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Strategies for Achieving Healthy Vascular Aging

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The population is aging rapidly worldwide, which will lead to an increased societal and economic burden of age-associated chronic disease, including cardiovascular diseases (CVD).[1, 2] CVD remain the leading cause of morbidity and mortality in developed nations, and chronological age is the primary risk factor for CVD.[3] Arterial stiffness and blood pressure (BP) both increase with advancing age[4–7] and are independent predictors of CV events and mortality.[8, 9] As such, there is strong, ongoing demand for evidence-based strategies that prevent, delay, or reverse age-associated increases in BP and arterial stiffness.[10, 11] Indeed, the need for new approaches is expected to grow as the burden of age- and accelerated aging-associated cardiovascular dysfunction and disease continues to rise. In this review, we discuss the concept of healthy vascular aging (HVA) with regard to definition and contributing mechanisms, existing and promising HVA-enhancing lifestyle- and pharmacological-based strategies, and future directions. The focus will be primarily on data from observational and intervention studies in humans.

Components of HVA and Related Implications

Arterial stiffening and increases in BP occur with advancing age,[4–7] although population-based studies indicate that this is not an inevitable consequence of aging, but rather results from an industrialized lifestyle.[12, 13] The prevalence of hypertension dramatically increases with advancing age, affecting approximately two-thirds of Americans 60 years of age and older.[3] Hypertension is also highly prevalent in populations with chronic disease, including chronic kidney disease (CKD) and type 2 diabetes.[14, 15] The most recent Joint National Commission (JNC) 8 guidelines increased the BP treatment goal for individuals greater than 60 years of age to <150/90 mmHg, with a goal of <140/90 mmHg in adults 30–59 years of age, including individuals with diabetes and non-diabetic CKD[16]. However, the recently completed multi-center randomized controlled trial (RCT), the Systolic Blood Pressure Intervention Trial (SPRINT), conducted nationwide in over 9,000 adults[17] challenged these guidelines. SPRINT was terminated early as a consequence of a 25% lower risk of the composite endpoint of CV events and death in individuals randomized to intensive BP lowering (systolic BP [SBP] <120 mmHg) compared to standard treatment (SBP <140 mm

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Hg). Notably, this finding was persistent across sub-groups including CKD and older adults (≥75 years of age).[18] Although the technique used for BP measurement in SPRINT has been discussed[19], the results of the trial have been influential, as a new report from the American College of Cardiology and American Heart Association Task Force of Clinical Practice Guidelines now defines high blood pressure as ≥130/80 mmHg for all ages.[20]

Large elastic artery stiffening (i.e., aorta and carotid arteries) also occurs with advancing age and is greater at any age in patients with chronic disease including CKD,[21] diabetes,[22] and hypertension.[23] As a result, these and other clinical disorders featuring such CV changes can be viewed as states of accelerated vascular aging. Multiple techniques exist to assess arterial stiffness, including local distensibility (e.g., ultrasound and tonometry-measured carotid artery compliance), the carotid or aortic augmentation index, aortic distensibility by magnetic resonance imaging, and pulse-wave velocity (assessed between 2 arterial segments), as reviewed elsewhere.[24–26] Of note, augmentation index is generally not considered an accurate marker of arterial stiffness as it is strongly influenced by heart rate, height, and contractility, and decreases in older age[24, 25]. As a result, augmentation index has not been included in the present assessment of the literature. Carotid-femoral pulse-wave velocity (CFPWV) is considered the gold-standard technique, measuring stiffness of the aorta,[27] and can be measured by applanation tonometry or Doppler flow recordings. Unlike arterial BP, no formal medical guidelines or targets exist for CFPWV, nor is CFPWV routinely measured clinically; however, both 12 m/sec and 10 m/sec have been suggested as cut-offs for increased risk of CV events.[27, 28]

Arterial stiffness and BP/hypertension are dynamically interconnected, with each factor influencing the other in a bidirectional manner (Figure 1). Although arterial stiffness was long considered to be a complication of hypertension, there is growing evidence that arterial stiffening can precede the increase in SBP, and that an elevation of SBP further augments arterial stiffness.[29–31]

Arterial stiffness increases in the aorta and carotid arteries with aging, with a lack of stiffening in the large peripheral muscular arteries, thus reducing peripheral impedance to the forward component of the arterial pulse-wave and increasing pulsatile energy transmission to the microcirculation.[32] This increased blood flow and pressure pulsatility can lead to damage of high flow, low impedance organs, including the kidneys and brain.[32] Indeed, increases in arterial stiffness are associated with declines in renal function[21, 33] and are considered a hallmark of end-stage renal disease.[34] CFPWV is also independently associated with cognitive decline,[35, 36] consistent with the concept of increased pulsatile energy transmission damaging the brain microcirculation and parenchymal tissues. Additionally, aortic stiffening-associated increases in pressure pulsatility and systolic load promote left ventricular remodeling featuring hypertrophy and dysfunction.[37, 38]

Recently in this journal, Niiranen et al. demonstrated in a community-dwelling cohort of middle-aged and older (MA/O) adults from the Framingham Heart Study, that HVA was independently associated with lower risk of incident CV events.[39] HVA was defined as CFPWV <7.6 m/sec (mean±2 S.D. of a reference group of individuals less than 30 years of age) in combination with absence of hypertension (using the previous guideline SBP/DBP

cutoff of 140/90 mmHg). These findings are consistent with evidence that increased CFPWV is an independent predictor of incident CV events and mortality[8, 9] and improves prediction over traditional risk factors alone, including blood pressure.[8, 40]

Building upon the concept of HVA, this review will discuss mechanisms influencing HVA, as well as preventive strategies and therapeutic approaches for preserving/attaining HVA. Of note, very few interventions have achieved HVA in individuals or groups that lack HVA status at baseline when applying the definition employed in the Framingham Heart Study.[39] As such, we will include studies that achieved significant CFPWV lowering, with or without changes in BP, even if full restoration of HVA status was not attained. Lastly, although the Framingham Heart Study definition of HVA used SBP and DBP to define BP component of this index, it should be emphasized that mean arterial pressure exerts an important physiologic influence on arterial stiffness[41], and must be considered when assessing changes in CFPWV in response to the preventive and treatment strategies discussed below.

Mechanisms Influencing HVA (Figure 2)

Modulation of BP with Aging

As the large elastic arteries become stiffer with aging, SBP increases, whereas diastolic BP decreases due to lessening of elastic recoil of the aorta;[29, 42] as a result, pulse pressure widens with advancing age.[43] Isolated systolic hypertension is the most common form of hypertension in individuals 50 years of age and older.[44] Increases in large elastic artery stiffness are a major contributor to these changes in BP with aging, ultimately promoting the development of systolic hypertension.[29–31] Age-associated endothelial dysfunction featuring decreased nitric oxide (NO) bioavailability and increased endothelin-1 production, as well as dysregulated vascular tone, further contribute to increased SBP.[45, 46] These events are mediated in part by increased oxidative stress associated with excessive superoxide production.[47] An interaction between the immune system and hypertension also may be involved, as immune activation and inflammation promoted by oxidative stress are implicated in the development of hypertension.[48] Additionally, with advancing age sympathetic nervous system activity increases, and the association between sympathetic nervous system activity and BP becomes stronger, particularly in women.[49] Furthermore, chronic activation of the renin angiotensin system promotes target organ damage, including the kidney and heart, as angiotensin II promotes both increased blood pressure as well as reactive oxygen species production.[50]

Modulation of Arterial Stiffness with Aging

Both functional and structural influences modulate arterial stiffness with aging. Functionally, arterial stiffness is modulated in part by the vasoconstrictor tone produced by the contractile state of vascular smooth muscle cells.[42] Age-associated vascular endothelial dysfunction interacts closely with arterial stiffness,[51] as endothelial NO synthase (eNOS) uncoupling can promote vascular remodeling and increased arterial stiffness via decreased NO bioavailability,[52, 53] which may be exacerbated by oxidative stress.[54, 55] Age-associated neurohumoral dysfunction, resulting from decreased sympathetic baroreflex sensitivity and increased sympathetic activation, also promotes arterial stiffness.[56] Systemic inflammation,

which also increases with aging, may contribute to arterial stiffness via immune activation and the development of hypertension.[57]

Structurally, extracellular matrix remodeling alters the composition of elastin and collagen in the large elastic arteries with advancing age. The medial layer undergoes elastin fragmentation and degradation,[43, 58] which is mediated in part by up-regulation of matrix metalloproteinases (MMPs).[59] Collagen deposition occurs, replacing the loss of elastin molecules,[43, 58] and accelerated formation of advanced glycation end products (AGEs) occurs, which promote cross-linking of structural proteins and exacerbate increases in arterial stiffness.[60] Oxidative stress and inflammation drive these structural changes via vascular damage, smooth muscle cell proliferation, collagen deposition, and arterial remodeling.[61, 62] Angiotensin II may also modulate structural contributions to arterial stiffness by stimulating collagen formation, reducing elastin synthesis, and promoting matrix remodeling, in addition to influencing NO-signaling and reactive oxygen species production.[63]

Not only do changes in the extracellular matrix contribute to arterial stiffness, but intrinsic stiffening of the vascular smooth muscle cells, as measured by atomic force microscopy, also occurs with aging as well as hypertension.[64, 65] Of note, intimal-medial thickening occurs with aging even in the absence of atherosclerotic plaques, mediated primarily by thickening of the intima,[10] and is positively correlated with CFPWV in older adults.[66, 67] Age-associated disease processes including diabetes (via impaired glucose tolerance)[68] and CKD (via vascular calcification)[69] can further exacerbate arterial stiffness.

It is difficult to separate hypertension and arterial stiffness due to their bidirectional interaction, common mechanisms, and overlapping presence in aging and age-associated disease. Although hypertension can promote aortic stiffening, large elastic artery stiffening may precede and promote an increase in SBP.[29, 38] Large elastic artery stiffness is an independent predictor of incident hypertension in multiple longitudinal cohorts.[30, 70, 71] Additionally, in rodents fed a high-fat, high sucrose-diet, increased aortic pulse-wave velocity is evident prior to an elevation in SBP.[31] Notably, there are some interventions that have reduced arterial stiffness in a manner deemed at least partially BP-independent.[72–75] Although, in general, interventions with the most profound influence on CFPWV typically also demonstrate a large SBP-lowering effect, there are examples in which arterial stiffness is reduced without lowering SBP. Of note, most of these latter examples have tended to be in populations without hypertension. Arterial stiffness and BP may be even more tightly intertwined when BP is already elevated.

Lifestyle-Based Strategies to Maintain or Restore HVA

In this section, we will focus on lifestyle-based strategies (aerobic exercise, caloric restriction-based weight loss, and changes in diet composition) with evidence from RCTs demonstrating a reduction in CFPWV, with or without changes in SBP. Using an approach employed previously[76], in Figure 3 we summarize current knowledge on the lifestyle-based strategies described below, including a semi-quantitative assessment of the weight of the available evidence for efficacy based on our review of the relevant literature.

Aerobic Exercise

The original observation associating aerobic exercise with HVA is from 1993 in rigorously screened healthy adults (primarily men) who participated in the Baltimore Longitudinal Study of Aging.[77] In this cohort, CFPWV was inversely related to maximal oxygen consumption, suggesting that aerobic exercise may attenuate the age-associated increase in arterial stiffness. Subsequently, a similar observation was made in postmenopausal women, even in the presence of normal BP.[78]

Consistent with these cross-sectional findings, intervention studies conducted in healthy MA/O adults have demonstrated a significant reduction in arterial stiffness with aerobic exercise training. This was first demonstrated as an improvement in carotid artery compliance following a 3-month walking program administered to men,[79] and later to postmenopausal women,[80] consistent with earlier evidence of reduced arterial stiffness with 4 weeks of exercise training in healthy young sedentary men.[81] Although a moderate intensity aerobic exercise intervention of similar duration was later shown to reduce CFPWV in healthy MA/O men[82] and women[83], the reductions in CFPWV were small and not clearly independent of small decreases in BP. Moreover, no improvement in CFPWV with exercise was observed in a year-long study conducted in healthy older adults[84], and similar findings were reported in a group of overweight MA/O adults.[85] Overall, the results of these trials suggest that aerobic exercise does not consistently lower SBP in healthy (non-hypertensive) MA/O adults.

The available evidence indicates a lack of efficacy of moderate intensity aerobic exercise for reducing CFPWV in MA/O adults with hypertension,[86, 87] although exercise has been reported to reduce CFPWV in young to middle-aged pre-hypertensive and hypertensive adults[88]. A recent meta-analysis of 14 aerobic exercise trials conducted in pre-hypertensive and hypertensive adults concluded that aerobic exercise does not reduce arterial stiffness, although various indices of arterial stiffness were combined in this analysis.[89]

The efficacy of an aerobic exercise intervention to reduce arterial stiffness in the setting of age-associated disease is mixed. Although reductions in CFPWV and SBP have been observed with exercise training in adults with metabolic syndrome,[90] aerobic exercise has been reported to both lower and have no effect on CFPWV and SBP in MA/O adults with type 2 diabetes.[91, 92] Similarly, aerobic exercise does not appear to reduce CFPWV or SBP in patients with moderate to severe CKD,[93, 94] although intradialytic exercise (i.e., during a dialysis session) may be efficacious in chronic dialysis patients.[95]

Overall, aerobic exercise appears to be an evidenced-based public health strategy for maintaining or restoring HVA in the setting of healthy (non-hypertensive) aging and in some diseases associated with accelerated vascular aging, although there are some inconsistencies across studies. The improvements in CFPWV appear at times to be independent of any change in BP, particularly in healthy MA/O adults who are free from hypertension. Of note, in contrast to aerobic exercise, resistance exercise training does not appear to reduce arterial stiffness,[96] and intensive resistance exercise training performed without complementary aerobic exercise activities may actually increase CFPWV in young healthy individuals,[97] consistent with earlier cross-sectional observations.[98] Of note to public health translation,

however, are data indicating limited adherence to aerobic exercise in long-term trials[99] and in accordance with federal activity guidelines.[100]

Weight Loss and Total Energy Intake

Short-term (i.e., 3 months or less) caloric restriction-based weight loss administered in MA/O healthy overweight and obese adults significantly reduces CFPWV.[101–103] Similar improvements are observed with one year of caloric-restriction based weight loss.[104] The SBP-lowering effect in these trials was also notable (between 6–15 mm Hg in individuals free from hypertension at baseline). Caloric restriction-based weight loss is also efficacious for reducing CFPWV when administered in conjunction with other lifestyle interventions. Weight loss from an energy restricted diet plus exercise reduces CFPWV and slightly decreases SBP in young overweight and obese adults.[105] In overweight and obese adults with moderately elevated SBP, caloric restriction-based weight loss in conjunction with the Dietary Approaches to Stop Hypertension (DASH) diet reduces both CFPWV and SBP.[106] Of note, these improvements may have been mediated, at least in part, by the 30% reduction in sodium intake associated with the diet rather than by weight loss alone. The combination of reduction in total energy intake, exercise, and sodium restriction also has a significant CFPWV- and SBP-lowering effect in young to middle-aged, normotensive, overweight and obese adults.[105, 107] Similarly, in adults with type 2 diabetes, the combination of weight loss via energy restriction, exercise, and the weight loss medication Orlistat promotes a profound lowering of CFPWV.[108]

In contrast to a shorter-term caloric restriction-based weight loss intervention, lifelong caloric restriction is challenging in humans due to adherence and has risk of negative side effects (such as loss of bone density and lean muscle mass observed in the recent 2 year Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy [CALERIE] trial of 25% caloric restriction in non-obese, healthy, younger adults).[109] Data in rodents support that lifelong caloric restriction (40% reduction) reduces aortic PWV and SBP.[110] Additionally, in a case-control study in MA/O humans, those self-practicing caloric restriction (n=18) for an average of 6 years had substantially lower SBP than age-matched healthy controls consuming a typical American diet, [111] and preliminary data indicate lower CFPWV as well in those practicing dietary restriction (Luigi Fontana, personal communication, 2017).

In summary, caloric restriction-based weight loss interventions have a consistent effect of reducing CFPWV as well as SBP and should be considered an important lifestyle-based strategy to restore or maintain HVA in overweight and obese adults. However, adherence to caloric restriction-based weight loss interventions in longer-term trials[112] as well as maintenance of weight loss[113] are large challenges, perhaps limiting public health translation. Improvements in HVA status may be mediated in part through modification of dietary components such as dietary sodium, which will be discussed more the subsequent section, or via administration through a combination lifestyle program, such as with exercise. Further evidence is needed regarding the efficacy of this strategy in diseases of accelerated CV aging such as CKD.

Dietary Components and Dietary Patterns

Dietary Sodium Restriction—The first observation linking dietary sodium intake to arterial stiffness is a case-control study from 1986, which compared CFPWV in normotensive adults who voluntarily followed a low sodium diet (mean intake 44 mmol/d) for an average of two years to controls with the same mean arterial pressure. CFPWV was substantially lower in MA/O adults who practiced dietary sodium restriction.[114] Subsequently, five trials of dietary sodium restriction have been conducted with CFPWV as an endpoint in MA/O, healthy adults of varying SBP (normotensive to hypertensive).[87, 115–118] CFPWV was significantly reduced in four of these trials,[87, 116–118] and SBP was lowered in all five. Of note, in two of these trials, individuals lacking HVA by the Framingham definition at baseline were restored to HVA-status by dietary sodium restriction (Figure 4).[87, 118] The efficacy of this intervention for restoring HVA is further supported by evidence that dietary sodium restriction rapidly improves carotid artery compliance, another index of arterial stiffness, in MA/O adults with moderately elevated SBP.[119]

Trials of dietary sodium restriction in populations of accelerated-aging diseases are lacking. One crossover trial of dietary sodium restriction has been conducted in hypertensive patients with stage 3–4 CKD, which demonstrated a non-significant reduction of CFPWV with a strong SBP-lowering effect.[120] It also merits mention that sodium intake interacts closely with dietary potassium intake to influence CV risk.[121] Evidence regarding the effect of potassium supplementation on CFPWV in healthy adults is mixed,[72, 122] and the interactions of dietary sodium and potassium intake on CFPWV warrant additional research. Overall, dietary sodium restriction has a consistent SBP-lowering effect and significantly reduces CFPWV in healthy MA/O adults. Thus, dietary sodium restriction represents an important public health strategy to maintain or restore HVA, although further research is needed in populations with clinical disorders. Despite challenges in adhering to a low sodium diet, policy changes implemented at a national level in Finland support that population-level reductions in dietary sodium intake are possible.[123]

Flavonoids—Flavonoids are low molecular weight compounds composed of a three-ring structure with various substitutions and are found in abundance in citrus fruits, seeds, olive oil, tea, and red wine.[124] Isoflavones are one class of flavonoids, found most often in legumes, including soybeans.[125] Administration of isoflavones or an isoflavone metabolite reduces CFPWV in healthy MA/O men and postmenopausal women, with or without altering SBP.[74, 126] Flavanones, flavanols, and anthocyanins are other classes of flavonoids[124] with evidence of reducing CFPWV.[73, 127–129] Grapefruit juice with high flavanones reduces CFPWV without lowering SBP in postmenopausal women with a large abdominal circumference.[73] Similarly, cocoa flavanols reduce CFPWV in healthy MA/O men,[127] as well as young healthy adults,[128] and postmenopausal women with type 2 diabetes,[129] along with possible reductions in SBP[127, 128]. Finally, cranberry juice with anthocyanins and polyphenols reduces CFPWV without changing SBP in MA/O adults with coronary artery disease.[75] Thus, there is evidence that flavonoids may reduce CFPWV, with or without changes in SBP. Notably, adverse reactions are rare and flavonoids appear to have an exceptional safety record.[124]

Dietary Patterns—Specific patterns of dietary intake may modulate HVA. In a longitudinal cohort followed for 27 years, vegetable intake in childhood, as well as persistently high consumption of fruits and vegetable intake across the study period, were independently associated with lower CFPWV in adulthood.[130] However, specific evidence on the effect of other dietary patterns such as the Mediterranean or vegetarian diet on CFPWV is currently lacking, although alternate measurements of arterial stiffness suggest that such patterns may lead to improvements.[76] In trials implementing dietary patterns including DASH, the Mediterranean diet, and high fruit and vegetable intake, BP is also significantly reduced.[131] This topic clearly represents an important and presently understudied area of future research.

Pharmacological-Based Strategies to Maintain or Restore HVA

Numerous pharmacological agents, both those routinely prescribed as well as novel agents, represent potential strategies for maintaining or restoring HVA. Agents that will be discussed in the upcoming sections include antihypertensive agents, statins, mammalian target of rapamycin (mTOR) inhibitors, AMP-activated protein kinase (AMPK) activators, sirtuin activators, anti-cytokine therapies, peroxisome proliferator-activated receptor-γ (PPAR-γ) activators, and antifibrotic agents. In Figure 5, we summarize current knowledge on the pharmacological strategies described below, including a semi-quantitative assessment of the weight of the available evidence for efficacy based on our review of the relevant literature.

Antihypertensive Agents and BP Lowering

Trials evaluating the effect of antihypertensive agents on CFPWV have primarily been conducted in individuals with hypertension, although additional evidence is provided from a few studies conducted in healthy volunteers.[132] Overall, most antihypertensive agents, including vasodilators[133], β-blockers[134, 135], calcium channel blockers,[136, 137], diuretics,[138] and angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)[138–141], appear to have some effect on CFPWV, with the best long-term evidence existing for ACEi/ARB agents. Of note, β-blockers may be less useful, as the slowing of HR can increase pulse pressure and central pressure augmentation.[142] Spironolactone also significantly lowers CFPWV in patients with stage 2–3 CKD already on ACEi/ARB with good BP control.[143]

It may be the degree of SBP-lowering induced that is more important than the medication class regarding the effect on CFPWV. In SPRINT,[17] CFPWV was measured in a sub-group of participants in an ancillary study, including a large number of patients with CKD and adults ≥75 years of age. The data are pending, but will provide important evidence regarding the influence of longer-term BP control (regardless of medication class) on arterial stiffness. A small study conducted in non-diabetic, hypertensive older adults suggests that intensive BP control does more effectively reduce CFPWV than standard BP management.[144] However, despite well-known benefits of antihypertensive therapies, adherence is often suboptimal, particularly among older adults with multiple co-morbid conditions, and both

drug-drug and drug-disease interactions increase the risk of adverse events with advancing age.[145]

Statins

Numerous trials have assessed the effect of statins (HMG-CoA reductase inhibitors) in CFPWV in MA/O adults with hypercholesterolemia, isolated systolic hypertension, or who are overweight/obese.[146–152] With the exception of one trial,[151] these studies have consistently reported significant reductions in CFPWV, generally without changing SBP.[146, 148–150] The combination of a statin and an ARB also lowers CFPWV in healthy middle-aged men.[153] Overall, statins appear quite effective at lowering CFPWV without changing SBP in MA/O adults. Statins have a well-established safety profile, although similar to antihypertensive agents, adherence can be sub-optimal, particularly with advancing age.[145] As both antihypertensive agents and statins are commonly prescribed medications with advancing age, they should be considered effective strategies to maintain or restore HVA. This conclusion also emphasizes the importance of considering these effects when studying the efficacy of other interventions in populations taking these agents at baseline.

mTOR Inhibitors, AMPK Activators, and Sirtuin Activators

With advancing age, nutrient sensing pathways including mTOR, AMPK, and sirtuins become dysregulated.[154] These pathways are among those modulated by chronic caloric restriction and, therefore, pharmacological manipulation might produce similar CV effects.[76, 155] As such, interventions targeting these pathways may help maintain or restore HVA.

In a clinical trial that converted kidney transplant recipients from immunosuppression with cyclosporine A to the mTOR inhibitor sirolimus (both in addition to mycophenolate mofetil), conversion significantly reduced CFPWV, suggesting that mTOR inhibition reduces arterial stiffness.[156] BP was also reduced, but may have been mediated by improved renal function and medication adjustments. The reduction in arterial stiffness is consistent with evidence that mTOR inhibition with rapamycin reduces aortic PWV in old mice (although without changing BP).[157] However, rapamycin has notable side effects, including the potential for metabolic dysregulation, which may limit its translation as an anti-aging therapy.[158] Consequently, safer analogs of rapamycin (rapalogs) are being developed as alternate anti-aging therapies.[159]

The AMPK activator metformin is another potential novel therapy to maintain or restore HVA. As proof of concept, metformin reduces CFPWV and BP in young women with polycystic ovary syndrome and is also well tolerated,[160] thus may also reduce arterial stiffness in other states of impaired AMPK activation, including aging. Finally, sirtuin activators, including resveratrol and NAD^+ precursors such as nicotinamide mononucleotide and nicotinamide riboside, are other potential strategies to reduce age-associated arterial stiffness. Resveratrol is a polyphenol found in red wine, grapes and other berries, and activates SIRT1.[155] In non-human primates, resveratrol ameliorates high-fat and high-sucrose diet- induced increases in aortic PWV, without changing BP.[161] Resveratrol also inhibits the mTOR/S6 kinase pathway.[162] Of note, resveratrol may have off-target effects when administered in combination with other healthy lifestyle practices.[155] Another

potential strategy to augment the age-associated decline in SIRT1 activity is to increase bioavailability of the co-substrate NAD^{+}.[163] For example, supplementation with nicotinamide mononucleotide reduces aPWV without changing BP in old mice,[164] and supplementation with nicotinamide riboside reduces BP and CFPWV in MA/O adults, particularly those with pre-hypertensive levels of SBP (Martens et al., in revision). However, additional research regarding the efficacy of NAD+ boosting compounds for reducing arterial stiffness in humans is needed, including data on clinical disorders of accelerating CV aging.

Anti-Cytokine Therapies

Anti-cytokine therapies are a potential novel therapeutic to restore HVA. Tumor-necrosis factor-α (TNF-α) antagonism reduces CFPWV without changing BP in chronic inflammatory diseases associated with increased aortic stiffness such as rheumatoid arthritis,[165–167] but the potential side effects of anti-cytokine therapies may limit use in healthy aging populations. Of note, in the very recently completed Canakimumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), which enrolled over 10,000 patients with stable coronary artery disease and elevated C-reactive protein levels, the interleukin-1β inhibitor canakinumab significantly reduced risk of major CV events by 15%.[168] These results provide initial support for the efficacy of anti-cytokine therapies for treating (and potentially preventing) CV diseases. However, the higher incidence of fatal infection observed with canakinumab may limit translation to a healthy again population.

PPAR- γ Activation

PPAR-γ is a regulator of fatty acid storage and glucose metabolism, and is activated by the thiazolidinedione pioglitazone. Short-term treatment with pioglitazone reduces brachial-ankle PWV in patients with type 2 diabetes[169] and carotid-radial PWV in obese men with impaired glucose tolerance,[170] without changing BP. However, the effects of these compounds on CFPWV and in the settings of age- and disease-associated arterial stiffening are currently unknown, and potential side effects of weight gain, edema, shortness of breath, and bone fracture need to be considered.[171]

Antifibrotic Agents

Pirfenidone is an antifibrotic agent that inhibits transforming growth factor-β, TNF-α, and other growth factors, and interferes with matrix formation.[172] It is prescribed clinically to treat idiopathic pulmonary fibrosis, and is generally safe with an acceptable side effect profile.[173] In a rodent model of diabetes, pirfenidone reverses cardiac fibrosis, attenuates cardiac stiffness, and also reduces renal fibrosis (without changing BP), and thus may hold promise in attenuating age-associated aortic stiffening.[174]

Overall, it is likely that novel pharmacological agents will have a future role in the treatment of diseases of accelerated vascular aging. Their use in the setting of healthy aging, to maintain or restore HVA, will require a more discerning consideration weighing potential side effects against potential benefits.

Mechanisms of Action

As discussed previously, arterial stiffness and elevated blood pressure share common mechanisms and bidirectional interactions. In general, shorter duration studies are more likely to modulate functional components of arterial stiffness (vascular smooth muscle tone) and to lower blood pressure than to change arterial structure (e.g., collagen or elastin composition), because the latter changes may require a longer-term treatment period (e.g., years) to induce.[79] Structural changes may be even more difficult to reverse in disease states such as CKD, which is additionally characterized by medial calcification.[175]

Lifestyle-Based Strategies

We will focus this section on mechanisms by which lifestyle-based strategies may modulate arterial stiffness rather than blood pressure, and the reader is referred elsewhere for a discussion of the latter.[176, 177] Lifestyle-based strategies to maintain or restore HVA appear more likely to influence functional components of arterial stiffness, although it is challenging to discern any structural changes that may occur if such interventions were maintained for a longer duration than typically evaluated in a RCT.

Aerobic exercise likely influences functional components of arterial stiffness, such as increased NO production,[85] although long-term aerobic exercise may also influence arterial wall structure, including AGE cross-linking of proteins.[178, 179] Indeed, results from preclinical work in mice supports the possibility that aerobic exercise may induce structural changes in the large elastic arteries of older animals, including reductions in collagen I and III, transforming growth factor-β1, and reduced smooth muscle α-actin[180, 181].

Collectively, regression analyses in trials of caloric-restriction based weight loss suggest that reductions in arterial stiffness are independent of BP changes. Improvements in stiffness in these studies over a relatively short time period (e.g., 12 weeks) suggests that regulation of smooth muscle tone likely plays a larger role than structural changes. Functional influences on arterial stiffness, including NO production, may be mediated in part by reductions in circulating insulin or changes in other hormones, such as leptin.[182]

Reductions in arterial stiffness with caloric-restriction based weight loss may also be influenced by changes in diet composition, including dietary sodium restriction. Dietary sodium restriction rapidly improves carotid artery compliance, again suggesting a larger contribution of functional versus structural changes.[119] Indeed, dietary sodium restriction both reduces vascular oxidative stress and increases NO bioavailability in humans,[183] and rising sodium concentrations increase endothelial cell stiffness measured by atomic force microscopy, while downregulating NO production.[184] Reductions in the endogenous Na+/K + ATPase inhibitor marinobufagenin may also modulate the reductions in CFPWV with dietary sodium restriction.[118]

At least with shorter-term administration, flavonoids appear to also modulate functional components of arterial stiffness. Isoflavones are vasodilatory, reducing endothelin-1, increasing NO bioavailability, and improving vascular endothelial function.[185] Flavanones may also increase NO bioavailability.[186] Finally, intake of fruits and vegetables may

modulate arterial stiffness via the effects of individual bioactive nutrients and phytochemicals, as well as via reductions in oxidative stress, inflammation, and insulin resistance.[187, 188]

Pharmacological-Based Strategies

Pharmacological-based strategies to maintain or restore HVA may modulate functional or structural components of arterial stiffness. Antihypertensive agents primarily target the functional (vasoconstrictive) component of arterial stiffness, through a direct modulation of BP.[142] However ACEi/ARB may be particularly effective at reducing arterial stiffness, and indeed are more efficacious in the long-term than other antihypertensive agents because they also have antifibrotic effects.[189] Statins also modulate smooth muscle tone via increased nitric oxide bioavailability,[190] as well as reduced sympathetic neural activity,[191] and oxidative stress.[192] Metformin promotes eNOS activation by activating AMPK in the endothelium[193], and additionally inhibits nuclear factor κ B signaling and decreases inflammation.[149] Metformin may also modify arterial stiffness as well as lower BP by promoting weight loss.[160]

Additional agents modulating functional regulation of arterial stiffness are rapamycin, which activates arterial AMPK and decreases oxidative stress,[157] and resveratrol, which increases eNOS activity, reduces superoxide generation by NAD(P)H oxidases, and reduces nuclear factor κ B -mediated inflammation and oxidative stress.[161, 194, 195] Little is known regarding underlying mechanisms by which NAD+ precursor may reduce BP and aortic stiffness, but SIRT-1 activation may be involved.[164] Anti-cytokine therapies likely lower arterial stiffness via anti-inflammatory effects,[166, 167] and PPAR-γ activation also reduces circulating markers of inflammation.[169, 170] Pharmacological agents may also target structural components of arterial stiffness, in particular antifibrotic agents.[142] Rapamycin also decreases collagen and AGEs in the aorta, suggesting reduced cross-linking of collagens by AGEs with treatment.[157]

Conclusions and Future Directions

In this review, we have discussed the concept of HVA and contributing mechanisms, while also summarizing lifestyle- and pharmacological-based strategies to maintain or restore HVA in both healthy adults and patients with accelerated CV aging-related clinical disorders. There are notable gaps in the currently available research literature on this topic and practical challenges to implementing these interventions (Figure 6). In particular, there remains an unmet need to translate effective strategies to maintain or restore HVA in the clinic and at the public health level. An example this is the ongoing effort to reduce sodium intake at a population-level through policy statements,[196] including government-industry partnerships to reduce sodium intake in several countries including Japan, Finland, and the United Kingdom.[197] At the same time, preclinical models should continue to be utilized to discern the mechanisms modulating HVA in both healthy aging and diseased populations (reverse translation).[198] Indeed, the combination of forward and reverse translational physiological approaches has been utilized effectively to better understand the mechanisms

by which prevention and treatment strategies such as dietary sodium restriction modulate BP and vascular health.[198]

Novel strategies to maintain or restore HVA continue to be developed and tested. Examples of promising lifestyle interventions include inspiratory muscle strength training (breathing against a resistive load), which lowers SBP in both normotensive adults and patients with sleep apnea,[199, 200] passive heat therapy, which lowers mean arterial BP and CFPWV even in young healthy adults[201], and novel dietary patterns that may mimic the beneficial effects of long-term caloric restriction, including different forms of intermittent fasting.[155] New pharmacological agents also continue to be developed, including anti-cytokine therapeutics and anti-senescence drugs. Additionally, a selective sodium-glucose cotransporter inhibitor (empaglifozin) was recently demonstrated to influence properties related to arterial stiffness, while lowering SBP in individuals with type 2 diabetes and established cardiovascular disease, thus may hold promise to maintain or restore HVA.[202]

Notably, in the Framingham Heart study, only about 1% of individuals over 70 years of age met the criteria for HVA.[39] This observation highlights that it is difficult to maintain HVA into older age and that trials testing the efficacy of novel strategies are particularly needed for older adults. The recent SPRINT trial results indicate that this age group can indeed be very responsive to an intervention, contrary to what may have been believed previously.[17] This was also the case for populations at high CV risk, including individuals with CKD. Thus, testing of novel interventions to restore HVA are also critically needed in diseases of accelerated CV aging, such as CKD and diabetes. An increased number of cardiovascular risk factors is also associated with greater annual increase in CFPWV, thus likely contributing to the progressive reduction in the prevalence of HVA with advancing age.[203] Ultimately, shifting the distribution to a higher number of individuals with HVA status will reduce the burden of CV events and mortality in the population.

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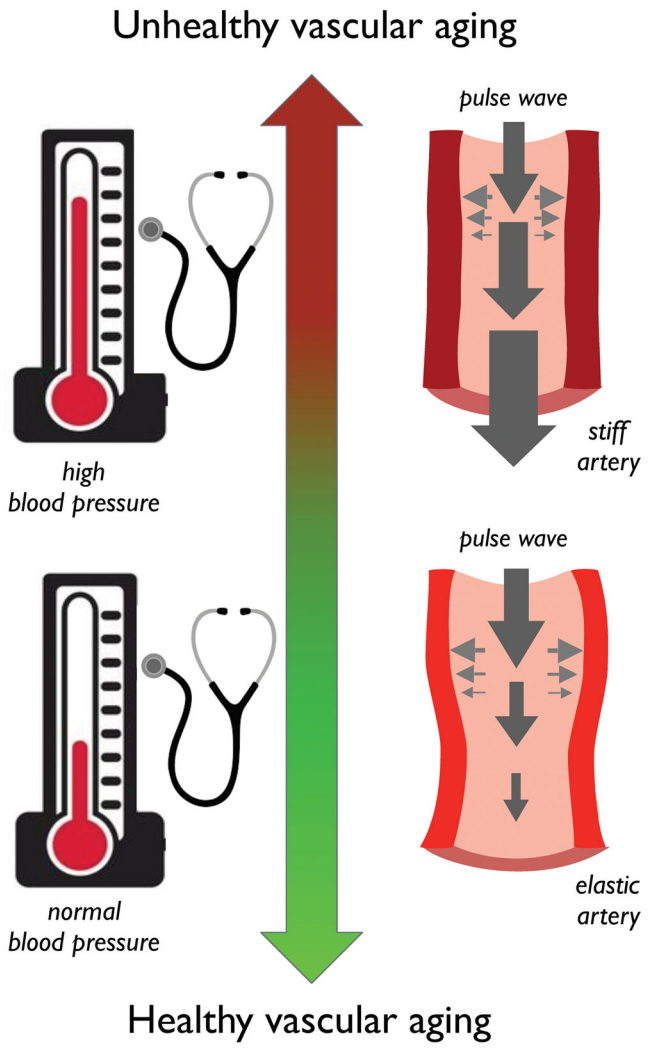

Figure 1. Components of healthy vascular aging

Arterial stiffness and blood pressure/hypertension are dynamically interconnected, with each factor influencing the other in a bidirectional manner. With a shifting profile towards healthy vascular aging, blood pressure is lowered to a non-hypertensive range, and arterial stiffness is also reduced.

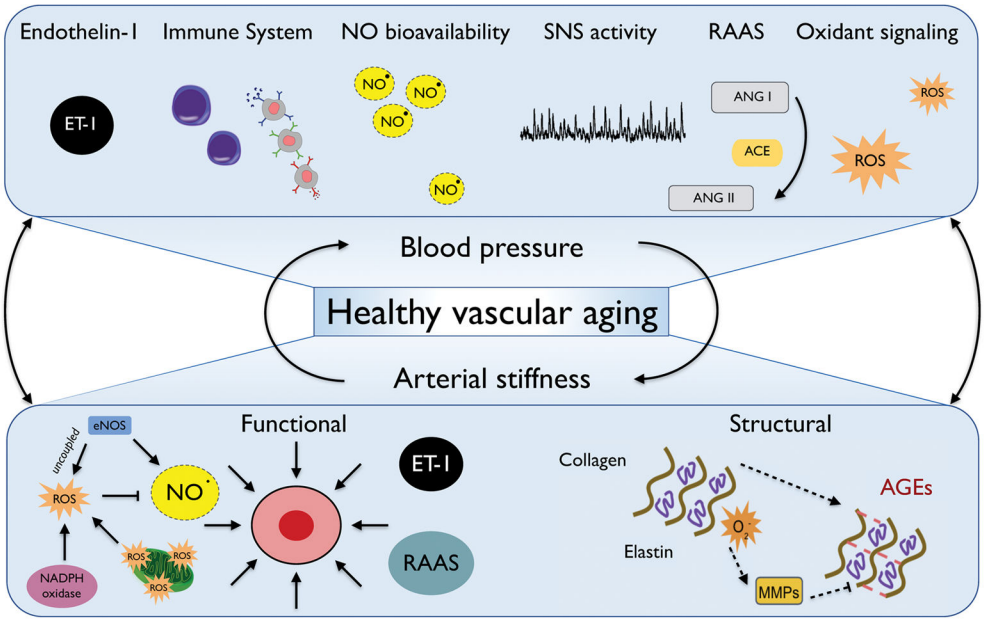

Figure 2. Mechanisms influencing healthy vascular aging

Mechanisms influencing modulation of blood pressure with aging include vasodilation and vasoconstriction (e.g., nitric oxide [NO] and endothelin-1 [ET-1] bioavailability), immune activation and inflammation, sympathetic nervous system (SNS) activity, renin-angiotensin system (RAAS) activation, and oxidant signaling. Arterial stiffness is modulated by both functional (vascular smooth muscle cell tone) and/or structural components (extracellular matrix remodeling, including elastin degradation by matrix metalloproteinases [MMPs] and the formation of advanced glycation end products [AGEs]).

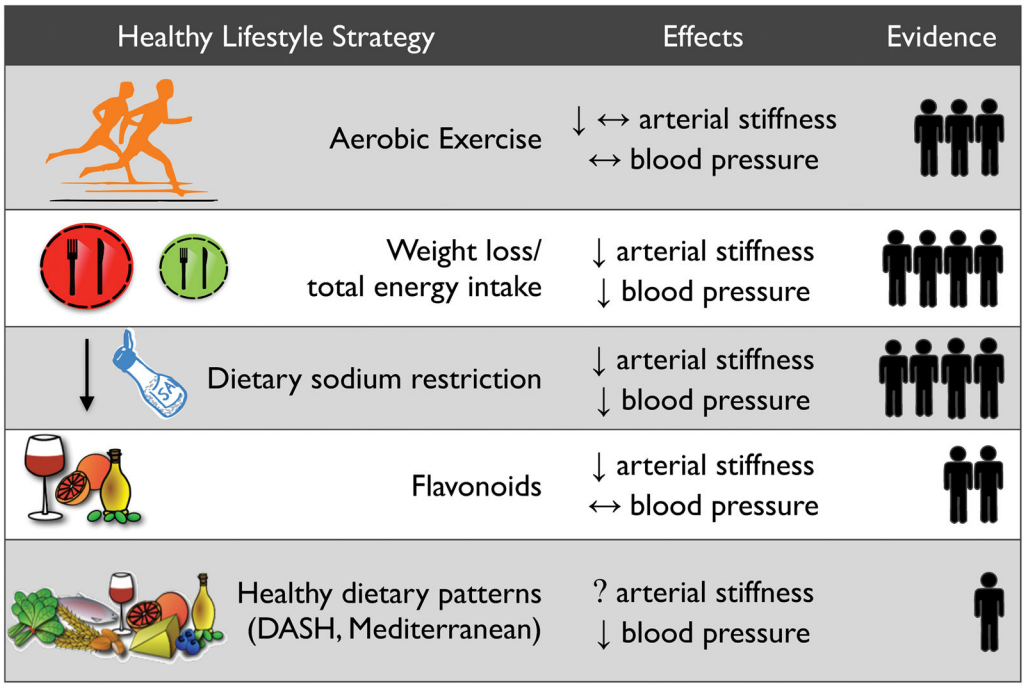

Figure 3. Summary of healthy lifestyle-based strategies to maintain or restore healthy vascular aging

Note: under "Effects", ↓ represents a reduction, ↔ represents weak or conflicting evidence, and (?) represents a lack of available data for the indicated outcome (for arterial stiffness, this refers specifically to data on carotid-femoral pulse-wave velocity). Under "Evidence", the human symbol represents clinical evidence and the number of symbols reflects the approximate semi-quantitative weight of evidence available for each strategy based on the authors' review of the literature. For details, see references/discussion in the text.

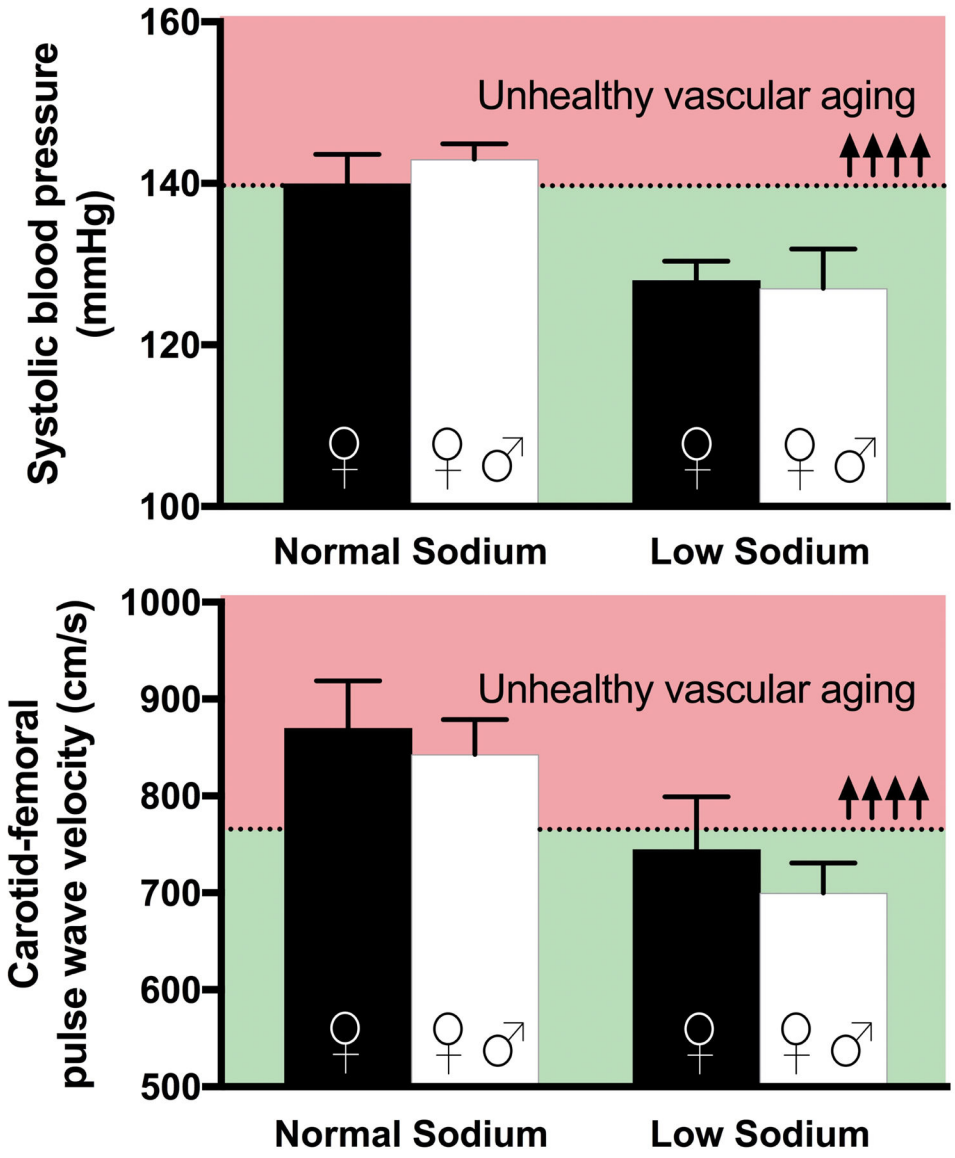

Figure 4. Dietary sodium restriction restores healthy vascular aging (HVA)

Changes in systolic blood pressure (SBP) (**top panel)** and carotid-femoral pulse-wave velocity (CFPWV) (**bottom panel**) in post-menopausal women (black bars) and post-menopausal women and middle-aged and older men (white bars) with elevated blood pressure in response to a low sodium diet (<90 mmol/d) compared to normal sodium intake (>120 mmol/d). Individuals lacking HVA by the Framingham definition at baseline were restored to healthy vascular aging status by dietary sodium restriction in both studies, as indicated by the reductions in SBP and CFPWV from the red- to the green-shaded zone (above and below the dashed line). Reproduced from[87, 183] with permission.

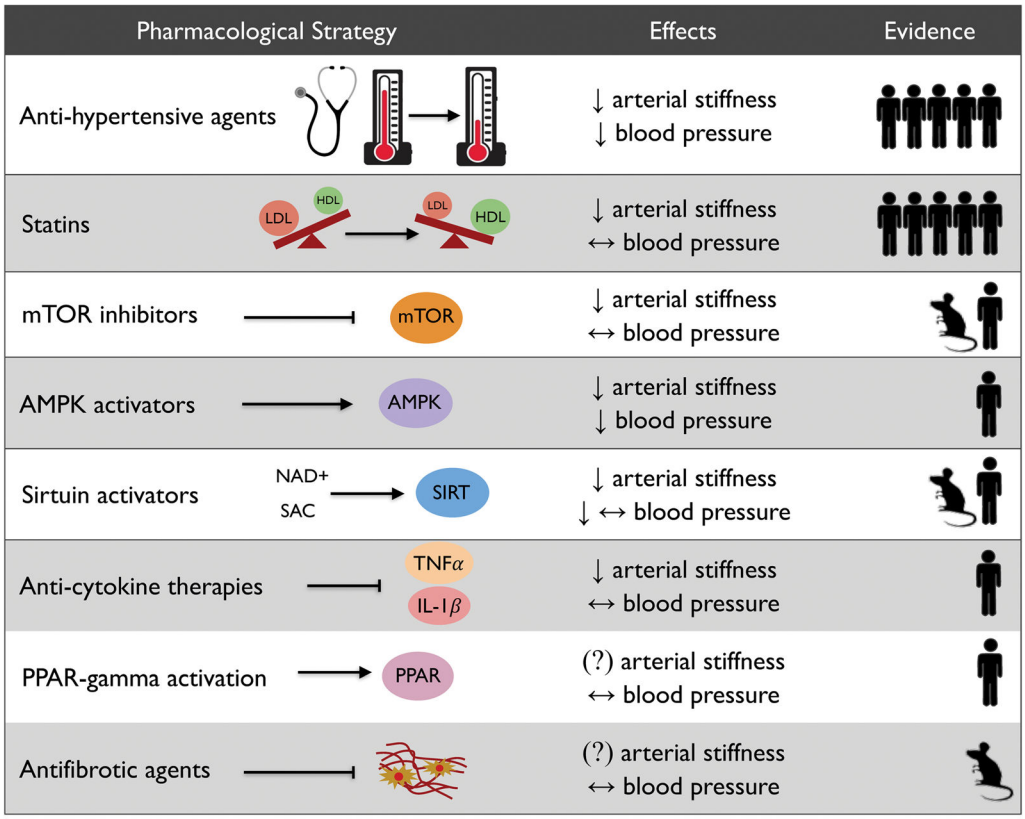

Figure 5. Summary of pharmacological-based strategies to maintain or restore healthy vascular aging

Note: under "Effects", ↓ represents a reduction, ↔ represents weak or conflicting evidence, and (?) represents a lack of available data for the indicated outcome (for arterial stiffness, this refers specifically to data on carotid-femoral pulse-wave velocity). Under "Evidence", human and mouse symbol represent clinical and preclinical evidence, respectively, and the number of symbols reflects the approximate semi-quantitative weight of evidence available for each strategy based on the authors' review of the literature. For details, see references/discussion in the text. mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; SAC, sirtuin activating compound; TNFα, tumor-necrosis factor-α; IL-1β, interleukin-1 β; PPAR-gamma, peroxisome proliferator-activated receptor-gamma

Strategy	Research Gaps/ Challenges
 Physical Activity	Efficacy in diseases/conditions associated with accelerated vascular aging Exercise-type specific effects (e.g., aerobic vs. resistance exercise) Limited adherence to exercise guidelines within general population
 Weight Loss/ Total Energy Intake	Safety and efficacy of novel caloric restriction-mimicking dietary patterns Challenges with weight maintenance after weight loss
 Diet composition	Efficacy in diseases/conditions associated with accelerated vascular aging Efficacy of specific dietary components or flavonoids vs. dietary patterns
 Pharmacological agents	Repurposing of prescription agents Efficacy of pharmacological agents vs. their safety profile and side effects Translation of novel agents identified in preclinical studies to humans

Figure 6. Current gaps in knowledge related to strategies to maintain or restore healthy vascular aging

Notable gaps in the currently available literature and challenges to implementing discussed interventions to maintain or restore healthy vascular aging (HVA).