake seems to ameliorate the CV consequences of sodium [34]. Additionally, the relationship between mineral intake and CV outcomes appears J-shaped [34]. And finally, the relationship between low sodium intake and atherosclerotic outcomes such as heart attack and stroke and arteriosclerotic outcomes like LAS may be discordant due to different pathogenetic mechanisms [35].

Mechanisms by which higher sodium intake could increase LAS include an indirect effect through increasing blood pressure, a direct effect by altering matrix metalloproteinase activity (particularly MMP2 and MMP9), promoting collagen increase and elastin reduction through

Fig. 1. LAS is shown as the central target (blue circle) with the closely linked ABP (red circle) overlapping it, since interventions which affect LAS also influence blood pressure and vice versa. Arranged around the LAS/ABP box are various interventions that lower LAS as discussed in the text. Green check marks indicate salutary effects, the red check mark indicates an adverse effect, the red and green question marks over RDN indicate the lack of consensus so far on its effect on LAS. LAS, large artery stiffness; ABP, arterial blood pressure; RDN, renal denervation.

fibrosis, increasing angiotensin receptor expression, reducing endothelial function, and promoting oxidative stress in the vascular wall [36]. A recent meta-analysis of randomized clinical trials with cross-over design of lower versus higher sodium intake modulation in 431 patients in 11 studies from 14 cohorts [18], including diverse patient types, concluded that the lower sodium intake had a PWV that was significantly lower compared with the higher sodium intake. The difference in sodium intake was 89 mEq per day, and the difference in PWV during the lower versus the higher sodium intake was about 3%. cfPWV was the more common method used (6 of 11 studies). On the higher salt intake, the average PWV across the studies was 9.9 m/s, which was about ~0.3 m/s higher than on the comparator diet. The authors attempted to control for the decline in blood pressure that attended most of the cohorts when the sodium intake was reduced. Although they state that “meta-regression analysis did not detect any influence of BP changes on the relationship between salt restriction and PWV,” the accompanying editorial points out the difficulties disentangling the effects of BP reduction from changes in PWV, particularly when short-term (<6 weeks) studies are con-

ducted, including some with patients on high blood pressure medications and of relatively small size in these studies [36]. A greater degree of adherence to the Atlantic Diet, which emphasizes more fish/potatoes/meat-broths compared with the Mediterranean or DASH diets reportedly lowers cfPWV by about 0.2 m/s independent of changes in blood pressure [37].

Exercise

Exercise as a therapy for CV risk modulation typically falls into 2 categories. Aerobic exercise is defined as repetitive, active, physical movement of muscles which increases oxygen consumption. Resistance exercise which is defined as employing muscle contraction opposing an external resistance as occurs with lifting weights or using stretch band elastics.

This sectional update focuses on exercise-related investigations that have been published since 2015; however, it is important for the sake of balance to acknowledge at the outset that the prior literature on the effects of exercise is mixed. In studies by Seals et al. [38] in postmenopausal women, by Ferrier et al. [39] in isolated systolic hypertension, and by Stewart et al. [40] in older un-

treated adults, aerobic exercise failed to show a significant reduction in large artery stiffness.

A recent meta-analysis by Lopes et al. [19] on the effect of exercise on PWV identified 14 randomized clinical trials enrolling 642 subjects, with a study duration ranging from 4 to 26 weeks and incorporating data from aerobic and resistive exercise approaches. The exercise intervention was typically done 3 times a week. This study combined different kinds of exercise and included patients with and without treated hypertension. Herein, we have broken their findings down by type of exercise.

Aerobic Exercise

Lopes et al. [19] reported that aerobic exercise training (5 studies, 87 subjects in the intervention arm and 67 subjects in the control arm) reduced PWV (3 studies cfPWV, one each using baPWV and femoral-ankle PWV) by a weighted mean difference (WMD) of 0.7 m/s (95% CI: 0.2–1.2). Two studies included hypertensives on medication, and 3 studies were of patients prehypertensive or hypertensive but unmedicated.

Resistive Exercise

Lopes et al. [19] reported that resistive (“isometric”) exercise (2 studies, 47 subjects intervention/32 subjects control) reduced cfPWV by a WMD of 1.0 m/s (95% CI: 0.7–1.24) in treated hypertensive subjects.

Combined Exercise Approaches

Finally, they observed that a combined exercise (aerobic and resistive; 6 studies, 188 subjects intervention/183 subjects control) yielded a WMD of 0.7 m/s (95% CI: 0.1–1.4). Three of these studies used cfPWV and 3 used baPWV, and subjects were a mix of treated and untreated hypertension.

Lopes et al. [19] also incorporated blood pressure, gender, and medication use as modifying factors in their assessments and concluded that PWV (without separating the method used for PWV determination) was reduced more in those with higher systolic blood pressure (≥ 140 mm Hg), higher diastolic blood pressure (≥ 80 mm Hg), and those with higher PWV at randomization (≥ 9.3 m/s).

Park et al. [20] randomized 20 obese sedentary older men on no blood pressure medication to either a *combined* aerobic and resistance training with 3 times a week sessions for 12 weeks ($n = 10$) compared to no intervention ($n = 10$). The mean arterial pressure declined about 1 mm Hg over the 12 weeks in the intervention group and rose about 1 mm Hg in the control group. Using baPWV, they observed a small but consistent fall of about 10 cm/s

in the intervention group and about a 6 cm/s increase in the control group.

Otsuki et al. [21] also tested the effects of a combined thrice-weekly aerobic and low-intensity resistive regimen over 6 weeks compared to nonexercise in 27 older, non-obese, normotensive adults using baPWV. They observed a decline of about 60 cm/s in the intervention group ($n = 12$) compared with no change in the control group [21]. The authors suggested that some of the less-impressive results on arterial stiffness with resistive exercise in older studies were related to intensity, arguing that the low intensity used in their study complemented rather than neutralizing the aerobic component. We could not determine the degree to which the small decline (3 mm Hg) in mean arterial pressure in the intervention group influenced the change in LAS.

Exercise appears to have some salutary effects on LAS. However, our impression is that in studies of older people, with or without hypertension at the time of study enrollment, although habitual aerobic exercise seems to blunt the age-related increases in large artery stiffness [41], overall it has less benefit on LAS in older compared with younger people.

Pharmacologic Therapies

Statins

In addition to cholesterol lowering, statins appear to also have antioxidant and anti-inflammatory properties, with improvements in endothelial function, which could influence arterial stiffness [42, 43]. A meta-analysis of 6 statin studies (4 using cfPWV, one each of ultrasound or baPWV) ranging from 2 weeks in duration to 12 months, with data on 303 participants, showed a standardized mean difference of 2.3 m/s (95% CI: 1.15–3.47) in those receiving compared with those not receiving a statin therapy [22]. This meta-analysis expands the findings in a prior long-term (18 months) study of rosuvastatin in patients with atherosclerotic disease and chronic inflammatory joint diseases [23] where PWV fell by about 0.4 m/s, but was accompanied by a fall in systolic blood pressure of about 5–6 mm Hg which again raises the issue of whether the improvement of LAS was independent of changes in BP (in the statistical analysis of the study, it was not independent). The authors of the rosuvastatin study noted that people with higher PWV at enrollment and higher systolic BP at enrollment had greater reductions on rosuvastatin compared to those with lower values [23]. The updated meta-analysis of D’Elia and colleagues [24], with 11 studies and 573 participants, reached similar conclusions.

Table 3. Effect of antihypertensive drugs on arterial stiffness (adapted from Boutouyrie et al. [44] and Ong et al. [45])

Agent class	Effect(s) on arterial stiffness	Comments
ACE inhibitors	↓	Likely among the strongest reducers of arterial stiffness
Aldosterone antagonist	↓	See text for expanded commentary
Alpha-blockers	↓	
ARB	↓	Likely among the strongest reducers of arterial stiffness
Beta-blockers	↔/↓	Heterogeneous group of drugs
CCB	↔/↓	? arterial stiffness improvement offset by sympathetic activation
Diuretics	↔/↓	Long-term trials show arterial stiffness reduction

Antihypertensive Medications

As noted in the 2015 AHA Science Statement, most agents that reduce blood pressure will concomitantly reduce PWV since the mean arterial pressure is a determinant of PWV [1]. Virtually, all classes of antihypertensive medication have been subjected to trials evaluating their effects on LAS, and Table 3 summarizes their relative effectiveness on LAS. For example, angiotensin-converting enzyme inhibitors are as effective as other antihypertensive classes in reducing PWV and better than placebo [46]. The magnitude of effect on LAS does appear to differ among the various classes of antihypertensive agents, and these differences underlie the purpose of the Strategy for Preventing cardiovascular and renal Events based on ARTERial stiffness (SPARTE) [47] wherein a destiffening strategy of preference for agents which block the renin system used at maximal tolerated dosages, in addition to an emphasis on dietary and exercise encouragement, is being compared with standard European Guidelines for hypertension treatment at hypertension centers in France. The study finished in 2020, but the results, though eagerly awaited, are still unpublished as of May 2021. There is an enormous literature on this topic, and the reader is referred to these selected references to pursue this area further [48–50].

There has been little new antihypertensive drug development since the introduction of aliskiren in 2008; however, new interest in the effectiveness of aldosterone blockers on LAS has surfaced with the recent announcement of positive outcomes with the nonsteroid aldosterone antagonist finerenone, and the balance of this section will focus on the area of mineralocorticoid receptor blockade since 6 of the 11 studies reviewed in the next section were published in 2015 or later.

A recent meta-analysis of the effects of aldosterone antagonists on LAS comprising 515 patients reported a sig-

nificant reduction in PWV of 0.75 m/s that was, according to the authors, independent of the blood pressure changes using a meta-regression coefficient [25]. There were 11 studies reviewed, and all patients in these studies had hypertension along with various comorbidities including kidney diseases, diabetes, and treatment-resistant hypertension. Nine of the 11 studies used cfPWV and 2 used baPWV. Some of the studies compared aldosterone antagonism to placebo ($n = 5$), thiazide diuretic ($n = 2$), thiazide-like diuretic ($n = 1$), standard care ($n = 2$), or renal denervation (RDN) ($n = 1$). Although Sakima et al. [25] indicated independence of the changes in PWV to changes in blood pressure, our analysis of the individual articles showed that 4 studies reported dependence, 3 specifically stated independence, and in the rest, independence of the changes in PWV from blood pressure was not specifically addressed by that study's authors.

Anti-Inflammatory Agents

Inflammation plays a role in the development and progression of LAS. In reviewing 10 studies of 208 patients before and after receiving antitumor necrosis factor treatment, using cfPWV as the metric in all but 1 study (which used baPWV), Vlachopoulos et al. [26] observed a change of -0.53 m/s (95% CI: -0.83 to -0.22) in studies ranging from 6 to 56 weeks in duration. The underlying disorder most often studied was rheumatoid arthritis which is more common in women than men, and the patients involved in the studies considered in this meta-analysis were mostly or exclusively women. Infliximab was used in 7 studies, with etanercept used in 5 studies and adalimumab used in 4 studies (several reports used all 3 agents). There was little change in blood pressure in the studies covered in this meta-analysis, generally 5 mm Hg systolic or less. That said, 3 of the studies did find a significant relationship between change in blood pressure

and change in PWV, while the others either did not report on this association (2 studies) or reported no association between changes in systolic blood pressure and PWV (5 studies). None of the 10 studies excluded hypertensive patients per se, unless their level of blood pressure was extreme (e.g., typically over 180 mm Hg systolic). When antitumor necrosis factor treatment was compared with disease-modifying antirheumatic drugs (DMARDs) like methotrexate, the DMARD-only arm usually showed little or no change in PWV.

Antidiabetic Medications

Both the sodium-glucose cotransporter-2 inhibitors and the glucagon-like peptide-1 receptor agonists have data indicating that in addition to blood sugar control, their usage also has CV benefits on heart failure and death. A short-term (2-day) study in 16 type 2 diabetic patients comparing therapy with dapagliflozin versus hydrochlorothiazide (HCTZ) showed a remarkable reduction in PWV of 1.2 m/s in the dapagliflozin group and no change in PWV in the HCTZ group [27]. Although the authors corrected for mean BP change and stated that the decline in PWV was independent of the 2-mm Hg mean arterial pressure change in the dapagliflozin arm, it remains surprising to see such a sizable change in large artery stiffness in so short a period of time in the dapagliflozin group, and no change, despite an 8-mm Hg reduction in mean arterial pressure, in the HCTZ group. In a different and larger study using tofogliflozin in 80 diabetic patients compared with standard care in 74 patients, treatment for 2 years in the tofogliflozin group showed a small decrease in baPWV while conventional care had a moderate increase in baPWV over the 2 years. The improvement in mean baPWV using the change in the tofogliflozin minus the change in standard care was 105 cm/s. Linear regression using several models that controlled for a variety of risk factors, including systolic blood pressure, indicated that the changes in baPWV between the 2 groups were independent of a number of CV risk factors including systolic blood pressure [28].

Device Therapies

Blood pressure treatment with devices which denervate the kidney arteries, usually through a percutaneous access to the lumen of the renal artery, and using radio-frequency energy, ultrasound, or an ablative chemical injected through the wall of the kidney artery into the adventitial, reduces blood pressure [51]. At this time, there is growing interest in using the RDN approach to blood pressure management as it overcomes the issues of drug

nonadherence and appears to exert antihypertensive effects for up to 3 years [52]. One study showed a rapid, and sustained, drop in cfPWV of 1 m/s after RDN which persisted over a year. This fall in cfPWV preceded and appeared to be independent of changes in office blood pressure [29]. Other studies, however, have found no changes in PWV after RDN [30]. A component of LAS is associated with sympathetic activity [53], and since RDN may reduce total sympathetic activity, it may also reduce LAS by this mechanism. Although some auspicious data exist, RDN is a relatively new technology, and we anticipate more LAS studies if the therapy is approved in the USA for hypertension treatment.

Section Summary

The effects of sodium restriction and balanced diets have modest salutary effects on large artery stiffness, as do a variety of exercise-based interventions, which is often made challenging by similar *pari passu* changes in blood pressure. Antihypertensive medication effects on LAS have been studied for many years, and interest is emerging on the value of aldosterone blockade in light of positive findings from recent studies of the nonsteroidal mineralocorticoid blocker finerenone. The effect of statin medications on LAS seems beneficial, but is, again, difficult to disentangle from the accompanying blood pressure reduction, as are the effects of anti-inflammatory agents. The jury is still out on the effects of RDN on large artery stiffness. We hope that this manuscript updating recent publications from interventional trials undertaken in multiple cohorts, along with other consensus documents, will help promote consideration of incorporating LAS measurements into the important arena of hypertension and CV risk management guidelines in the future.

Conclusion

Measurements of LAS provide independent prediction of CVD events and complement blood pressure readings in this regard. At this time, incorporation of LAS measurements into CVD and hypertension guidelines is negligible, in part related to the difficulty demonstrating the value of reductions in LAS independent of reductions in blood pressure. Despite this, a growing number of clinical investigations are incorporating LAS measures as an outcome in their studies, and it remains our hope that updates such as this will continue to kindle interest in this important measurement.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

Author Contributions

Each author conceived and contributed to the manuscript design and writing. Both authors have had full access to the manuscript at all stages of development and submission.

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