Drug Treatment of Hypertension: Focus on Vascular Health

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Abstract

Hypertension, the most common preventable risk factor for cardiovascular disease and death, is a growing health burden. Serious cardiovascular complications result from target organ damage including cerebrovascular disease, heart failure, ischaemic heart disease and renal failure. While many systems contribute to blood pressure elevation, the vascular system is particularly important, because vascular dysfunction is a cause and consequence of hypertension. Hypertension is characterised by a vascular phenotype of endothelial dysfunction, arterial remodelling, vascular inflammation and increased stiffness. Anti-hypertensive drugs that influence vascular changes associated with high blood pressure have greater efficacy for reducing cardiovascular risk than drugs that reduce blood pressure but have little or no effect on the adverse vascular phenotype. Angiotensin converting enzyme (ACE) inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) improve endothelial function and prevent vascular remodelling. Calcium channel blockers also improve endothelial function, although to a lesser extent than ACEI and ARBs. Mineralocorticoid receptor antagonists improve endothelial function and reduce arterial stiffness and have recently become more established as anti-hypertensive drugs. Lifestyle factors are essential in preventing the adverse vascular changes associated with high blood pressure and reducing associated cardiovascular risk. Clinicians and scientists should incorporate these factors into treatment decisions for patients with high blood pressure, as well as in the development of new anti-hypertensive drugs that promote vascular health.

Key Points

- **Hypertension is characterized by a vascular phenotype of endothelial dysfunction and structural remodeling.**
- **Anti-hypertensive drugs that target the vascular changes associated with hypertension appear to be most efficacious**
- **New anti-hypertensive drugs should promote vascular health as well as reducing blood pressure**

1. Introduction

Hypertension is a common chronic condition that affects 30% of the adult population[1]. It is the largest contributor to the global burden of cardiovascular disease and represents the most important modifiable risk factor for stroke, ischaemic heart disease, heart failure, renal failure and peripheral vascular disease[2,3]. The World Health Organisation (WHO) estimates that the global prevalence of hypertension will increase by 50% from 1 billion to 1.5 billion adults by 2020[2]. Effective blood pressure control is therefore an urgent and essential public health priority to prevent the significant cardiovascular morbidity and mortality that can result from the potentially serious clinical complications and sequelae associated with hypertension[3].

Hypertension is associated with structural, mechanical and functional changes within the vasculature that contribute to a vascular phenotype characterised by increased arterial stiffness, reduced elasticity, increased vascular tone and endothelial dysfunction[2]. Molecular mechanisms contributing to these vascular changes involve reduced nitric oxide (NO) bioavailability, increased production of reaction oxygen species (ROS) (oxidative stress), increased intracellular free Ca^{2+} concentration, activation of pro-inflammatory and mitogenic signalling pathways and vascular fibrosis and calcification[4]. Although many different classes of anti-hypertensive drugs are currently available, more than 70% of patients with hypertension continue to have elevated blood pressure and sub-optimal control. The importance of hypertension as a risk factor for cardiovascular diseases and all-cause mortality was recently highlighted in the SPRINT study, which demonstrated that aggressively lowering systolic blood pressure to less than 120 mmHg is associated with a significant reduction in major cardiovascular events and death[5]. Accordingly treating to optimal blood pressure targets is essential in reducing hypertension complications and cardiovascular risk.

Hypertension-associated cardiovascular complications are prevented or ameliorated by antihypertensive drugs through blood pressure lowering and through direct effects on target

organs. It is becoming increasingly apparent that some antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors (ACEI), angiotensin II receptor blockers (ARB) and mineralocorticoid receptor blockers amongst others, may have a direct effect on cardiac, renal and vascular function. Accordingly, drugs that lower blood pressure and that are organ-protective are likely to have added benefit. In particular, there is growing interest in targeting the vascular system to prevent or repair vascular damage and to promote vascular health[6]. Here we provide a discussion from review of contemporary literature that highlights the vascular changes which characterise hypertension and discuss the importance of targeting the vasculature from a therapeutic viewpoint.

2. Vascular biology of hypertension

The vascular biology of hypertension involves a phenotype that is characterised by functional, structural and mechanical changes that include endothelial dysfunction, vascular remodelling, inflammation, calcification and increased arterial stiffness **(Figure 1)**[2,6]. These changes reduce the ability of arteries to react and adapt to tissue oxygen demands and culminate in tissue ischaemia, infarction and injury[2]. The overall vascular phenotype depends on multiple interacting factors including genetics, physiological systems, diet, smoking, diabetes, dyslipidaemia and obesity[2,7,8]. When these factors are combined with pro-hypertensive factors there is exaggerated vascular injury and arterial stiffening. Experimental and clinical studies demonstrate that the vascular phenotype of young hypertensive patients resembles that of healthy elderly patients, which has led to the concept that hypertension results in early vascular ageing[2].

Arterial stiffening results from excessive fibrosis, with associated collagen deposition, elastin fibre fragmentation and degeneration, laminar medical necrosis, calcification and collagen cross-linking by advanced glycation end-products[2]. Fibrosis initially occurs as a reversible and adaptive repair process that subsequently progresses and extends into the neighbouring

interstitial spaces with further arterial stiffening[2]. In large vessels, arterial stiffening reduces the pressure damping effects of normal vascular elasticity that serves to protect the peripheral vasculature under normal conditions. In peripheral arteries, the vessels important in blood pressure regulation, increased fibrosis and arterial stiffness contribute to impaired endothelial function, increased vasomotor tone, vascular rarefaction and reduced tissue perfusion[2,9].

The pro-hypertensive phenotype involves activation of the renin-angiotensin-aldosterone system (RAAS), vascular inflammation, oxidative stress, excessive salt consumption and genetic factors, which contribute to extracellular matrix deposition and amplification of hypertension-associated vascular injury. The excessive fibrosis extends from small arteries to replace parenchymal tissue, resulting in tissue fibrosis, scarring and target organ damage. In hypertension, these changes typically affect the heart, brain and kidney and can therefore lead to the clinical consequences and complications often seen in patients with inadequately controlled hypertension, including heart failure, cerebrovascular disease, ischaemic heart disease and renal failure[2].

Molecular and cellular mechanisms that underpin the vascular changes associated with hypertension include reduced NO production, increased ROS generation, aberrant signal transduction, pro-inflammatory and pro-fibrotic transcription factor activation, reduced collagen turnover, vascular calcification, smooth muscle cell proliferation and extracellular matrix (ECM) remodelling[2,6]. The overall result is further increased fibrosis and damage, which can lead to a feed-forward amplifying phenomenon. This is exacerbated by increased levels of of pro-hypertensive vasoactive factors, including angiotensin II (Ang II), endothelin-1 (ET-1) and aldosterone. These agents stimulate pro-fibrotic and mitogenic signalling cascades that include p38mitogen-activated protein kinases (p38MAPK), extracellular signal regulated kinases 1/2 (ERK1/2) and transforming growth factor-β (TGF-β)/SMAD, activation of pro-inflammatory transcription factors, increased galectin-3 and

dysregulation of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Signalling through these pathways contribute to extra-cellular matrix remodelling and result in further vascular fibrosis[2].

3. Endothelial dysfunction

The vascular endothelium is a monolayer of cells that forms the lining of all blood vessels and plays an essential role in vascular function through the synthesis and release of biologically active substances that act in an autocrine or paracrine fashion to influence vascular tone and function[4,6]. Examples include NO, prostacyclin (PGI_2) and endothelium derived hyperpolarising factor (EDHF)[4]. NO is the best characterised relaxing factor and is derived from transformation of L-arginine into citrulline via NO synthase (NOS) which is constitutively expressed in endothelial cells[10-13]. NO may also be produced and released under the influence of stimuli such as acetylcholine, bradykinin, substance P, serotonin, and mechanical shear stresses[4]. The endothelium also produces endogenous vasoconstrictors, such as endothelin-1 (ET-1), which is particularly potent[4,14,15]. Human ET-1 is derived from pre-pro-ET-1 which is enzymatically cleaved to form big ET-1 which is further processed to form the active peptide by endothelin-converting enzyme[16]. ET-1 acts through ET_A and ET_B receptors. ET_A receptors are found on vascular smooth muscle cells where they promote vasoconstriction, whilst ET_B receptors are found on both endothelial and smooth muscle cells[17,18]. Activation of smooth muscle ET_B receptors promotes vasoconstriction, whereas endothelial cell ET_B receptors induce vasodilatation through production of substances such as NO and PGI_2[18-20]. The magnitude of the the vasoconstrictor effect of ET-1 therefore depends upon the relative balance between vasoconstriction mediated via vascular smooth muscle cell ET_A and ET_B receptors, and vasodilatation due to upregulation of NO and PGI_2 activity via endothelial cell ET_B receptors[4,21].

Healthy endothelium has a vasodilator, anti-inflammatory and anti-thrombotic phenotype, whilst endothelial dysfunction is characterised by an endothelium that is pro-inflammatory, pro-thrombotic with impaired vasodilator responses[6]. Endothelial dysfunction is a central component of the phenotypical changes that occur in the development of hypertension and is associated with increased atherosclerosis and cardiovascular risk[1].

3.1 Measuring Endothelial Function

Endothelial function can be measured functionally using invasive and non-invasive techniques that assess vasodilator responses to pharmacological or mechanical stimuli, such as bradykinin, acetylcholine or shear stresses[1]. Vasodilator responses are mainly related to NO production, which is released by healthy and intact endothelium via eNOS[1,6]. Reduced NO bioavailability is a key characteristic of endothelial dysfunction, and results in part from increased ROS generation which inhibits eNOS activity[6]. Endothelial dysfunction can also be detected at the cellular and molecular level by assessing endothelial cell proliferation, platelet adhesion/aggregation, vascular permeability and leucocyte/endothelial cell interactions[22].

Invasive methods of assessing endothelial function, such as those performed in the coronary arteries using acetylcholine or pharmacologically-induced flow manipulation, have largely been superseded by simpler, cheaper and less invasive methods. These include brachial artery flow-mediated dilatation and venous occlusion plethysmography[1,23]. Severity of hypertension correlates with impairment of endothelial function and anti-hypertensive therapies that improve endothelial function in addition to lowering blood pressure may be associated with greater improvements in overall cardiovascular risk[1,24,25].

In vitro methods of assessing endothelial function include evaluation of endothelium-dependent relaxation or dilatation in isolated arteries from hypertensive patients using

agonists such as acetylcholine, bradykinin, substance P, ADP, serotonin and histamine. Circulating markers of endothelial function include NO metabolites, pro-inflammatory markers such as intracellular adhesion molecules, selectins, and markers of fibrinolysis, such as tissue plasminogen activator and plasminogen activator inhibitor. Endothelial microparticles have also recently emerged as a novel marker of endothelial function[22].

3.2 Endothelial Dysfunction and Hypertension

Endothelial dysfunction is recognised as a hallmark of the vascular phenotype in patients with hypertension and many studies have demonstrated impaired endothelial function in patients with hypertension[4,26-34]. Patients with hypertension have reduced forearm blood flow responses to acetylcholine and bradykinin at the level of resistance arteries, whilst alterations in flow-mediated vasodilatation have been observed in large epicardial coronary arteries of hypertensive patients[22,26,34-37].

3.3 Mechanisms of Hypertension-Associated Endothelial Dysfunction

Reduced NO bioavailability is central to the pathophysiology of endothelial dysfunction associated with hypertension, which mainly results from reduced NO production and increased inactivation due to oxidative stress and vascular inflammation[1,22,38]. Oxidative stress contributes to reductions in NO bioavailability since NO reacts with reactive oxygen species, mainly superoxide (O_2^-), to destroy NO-producing peroxynitrates[4]. In physiological settings, endogenous antioxidant systems maintain equilibration between NO and O_2^-. In hypertension, however, there is an imbalance in this equilibrium which results in increased production of O_2^- and reduced NO bioavailability[22]. This imbalance promotes vasoconstriction and contributes to local inflammatory responses, leucocyte adhesion, arterial remodelling and increased arterial stiffness. Additional factors which may contribute to reduced NO bioavailability include deficiency in L-arginine, the substrate for NO synthase

(NOS), increased concentrations of endogenous NO inhibitors, reduced cofactors for eNOS, eNOS uncoupling, decreased eNOS expression and altered signal transduction[22].

In the clinical setting, hypertension is associated with increased production of ROS and reduced antioxidants. Ascorbic acid or vitamin C is a ROS scavenger which restores NO production and can improve endothelial function in hypertension[22]. Ascorbic acid can improve vascular responses to acetylcholine in the peripheral and coronary epicardial circulations of patients with hypertension[4]. This provides further evidence to support the contribution of oxidative stress to hypertension-associated endothelial dysfunction and the potential benefits of targeting these changes with measures to restore antioxidant balance[22]. Mitochondria are an important source of ROS and mitochondrial oxidative stress is implicated in the pathogenesis of hypertension-associated target organ damage. Dysfunction of mitochondrial proteins and interactions between mitochondria and other sources of ROS, such as NADPH oxidase, are important contributory factors in the development of endothelial dysfunction, cardiac, renal and cerebral end-organ damage associated with hypertension[39,40]. The mitochondria-targeted anti-oxidant MitoQ10 has been shown to protect against the development of hypertension, endothelial dysfunction and cardiac hypertrophy in young stroke-prone spontaneously hypertensive rats[41]. Mitochondria-targeted antioxidants may therefore have a role in preventing hypertension-associated target organ changes. While oral antioxidant therapy has not yet been definitely proven to be effective at reducing the risk of cardiovascular disease this may reflect the fact that most anti-oxidant approaches to date have focused on quenching reactive oxygen species[42]. In future, strategies targeted at reducing ROS production may be more successful and ongoing research into the protective vascular effects of antioxidants should focus on this approach.

Interactions between NO systems and endogenous vasoconstrictors such as ET-1 and AngII may also contribute to the pathogenesis of endothelial dysfunction in hypertension[4].

Imbalance between NO and ET-1 systems may result in increased ET-1 activity and vasoconstriction[4,21,43]. AngII also interacts with the NO system to cause NO breakdown via AT1 receptors and subsequent activation of NAD(P)H-dependent oxidases that contribute to oxidative stress[4,44,45].

3.4 Endothelial Dysfunction and Atherosclerosis

There is a close association between endothelial dysfunction in hypertension and progression of atherosclerosis. Endothelial dysfunction contributes to platelet aggregation, vascular smooth muscle cell proliferation and monocyte adhesion which contribute to progression of atherosclerosis and associated plaque rupture and thrombosis[4,46-49]. This is a key mechanism through which endothelial dysfunction can contribute to increased risk of serious and potentially fatal cardiovascular events such as myocardial infarction and stroke. In patients with hypertension, reduced forearm responses to the endothelium-dependent vasodilator, acetylcholine, correlate with increased carotid intima-media thickness, a marker of atherosclerosis[4,50]. Furthermore, in a longitudinal study of patients with mild coronary artery disease, only those with severe endothelial dysfunction suffered cardiovascular events over approximately two years follow-up[51]. Similarly, during a follow-up period of approximately eight years there was a significant association between coronary endothelial dysfunction and risk of cardiovascular events[52]. There is also an association between endothelial dysfunction as measured by brachial artery flow-mediated dilatation and risk of cardiac events[4,53]. Collectively, these data reinforce the association between hypertension-associated endothelial dysfunction and increased risk of cardiovascular events. They support the need to treat both the vascular changes associated with hypertension, as well as achieving absolute reductions in blood pressure.

4. **Vascular remodelling**

Vascular remodelling refers to the active process of structural, mechanical and functional changes that occur within the vasculature during the initiation and progression of hypertension[2,54-56]. The remodelling of small arteries in hypertension is classically associated with increased media thickness and may be either eutrophic or hypertrophic depending on whether the media cross-sectional area is enlarged **(Figure 2).** In eutrophic remodelling, which is generally found is essential (primary) hypertension, the media:lumen ratio is increased but the media cross-sectional area is not. Hypertrophic remodelling, which is typically found with secondary forms of hypertension such as renovascular hypertension and primary aldosteronism, is characterised by an increase in both media:lumen ratio and media cross-sectional area[54].

Mechanisms contributing to eutrophic remodelling include expansion of the extracellular matrix with collagen deposition and an increased collagen:elastin ratio that results in vascular fibrosis and increased arterial stiffening. Low-grade inflammation also contributes to vascular remodelling in hypertension and is characterised by infiltration of inflammatory cells, upregulation of inflammatory mediators such as tissue necrosis factor α (TNF-α), interleukin (IL)-6, vascular cellular adhesion molecule 1 (VCAM-1), inter-cellular adhesion molecule 1 (ICAM-1), nuclear factor (NF)-κB, plasminogen activator inhibitor 1 (PAI-1), von Willebrand factor (vWF) and C-reactive protein (CRP)[54,56-61].

5. Oxidative stress

Oxidative stress contributes to many of the molecular and cellular processes that underpin the vascular changes associated with the development of hypertension. These include pro-inflammatory responses, oxidative modification of proteins that regulate vascular contraction and relaxation, fibrosis and calcification, altered calcium homeostasis and redox-sensitive pro-inflammatory and pro-fibrotic transcription factor activation. Excess production of ROS through NADPH oxidase (Nox) and/or reduced antioxidant capacity leads to alteration of

vascular function and vascular remodelling[62]. Oxidative modification of proteins, DNA and lipids accumulate in cells and cause impairment of cellular and vascular function with activation of molecular mechanisms that result in endothelial and vascular smooth muscle cell apoptosis, cell migration and extracellular matrix reorganisation[6].

A state of chronic, low-grade inflammation develops which is regulated by enzyme systems that include NADPH oxidases, uncoupled eNOS, xanthine oxidase and the mitochondrial respiratory chain[62]. NADPH oxidases (Nox) are enzymes that produce superoxide by electron transfer from NADPH to molecular oxygen and are important sources of ROS and oxidative stress in patients with hypertension[62]. Nox upregulation is associated with the development of endothelial dysfunction and appears particularly important in the pathological vascular remodelling observed in hypertension[6,63-66]. eNOS normally produces NO via oxidation of L-arginine to L-citrulline, although under pathophysiological conditions eNOS can transfer electrons from NADPH to the oxygen molecule rather than L-arginine, resulting in the formation of superoxide instead of NO. This process is termed eNOS uncoupling[62]. Xanthine oxidase is another potential source of ROS within the vasculature that may contribute to oxidative stress associated with hypertension, although its precise role remains to be fully understood[62]. The mitochondrial electron transport chain can also produce superoxide as a by-product of electron transport during oxidative phosphorylation and may also therefore contribute to oxidative stress associated with hypertension[62].

The combination of vascular remodelling, inflammation and oxidative stress contribute to the progression of atherosclerosis and atherosclerotic cardiovascular disease in patients with hypertension, increasing the risk of cerebrovascular disease and ischaemic heart disease.

6. Arterial Stiffness

Hypertension-associated arterial stiffening is contributed to by multiple factors at the systemic, vascular, cellular and molecular levels. These include haemodynamic factors, altered vascular contraction and dilatation, ECM remodelling, cytoskeletal organisation, pro-inflammatory responses and oxidative stress[2]. There is endothelial cell and vascular smooth muscle cell dysregulation, up-regulation of adaptive immune responses, vascular smooth muscle cell growth and migration within the media, changes in collagen to elastin ratio within the vessel wall and vascular calcification[2,6].

Conduit arteries normally distend to accommodate pressure from the heart during systole and facilitate tissue perfusion during diastole. This physiological feature is predominantly determined by the elasticity, distensibility and compliance of the arterial system. The structural changes in the vasculature associated with hypertension result in reduced compliance, reduced elasticity and increased arterial stiffness. This demands greater force and pressure to accommodate blood flow and results in further increases in systolic blood pressure. These changes place an increased work load on the myocardium and result in target organ damage and left ventricular hypertrophy[6]. There is therefore a vicious cycles through which hypertension causes increased arterial stiffness which in turn promotes further increases in systolic blood pressure and is an independent predictor of future cardiovascular events[2]. Reduced diastolic blood pressure may occur in the context of increased arterial stiffness, resulting in widening of the pulse pressure, an important independent predictor of future cardiovascular risk[6,67]. This may reflect that coronary blood flow occurs predominately in diastole and reductions in diastolic blood pressure may therefore reduce coronary flow reserve.

Methods to assess arterial stiffness include measuring pulse wave velocity (PWV), pulse wave analysis, augmentation index (AIx), 24-hour ambulatory blood pressure monitoring and brachial artery flow-mediated dilatation (FMD)[2,68]. Increased PWV occurs mainly in the pre-

hypertensive phase, suggesting that vascular changes may precede the onset of established hypertension[6]. Increased PWV predicts increased risk of cardiovascular morbidity and mortality in patients with hypertension, diabetes mellitus and end-stage renal[69,66]. PWV may therefore be a useful marker to identify patients in the early pre-hypertensive phase and allow lifestyle changes to be implemented, alongside blood pressure lowering medication if necessary, to prevent worsening high blood pressure and the development of hypertension.

7. The Extracellular matrix and vascular fibrosis

The extra-cellular matrix (ECM) is a fundamental component of the connective tissue surrounding cells that maintains cellular and vascular integrity, as well as playing a critical role in cell signalling and regulation of cell-cell interactions. Many structural proteins, including collagens, elastin, fibronectin and proteoglycans are found within the ECM and the relative quantities of collagen and elastin determine a vessel's biomechanical properties[2,70,71]. There is a dynamic and continuous turnover of these ECM components through tightly regulated systems including activation of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Imbalance in these processes leads to excess deposition of proteins, particularly collagen and fibronectin, which contributes to vascular fibrosis and stiffening associated with the development of hypertension **(Figure 3)**[2]. Collagens are the most abundant and stiffest proteins within the ECM and increased collagen content, combined with destruction of elastin fibres and a pro-inflammatory microenvironment, contributes to ECM remodelling, increased intima-media thickness and vascular stiffening in experimental models of hypertension[2,71].

7.1 MMPs and TIMPs

MMPs are a family of endopeptidases activated by many factors associated with hypertension, including pro-inflammatory signalling molecules such as cytokines and

interleukins, growth factors, vasoactive agents including Ang II, ET-I and aldosterone, and reactive oxygen species (ROS). The activity of MMPs is regulated at the levels of gene transcription, proenzyme activation and activity inhibition[2,72]. p38MAPK signalling is involved in regulating MMP transcription and can enhance or repress MMP expression in a cell type-dependent manner. MMPs are generally activated in the pericellular space by other MMPs or serine proteases like plasmin and chymase. Once activated, they degrade collagen and elastin, which results in a modified ECM that is associated with a pro-inflammatory microenvironment. This shifts endothelial and vascular smooth muscle cells to a secretory, migratory, proliferative and senescent phenotype that contributes to fibrosis, calcification, endothelial dysfunction and increased intima-media thickness, exacerbating vascular remodelling and arterial stiffness[2].

Both inhibitory and stimulatory modification of vascular fibrosis by MMPs have been observed in hypertension, which most likely reflects activation of different MMP isoforms and down-stream signalling pathways[2,73]. For example, MMP2 and MMP9 activation by TGF-β/SMAD signalling in hypertension is associated with collagen accumulation, whereas MMP8 and MMP13 activation is associated with collagen degradation which may contribute to plaque rupture and thrombosis[2,74,75]. Furthermore, pro-hypertensive factors such as angiotensin II, ET-1 and salt, as well as mechanical shear stresses and physical pressure, activate MMP8 and MMP9 and contribute further to hypertension associated vascular fibrosis and remodelling. TIMPs are endogenous inhibitors of MMPs and alterations in the fine balance between MMPs and TIMPs in the ECM may contribute to the hypertension-associated pro-fibrotic phenotype[2,73].

7.2 Transforming Growth Factor-β (TGF-β)/SMAD Signalling

Disruption of the transforming growth factor-β (TGF-β) pathway has been associated with vascular fibrosis. There are three isoforms of TGF-β (TGF-β1, -2 and -3), with TGF-β1 being most commonly associated with ECM remodelling and vascular fibrosis. TGF-β-1 is expressed in endothelial cells, vascular smooth muscle cells, myofibroblasts and adventitial macrophages. Signalling of TGF-β occurs mainly through cytoplasmic proteins which act as transcription factors and are known as SMADs. Vascular TGF-β1 activation and subsequent increased SMAD activity increases synthesis of ECM proteins such as fibronectin, collagen and plasminogen activator inhibitor-1 (PAI-1)[2,76,77].

TGF-β activation also reduces collagenase production and stimulates TIMP expression, thus resulting in excessive accumulation of ECM, in part, due to reduced ECM degradation[2,78]. Additional non-SMAD pathways that contribute to pro-fibrotic signalling via TGF-β include ERK, c-JNK, p38 MAPK and PI3K/Akt[2,79]. TGF-β1 activation and signalling are increased in the aortic wall during the development of hypertension[80], whilst angiotensin II[81,82], mechanical stress[77,83], ET-1[84] and ROS[85] all mediate TGF-β activation and contribute to vascular fibrosis[2]. Furthermore, MMPs, especially MMP2 and MMP9, enhance TGF-β-1 release, with the result being reduced ECM degradation, further ECM accumulation, vascular remodelling and fibrosis[2].

7.3 Plasminogen activator inhibitor-1

Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of the serine proteases, urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). It therefore inhibits fibrinolysis, and can regulate fibrin dissolution and inhibit ECM degradation by reducing plasmin generation. In pathophysiological conditions, up regulation of PAI-1 contributes to ECM protein accumulation and tissue fibrosis by reducing tissue proteolysis and collagen degradation[2]. PAI-1 activity and expression are up regulated in hypertension

and may represent further mechanisms that contribute to the development of a hypertension-associated, pro-fibrotic phenotype[2,86].

7.4 Galectin-3

Galectin-3 is an important biomarker of cardiovascular fibrosis expressed on the cell surface of cell types including fibroblasts, endothelial cells and inflammatory cells. It is mainly secreted by activated macrophages, whilst other ligands that stimulate galectin-3 secretion include collagen, elastin, fibronectin and integrin. It acts to stimulate cell proliferation, adhesion and fibrosis and is important in fibrosis and tissue remodelling[2]. In the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, plasma galectin-3 levels correlated with cardiovascular risk factors, including hypertension[87]. The mechanisms by which galectin-3 contributes to ECM remodelling and vascular fibrosis remain unclear but JAK, STAT and PKC pathway activation, as well as oxidative stress and inflammation may play a role[2,88,89].

7.5 The Renin-Angiotensin-Aldosterone System (RAAS) and Endothelin-1

The RAAS is critically involved in the functional, structural and mechanical vascular changes that occur with the development of hypertension[2,6]. Ang II, aldosterone and ET-1 activate pro-fibrotic pathways and downstream signalling from these agents results in activation of redox-sensitive transcription factors, TGF-β-1, MMPs, galectin-3 and MAP kinases that contribute to vascular stiffness and fibrosis[2,6,90-94].

7.6 Angiotensin II, Aldosterone and Endothelin-1

Angiotensin II acts through two receptors – AT1 and AT2, with AT1 activation playing a major role in the production of ECM proteins and vascular fibrosis[2,95-98]. Whilst the precise mechanisms involved in angiotensin II related vascular fibrosis remain to be fully defined, increased activity of TGF-β-1, galectin-3, p38 MAPK and MMPs/TIMPs may all contribute.

Agents which block angiotensin II activity, such as ACE inhibitors and angiotensin receptor antagonists, have been shown to confer vascular protection and improve endothelial function, which may be related to increased NO bioavailability[6]. Aldosterone is an important mediator of vascular remodelling through promotion of vascular hypertrophy, fibrosis, inflammation and oxidative stress. Chronic blockade of mineralocorticoid receptors reduces cardiovascular fibrosis in both animal models and clinical trials of hypertension[2].

Endothelin-1 is a potent endogenous vasoconstrictor that is strongly implicated in the pathogenesis of hypertension and endothelial dysfunction[99-101]. As well as evoking vasoconstriction, activation of vascular smooth muscle ET_AR and ET_BR stimulates vascular remodelling[101,102]. ET-1 has well-established hypertrophic and mitogenic properties and stimulates fibroblast-induced collagen synthesis to modulate ECM remodelling. Treatment with an endothelin antagonist normalises expression of the collagen I gene with regression of renal vascular fibrosis and improved survival[2,103].

8. Why should we target the vascular system in the treatment of hypertension?

The association between endothelial dysfunction and hypertension is well established[1]. The endothelium is an important early target of hypertension and endothelial dysfunction is a risk marker for future cardiovascular events[22]. Targeting the adverse vascular changes associated with hypertension should be an additional focus of treatment, in addition to achieving absolute reductions in blood pressure **(Figure 4)**[4,22]. This is particularly relevant since endothelial dysfunction promotes atherosclerosis and thrombosis, two of the most important mechanisms through which hypertension leads to serious cardiovascular sequelae and target organ damage[4].

Anti-hypertensive agents with the capacity to reverse endothelial dysfunction as well as reducing blood pressure may reverse or prevent the progression of atherosclerosis and

thereby reduce the risk of serious complications of hypertension, such as myocardial infarction and stroke[4]. ACE inhibitors, ARBs and calcium channel blockers all have been shown to improve endothelial function with associated improvements in markers of oxidative stress[22]. ACE inhibitors and ARBs reduce the production of ROS, while calcium channel blockers have anti-oxidant effects through improvements in the cellular redox and antioxidant state **(Table 1)**[4]. β-blockers, despite lowering blood pressure, generally do not improve endothelial function. Nebivolol and perhaps also carvedilol are the exceptions as these β-blockers may lead to some improvement in endothelial function, since nebivolol has NO donor properties and carvedilol may act as a scavenger of oxygen free radicals[4,22].

Anti-hypertensive strategies that improve endothelial function as well as lowering blood pressure may be more effective in reducing overall cardiovascular risk than approaches which lower blood pressure but have no effect on endothelial function[1,24,104]. Indeed, the Telmisartan versus Ramipril in renal ENdothelial Dysfunction (TRENDY) study showed that both telmisartan and ramipril improved endothelial function in a diabetic population with hypertension and early-stage nephropathy[105,106]. The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, which compared losartan to atenolol-based therapy, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, which compared ACE inhibitor plus amlodipine versus ACE inhibitor plus diuretic, and the Heart Outcomes Protection Evaluation (HOPE) study have all shown superior clinical outcomes for treatment strategies which include agents that improve endothelial function, such as RAAS blockers and calcium channel blockers[1,107-110]. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial showed that there were no differences between chlorthalidone, amlodipine, or lisinopril in reducing the risk of cardiac death or myocardial infarction[1,111]. However, ALLHAT included a relatively older population who had almost all

been on previous therapy and with an unreported duration of hypertension. Furthermore, blood pressure reductions were greater in the chlorthalidone group, which may account for the slightly different picture observed from this study. It may not be appropriate to generalise these findings to younger patients who have a shorter duration of hypertension and less vascular disease at baseline[1].

Overall, the evidence would suggest that clinicians should consider the vascular effects of anti-hypertensive drugs and non-pharmacological approaches to lowering blood pressure. Strategies that improve endothelial function, as well as lowering blood pressure, may achieve the best overall improvements in cardiovascular risk for patients. Furthermore, when developing new anti-hypertensive treatments clinicians and scientists should consider targeting the adverse vascular changes that contribute to the development of hypertension, to ensure we have drugs that can deliver the absolute best improvements in cardiovascular risk for our patients.

9. Anti-hypertensive drugs and vascular health

9.1 ACE Inhibitors and angiotensin II receptor blockers

ACE inhibitors improve endothelial function in animal models and clinical studies of hypertension[22]. They inhibit bradykinin breakdown and thereby increase plasma concentrations of this endothelium-dependent vasodilator[4]. This may be one of the mechanisms through which ACE inhibitors improve endothelial function in large coronary and peripheral arteries[4].

In the spontaneously hypertensive rat (SHR), ACE inhibitors improve endothelium-dependent responses to acetylcholine[112], whilst the ACE inhibitor-diuretic combination perindopril-indapamide restores NO production and decreases endothelial contractile responses[22,113,114]. ACE inhibitors may also have direct protective effects on endothelial

function, since in low-renin models of hypertension they have been shown to improve endothelial function despite no observed reduction in blood pressure[115].

In clinical studies, ACE inhibitors improve endothelial function in subcutaneous, epicardial, brachial and renal circulations, and selectively improve endothelium-dependent vasodilator responses to bradykinin[4]. In patients with essential hypertension, treatment with cizalapril for 2 years and lisinopril for 3 years improved vascular responses to acetylcholine in the subcutaneous microcirculation[4,116-118]. Furthermore, within the peripheral circulation, perindopril, ramipril, quinapril and the perindopril-indapamide combination improve flow-mediated dilatation, which most likely relates to increased NO bioavailability and prevention of angiotensin-II induced oxidative stress[4,35,37,115,119-121]. ACE inhibitors may also potentiate bradykinin activity, which stimulates release of NO, PGI_2 and EDHF from the endothelium[22].

Most studies of ACE inhibitors in hypertension demonstrate greater lowering of central aortic than brachial artery BP, suggesting a beneficial effect on arterial compliance[69,122]. This may in part relate to reduced oxidative stress and increased vasodilatation through inhibition of angiotensin II and increased smooth muscle relaxation[69,123]. In a randomized, placebo-controlled crossover study enalapril and perindopril both led to significant improvements in peripheral and central BP as well as augmentation index after 4 weeks of treatment. Furthermore, there was a greater effect on central than brachial BP, illustrating improvements in arterial stiffness[69,124]. Acute improvements in arterial stiffness, augmentation index, central and brachial BP have been observed 5 hours after administration of ramipril in patients with high cardiovascular risk[69,123]. In patients with mild essential hypertension both enalapril and indapamide reduce brachial BP, mean arterial pressure and pulse pressure, with more pronounced effects on central BP and pulse pressure with enalapril compared to indapamide. Enalapril was also associated with improvements in augmentation index,

providing further evidence to support the beneficial effects of ACE inhibitors on central BP and arterial stiffness[69,125].

ARBs are effective blood pressure lowering agents that may also have beneficial effects on endothelial function. Ang II contributes to endothelial dysfunction through upregulation of ET-1, inhibition of NOS via protein Nox[4,126,127]. The angiotensin type-1 (AT1) receptor antagonist losartan diminishes superoxide production, whilst blockade of AT1 receptors allows Ang II to bind to free AT2 receptors and subsequently stimulate AT2-receptor induced NO synthesis and release. This may be one of the mechanisms through which angiotensin II receptor blockers can restore NO bioavailability and improve endothelial function[4,45,128-130]. In patients with hypertension, losartan restores vasodilator responses to acetylcholine and may also block positive feedback effects of angiotensin II on endothelin synthesis[4,131]. Losartan also has beneficial effects on flow mediated dilatation responses similar to those observed with ramipril[4,120]. Overall, angiotensin II receptor antagonists may have beneficial effects on endothelial function in patients with hypertension as a result of increased NO release via AT_2 receptor stimulation[22] and reduced vasoconstrictor responses to ET-1[4].

While ACE inhibitors and ARBs have comparable blood pressure-dependent reductions in overall cardiovascular risk, ACE inhibitors also have blood pressure-independent effects in reducing the risk of coronary heart disease that have not been observed with ARBs[132]. Furthermore, in patients with type 2 diabetes and overt nephropathy, the ARB olmesartan was associated with an increased risk of cardiovascular mortality compared to placebo, although there was no difference in risk of major adverse cardiovascular event or all-cause mortality[133]. It is possible that the bradykinin effects of ACE inhibitors may contribute to differential effects of ACE inhibitors and ARBs on coronary artery disease. Overall, ARBs are effective blood pressure lowering agents that reduce cardiovascular risk and should be considered in patients intolerant of ACE inhibitors[132,134].

9.2 Calcium Channel Blockers

Calcium channel blockers are well-established anti-hypertensive drugs that improve endothelial function in both experimental and clinical models of hypertension[22,36,115]. This is particularly true for the dihydropyridine calcium channel antagonists, such as amlodipine, which antagonize the L-type calcium channel and have anti-oxidant effects[4,69]. The rate-limiting calcium channel antagonists such as verapamil and diltiazem may also have beneficial effects on endothelial function in patients with essential hypertension, suggesting that the benefits of calcium channel antagonists may be a class effect related to NO bioavailability[4].

In gluteal resistance arteries from patients with essential hypertension treatment with the calcium channel blocker nifedipine for 1 year improved vascular relaxation responses to acetylcholine, a finding not observed with atenolol[4,135]. Furthermore, within the coronary vasculature, nicardipine and diltiazem can reverse endothelial dysfunction in non-stenotic segments from patients with hypertension and in stenotic segments from both normotensive and hypertensive patients[4,136]. Nifedipine exhibits a blood pressure–lowering effect, reduces ET-1 induced vasoconstriction and improves endothelium-dependent vasodilation in patients with essential hypertension[137]. Nifedipine has also been shown to increase coronary vascular responses to acetylcholine compared with placebo[4]. Amlodipine has been shown to increase basal NO release, whilst lacidipine increases vasodilator responses to both acetylcholine and bradykinin within the forearm circulation of patients with hypertension[4,138].

Endothelial cells do not express voltage-gated calcium channels and the improvements in endothelial function observed with calcium channel blockers are therefore unlikely to be calcium-dependent[4,139]. Rather, calcium channel blockers appear to have anti-oxidant effects that may protect endothelial cells from oxygen free radicals, thus improving NO bioavailability and subsequently improving endothelial function[4,140,141]. Nifedipine and

lacidipine reduce markers of oxidative stress and improve NO bioavailability in patients with hypertension and it may be through this mechanism that calcium channel antagonists improve vasodilator responses and restore endothelial function in patients with hypertension[4,142].

In patients with end-stage renal disease, nitrendipine significantly reduces brachial and central BP, as well as improving PWV and augmentation index, suggesting reduced arterial stiffness[69,143]. In elderly patients with untreated essential hypertension, both felodipine and amlodipine showed a more pronounced effect on central than brachial BP as well as improvements in pulse pressure and augmentation index compared to placebo[69,124]. This may be particularly clinically relevant in the context of elderly patients who are more likely to have isolated systolic hypertension with increased pulse pressure and increased arterial stiffness. Hence, dihydropyridine calcium channel blockers may be the most appropriate anti-hypertensive drugs in elderly patients. However, while the dihydropyridine calcium channel blockers are associated with improvements in endothelial function, this is to a lesser degree than the benefits observed with ACE inhibitors for similar reductions in blood pressure. ACE inhibitors should therefore remain first-line anti-hypertensive drugs used to treat younger patients with high blood pressure[22].

9.3 Mineralocorticoid receptor antagonists

Aldosterone is a mineralocorticoid synthesised by the adrenal cortex and perhaps also in blood vessels[144,145]. It exerts blood pressure elevating effects through interactions with the kidney that influence salt and water balance and may have additional direct effects on blood vessels[56,145,146]. Mineralocorticoid receptor activation may contribute to cardiovascular dysfunction, inflammation and fibrosis[56]. Spironolactone and eplerenone are mineralocorticoid receptor antagonists that are now used frequently as anti-hypertensive agents that also improve endothelial function and reduce arterial stiffness. These benefits are at least in part independent of blood pressure reductions, and the additional protective

vascular effects of mineralocorticoid receptor antagonists may reflect blockage of aldosterone's pro-inflammatory and pro-fibrotic actions[69].

Spironolactone reduces PWV and augmentation index in patients with essential and resistant hypertension[147]. Furthermore, aldosterone impairs endothelial function in normal resistance vessels, whilst aldosterone can reverse hypertension-related endothelial dysfunction in arterioles[148]. Similar benefits have been observed with eplerenone which reduces vascular stiffness, collagen/elastin ratio, pro-inflammatory mediators and systemic inflammatory markers in patients with hypertension. Together, mineralocorticoid receptor blockade reduces collagen deposition and vascular stiffness and may also exert additional anti-inflammatory benefits beyond absolute reductions in blood pressure[52]. Mineralocorticoid receptor antagonism may therefore be an effective target to prevent the adverse phenotypical changes that occur in the development of hypertension.

9.4 β-blockers

There is relatively little evidence to suggest that β-blockers improve endothelial function and atenolol may in fact have a negative effect within peripheral subcutaneous and muscle microcirculations[4]. Atenolol treatment for 1 or 3 years did not improve endothelium-dependent vasodilator responses to acetylcholine or bradykinin[4]. Nebivolol is a selective β_1-blocker which also has vasodilator and NO donor properties, through activation of the L-Arginine—NO pathways, and may improve endothelial function in patients with hypertension through this mechanism[4,22,149,150].

In patients with isolated systolic hypertension both atenolol and nebivolol were associated with similar reductions in brachial BP and PWV, whilst pulse pressure was significantly lower in the nebivolol group, suggesting nebivolol may have greater beneficial effects on arterial stiffness[69,151]. Furthermore, in patients with untreated hypertension nebivolol has

more pronounced effects on both pulse pressure and augmentation index[69,152]. Nebivolol was also compared with metoprolol in a randomized, double-blind study involving 80 patients and whilst similar effects were seen in terms of brachial BP, mean arterial pressure, augmentation index and PWV, nebivolol was associated with significantly greater improvements in central aortic BP, pulse pressure and LV septal wall thickness. Furthermore, the changes in septal wall thickness correlated with reductions in central aortic blood pressure and pulse pressure, suggesting these changes related to improvements in blood pressure rather than a direct cardio-protective effect. Overall, the potential beneficial vascular effects of nebivolol appear most likely related to enhanced release of endothelium-derived NO with associated improvements in endothelial function and reduced arterial stiffness[69,153].

Carvedilol is another selective β_1-blocker that also has α1-adrenoceptor antagonistic properties as well as strong anti-oxidant effects and as such may improve endothelial function through this mechanism[4]. As a general class of drugs however, β-blockers are less effective in improving endothelial function than RAAS blockers and calcium channel blockers[4].

9.5 SPRINT Trial

Recent data from the SPRINT trial have suggested that aggressive lowering of blood pressure, to less than 120 mmHg systolic, may be effective at reducing the risk of major cardiovascular events and death in selected patients with hypertension[5]. The intensive treatment group in the SPRINT trial was characterised by patients who received a number of anti-hypertensive agents, including RAAS blockers and calcium channel blockers. The reductions in cardiovascular risk observed in the intensive treatment group in SPRINT may therefore be explained, at least in part, by the combined protective vascular effects of these drugs, as well as the observed reductions in blood pressure.

10. Other strategies to improve vascular health in hypertension

Lifestyle modifications including dietary improvements, reduced salt consumption, exercise, weight loss and smoking cessation all reduce cardiovascular risk and should be strongly encouraged in all patients[154,155]. Maintaining normal body weight, restricting salt intake, limiting alcohol consumption to ≤ 3 units/day for men and ≤ 2 units/day for women, engaging in regular physical exercise, consuming at least 5 portions of fruit and vegetables and reducing dietary intake of total and saturated fat are important lifestyle modifications suggested by major hypertension guidelines. Lifestyle advice should be reinforced at regular intervals as this approach can prevent age-associated increases in blood pressure and may avoid progression to anti-hypertensive drug therapy in patients with borderline high blood and complement blood pressure lowering effects of anti-hypertensive drugs in treated patients[154].

10.1 Diet

The British Hypertension Society and American Heart Association make specific recommendations for dietary interventions that can lower blood pressure [3,156,157] and likely improve vascular health. In patients with normal blood pressure or prehypertension, dietary changes can reduce blood pressure and thereby reduce the risk of hypertensive complications. When applied at a population level, this results in significant public health benefits. A 3 mmHg reduction in BP is associated with 8% reduction in stroke mortality and 5% reduction in mortality from ischaemic heart disease[157,158]. In treated hypertensive patients, dietary changes, particularly reduced salt intake, can lower BP and lead to a reduced number of medications required to achieve BP control[157].

10.2 Salt Intake

Dietary salt intake is associated with increased blood pressure[157] and reduced salt intake is an essential lifestyle measure in treating high blood pressure. Reducing dietary salt intake can

reduce systolic blood pressure by as much as 5 mmHg in patients with hypertension[157,159]. Clinical studies have shown that reduced salt consumption can also prevent hypertension, as well as lowering BP and facilitating better BP control in patients treated for hypertension[157,160-164]. These improvements may be related to improved endothelial function since the hypertensive effect of salt loading appears linked to oxidative stress and reduced NO bioavailability, which can be exacerbated by NO inhibition[1,165-167]. In patients with mild hypertension those with lower self-reported daily sodium intake had significantly higher brachial artery flow-mediated dilatation, suggesting improved endothelial function in patients with lower sodium intake[1,168].

Guidelines recommend a sodium intake of < 100 mmol/day[157,169,170], which is felt to be realistic and achievable given currently available food supplies. However, approaches to lower salt intake and achieve associated improvements in vascular function and blood pressure should be focussed at a population level. More than 75% of salt consumed comes from processed foods and food manufacturers and restaurants should aim to progressively lower the salt content of the food by 50%[157,169,171,172].

10.3 Fruit, Vegetables and Fish

Increased intake of fruit, vegetables and fish is a key lifestyle factor that can reduce blood pressure in patients with hypertension. This is best-evidenced from the DASH (Dietary Approaches to Stop Hypertension) trial where increased fruit, vegetable and fish consumption, combined with reductions in saturated fat and dairy products, significantly reduced blood pressure amongst patients with hypertension who were not previously taking medication[156,173]. Similarly, the Lyon Diet Heart Study found that specific dietary advice to increase fruit, vegetable, fish and α–linolenic acid consumption after myocardial infarction was strongly associated with reduced cardiovascular mortality. This led the study to be stopped after only 12 months due to a clear benefit which persisted after 5 years[156,174,175].

Furthermore, in a study of fruit and vegetable intake in patients with hypertension conducted over 12-weeks, each additional portion of fruit and vegetable consumed per day was associated with an approximately 6% improvement in endothelium-dependent forearm blood flow responses, measured using venous occlusion plethysmography[156]. This may be related to high polyphenol content in fruit and vegetables which can increase NO bioavailability[1,156,176,177]. There was also a trend towards reduced systolic blood pressure with increasing fruit and vegetable consumption, although the study was not powered to detect differences in this endpoint. Importantly, there was no improvement in forearm vascular responses to the endothelium-independent vasodilator sodium nitroprusside, which suggests that the beneficial effects of fruit and vegetable intake are related to protective effects on the endothelium[156]. The data from this study are in contrast to forearm plethysmography studies that assessed the effect of ascorbic acid on forearm vascular responses and suggest that a balanced, pragmatic approach that considers whole food and dietary patterns may be the best means of improving the overall vascular phenotype of patients with hypertension[156,178-180]. Increased fruit and vegetable consumption may also make patients more likely to adopt other favourable dietary modifications, such as reduced salt and fat consumption.

Overall relatively small and achievable increases in fruit and vegetable intake are associated with improvements in a vascular measure of clinical prognostic value. When extrapolated to a population-level these data suggest that clinically relevant reductions in blood pressure can be achieved through simple dietary interventions. Furthermore, while endorsing the "5-a-day" public health message for increased fruit and vegetable consumption, it also suggests that smaller increases in fruit and vegetable intake still have prognostic benefits. This is an important public health message that must be clearly conveyed to the public: small increases in fruit and vegetable intake are beneficial, since some individuals may perceive a target of 5-

a-day unattainable[156]. Increased consumption of fruit, vegetable and fish improves endothelial function and reduces blood pressure and should therefore be strongly encouraged to all in society, including patients with hypertension or borderline high blood pressure and the wider community, as part of public health campaigns[3,154,156].

10.4 Weight Loss

Weight loss reduces blood pressure and even modest reductions can prevent hypertension by approximately 20% in individuals who are pre-hypertensive and overweight[157,160]. Furthermore, approximately 5 kg weight loss, which should be achievable for most individuals, can reduce systolic blood pressure by over 4 mmHg. When applied to a population, relatively small individual changes could therefore translate into significantly reduced cardiovascular morbidity and mortality[157,181]. Overall, evidence strongly supports weight reduction in the prevention and treatment of high blood pressure and maintenance of a BMI <25 kg/m^2 appears the most effective target[157]. It is important to ensure that any reductions in weight are sustained to maintain cardiovascular benefits[157].

10.5 Alcohol Consumption

Alcohol intake and blood pressure are positively associated, particularly at greater than two units of alcohol per day, independent of potential confounders such as age, obesity and salt intake[157,182,183]. Furthermore, there is a dose-dependent relationship between percentage reduction in alcohol intake and reduced blood pressure[157,183]. Light alcohol consumption may confer some protection against ischaemic heart disease and alcohol consumption should therefore be limited to ≤ 3 units per day for men and ≤ 2 units per day for women, whilst patients with hypertension who drink excessively should be strongly encouraged to reduce their alcohol intake[3,154].

10.6 Exercise

Regular exercise can reduce blood pressure and patients should be encouraged to exercise for at least 30 minutes on most days of the week and at least 3 days of the week[3,154]. Regular exercise protects against the development of arterial stiffness and endothelial dysfunction that occur with advancing age[184] and it is likely that exercise has similar beneficial vascular effects in patients with hypertension. Aerobic exercise reduces oxidative stress and inflammation and restores NO bioavailability[184]. Interestingly, whilst aerobic exercise reduces arterial stiffness, resistance training alone may in fact increase arterial stiffness and resistance training should therefore be combined with aerobic training to ensure cardiovascular benefits are maintained[184]. The vascular benefits of exercise may be most marked with high intensity training, since moderate physical activity improves endothelial function but had no effect on arterial stiffness after 12 weeks[185]. Future research should aim to determine the dose-response effect of physical activity and improvements in vascular function. In animal studies, increased physical activity reduces carotid artery stiffness and reverses makers of oxidative stress, collagen types I and III, and the pro-fibrotic cytokine TGF-β1[184,186]. Overall, this suggests that aerobic exercise may reverse arterial stiffening by normalizing key structural factors and markers of oxidative stress within the vasculature[184].

In clinical studies, aerobic exercise improves brachial artery flow-mediated dilatation in older males and females with low oestrogen but not women treated with oestrogen supplementation[184,187,188]. This suggests that oestrogen may be permissively involved in the beneficial effects of aerobic exercise on endothelial function in women[184]. Aerobic exercise also improves forearm vascular responses to acetylcholine in older men when assessed using venous occlusion plethysmography[184,189] and the observed differences can be abolished by inhibition of eNOS, suggesting that the benefits of aerobic exercise are at least in part mediated by increased NO bioavailability[184,190].

Aerobic exercise suppresses oxidative stress within the vasculature through inhibition of pro-oxidant pathways and stimulation of antioxidant mechanisms[184]. In old previously sedentary mice, a 3-month programme of voluntary wheel running reduced aortic nitrotyrosine and NADPH oxidase expression[184,191]. In clinical studies, aerobic exercise restores SOD expression and activity in sedentary older men to levels seen in younger men[184,192]. Reduced vascular inflammation may be another mechanism through which aerobic exercise improves vascular structural and function[184]. In mouse models, 10-14 weeks of voluntary running is associated with reduced expression of NF-κB and pro-inflammatory cytokines[184,193]. Vitamin C infusion improves flow-mediated dilatation in older sedentary men and oestrogen-deficient women, reinforcing the concept that reduced oxidative stress is a key mechanism through which aerobic exercise can reduce vascular inflammation and improve endothelial function[184,187,190,194]. Aerobic exercise may also protect the vasculature from adverse effects of other cardiovascular risk factors such as elevated LDL cholesterol and impaired glycaemic control[184,195,196]. This potential benefit of aerobic exercise also appears to be mediated by reduced oxidative stress and improved NO bioavailability[184,197].

10.7 Smoking cessation

Smoking is one of the most important preventable risk factors for the development of atherosclerosis and potentially devastating cardiovascular sequelae such as myocardial infarction and stroke[198,199]. Smoking causes 6 million deaths per year and accounts for 10% of all cases of cardiovascular disease[199,200]. It contributes to the initiation and acceleration of vascular injury and atherosclerotic cardiovascular disease through endothelial dysfunction, oxidative stress, reduced NO bioavailability, vascular inflammation, increased arterial stiffness and a shift towards a pro-thrombotic state[198,199]. Smoking reduces brachial artery FMD in a dose-dependent manner, as a result of reduced NO bioavailability within the vasculature[199,201].

Cigarette smoke contains oxidants and free radicals that contribute to a pro-oxidative environment through lipid oxidation and oxidative modification of biomolecules[199,202]. This shift towards a pro-oxidative state is characterised by activation of NADPH oxidases which increase ROS generation and leads to reduced NO bioavailability[199]. The pro-oxidative environment also contributes to local and systemic immune system activation and inflammation[199]. Smokers have increased concentrations of neutrophils, lymphocytes and monocytes, as well as pro-inflammatory factors TNF-α, IL-1β, and CRP[199,203-207]. Increased local inflammation is illustrated by increased expression of IL-6, Il-8 and VCAM-1[199,208]. Inflammation and oxidation contribute to activation of macrophages, endothelial cells and platelets, with subsequent endothelial cell damage, dysfunction and premature cell death[199]. Smoking also increases vascular smooth muscle cell proliferation and migration through activation of the platelet-derived growth factor-protein kinase C signalling cascade and alterations in the extracellular matrix and tissue remodelling through increased expression of matrix metalloproteinases (MMP-1/8/9)[199,209-211]. Overall, smoking contributes to endothelial damage and dysfunction, with a shift towards a pro-oxidative and pro-inflammatory state that accelerates atherogenesis and increases the risk of atherosclerotic cardiovascular events[199].

The effects of smoking on blood pressure are less well defined. Whilst smoking causes acute increases in blood pressure and is associated with malignant hypertension, any chronic independent effects of smoking on blood pressure appear small[212,213]. A number of studies have found that smokers generally have BP levels equivalent to or lower than non-smokers[212,214,215]. However, these studies are generally based upon isolated clinic blood pressures and therefore are unlikely to reflect blood pressure trends occur over the course of a day. This is particularly relevant in smokers who may be exposed to a number of periods of acute blood pressure rises over the course of a day, around the times when they are smoking. Indeed, in a study of 24-hour ambulatory BP monitoring smokers maintained higher average

daytime systolic blood pressures than non-smokers, despite similar clinic blood pressures[212,216]. Given the recent emphasis on 24-hour ambulatory monitoring to diagnose and monitor high blood pressure, this investigation should perhaps be considered more readily in smokers and not be inappropriately reassured by isolated clinic blood pressure measurements[212]. The acute rises in blood pressure to which smokers are exposed to are likely to be harmful and all smokers should be encouraged to stop[3,154]. Furthermore, it is well established that smoking exerts toxic effects on the endothelium which, combined with the adverse vascular effects of high blood pressure, leads smoking and hypertension to have synergistic deleterious effects on vascular function and overall cardiovascular risk[212]. Smoking cessation is therefore one of the most important lifestyle changes that patients with high blood pressure can make to reduce their overall cardiovascular risk[3,154,198].

11. Conclusions

Hypertension is characterised by a phenotype of vascular changes that include endothelial dysfunction, increased vasoconstriction, vascular remodelling, inflammation, fibrosis and increased arterial stiffness. These factors work in synergy with high blood pressure to increase cardiovascular risk through further increases in blood pressure and progression of atherosclerosis. Hypertension is an increasing public health burden with many patients having sub-optimal blood pressure control, putting them at increased risk of hypertension-associated target organ damage and cardiovascular disease. With the many antihypertensive drugs available (69 approved by the FDA)[201] optimal treatment remains a challenge. This may be due, in part, to the fact that many of these drugs do not specifically target the vascular system to ameliorate vascular damage associated with hypertension. However, some of the effective antihypertensive drugs currently used do promote vascular health, such as ACEIs, ARBs, calcium channel blockers and mineralocorticoid receptor blockers. Some newer cardiovascular drugs, such as agonists of the AT_2R, vasopeptidase inhibitors, dual acting

ARB-neprilysin inhibitors, and ET-1 receptor blockers, may have potent blood pressure-lowering actions as well as positively influencing vascular function. The key outstanding study is one which compares standard guideline based therapy to endothelial function directed therapy, in order to determine the overall clinical efficacy of an endothelial targeted approach. Lifestyle factors can also contribute to the vascular changes associated with high blood pressure and patients should therefore be encouraged to reduce dietary salt intake, maintain a healthy body weight, engage in regular aerobic exercise, consume fish, fruit and vegetables, moderate their alcohol consumption and not smoke. Pharmaceutical development should focus on collaboration to develop new blood pressuring lowering treatments that better target the vascular changes associated with hypertension. Advancing knowledge in the understanding of vascular mechanisms that cause high blood pressure will facilitate efficient drug discovery to reduce the enormous clinical and economic burden of hypertension.

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Table 1

Anti-hypertensive drugs and beneficial vascular effects

Drug class	Example drugs	Possible beneficial vascular effects
ACE inhibitors	Lisinopril Perindopril Enalapril Ramipril	↑ NO bioavailability, ↓ Production of reactive oxygen species Vasodilation, anti-inflammatory
Angiotensin-II receptor blockers	Losartan Valsartan Candesartan	↑ NO bioavailability ↓ Production of reactive oxygen species Vasodilation, anti-inflammatory
Calcium channel blockers	Amlodipine Lercanidipine Nifedipine	Improved cellular redox state
Mineralocorticoid receptor antagonists	Spironolactone Eplerenone	↓ Pro-inflammatory/pro-fibrotic changes
β-blockers	Nebivolol Carvedilol	↑ NO bioavailability Reactive oxygen species scavenger

ACE, angiotensin converting enzyme; NO, nitric oxide.

Figure legends

Figure 1

Factors contributing to vascular changes associated with hypertension. Activation of pro-inflammatory, pro-fibrotic, redox-sensitive and growth/apoptotic pathways lead to structural, functional and mechanical changes with arterial remodelling, vascular calcification and endothelial dysfunction. RAAS, renin angiotensin aldosterone system; Ang II, angiotensin II, ET-1, endothelin-1; NO, nitric oxide.

Figure 2

Schematic demonstrating changes that occur during vascular remodelling associated with hypertension. Vascular remodelling is associated with an increase in media-to-lumen ratio (M:L) and variable changes in cross sectional area (CSA).

Figure 3

Extracellular matrix remodelling in hypertension. Angiotensin II, aldosterone, ET-1 and other hypertensive factors promote ECM remodelling through activation of transforming growth factor-β (TGF-β), mitogen-activated protein kinase (MAPK) and SMAD pathways and reactive oxygen species (ROS). This leads to matrix metalloproteinase (MMP) and connective tissue growth factor (CTGF) activation and upregulation of galectin-3. Collagen, fibronectin and proteoglycan deposition is increased, which leads to fibrosis and increased arterial stiffness. Adapted from Harvey, et al. 2016.

Figure 4

Therapeutic approaches to promote vascular health and improve vascular function in hypertension. Antihypertensive drugs and lifestyle modifications can repair and ameliorate vascular damage. These vascular actions together with blood pressure-lowering effects reduce cardiovascular risk and complications of hypertension.

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