anuscript of the following book chapter: Touyz, R. M., Camargo, L. L., Rios, F. J., Alves-Lopes, R., Neves, K. B., Eluwole, O., Maseko, M. J., Lucas-Herald, A., Blaikie, Z.
Arterial hypertension. In T. Kenakin (Ed.), Comprehensive Pharmacology
(pp. 469-487). [4.20] Elsevier.
https://doi.org/10.1016/B978-0-12-820472-6.00192-4

Comprehensive Pharmacology.

Chapter 00158

Arterial Hypertension

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Key words: vascular remodeling, vasoconstriction, endothelial dysfunction, vascular phenotype, inflammation, fibrosis, perivascular adipose tissue, vascular aging, blood pressure, hypertension.

Short title: Hypertension

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Abbreviations

Ang II	angiotensin II
ACEi	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker
BP	blood pressure
CCB	calcium channel blocker
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
ER	endoplasmic reticulum
ET-1	endothelin-1
IL	interleukin
MAP	mitogen-activated protein kinase
MR	Mineralocortioid receptor
NO	Nitric oxide
Nox	NADPH oxidase
PVAT	perivascular adipose tissue
RAAS	renin angiotensin aldosterone system
ROS	reactive oxygen species
SBP	systolic blood pressure
TLR	toll-like receptor

Glossay

Angiotenin II	a hormone that plays an important role in the development of hyperteson

Hypertension	elevated blood pressure
Oxidative stress	Increased bioavailaibility of reactive oxgen species
Primary hypertension	High blood pressure when the cause is unknown
Renovascular hypertension	high blood pressure caused by the narrowing of arteries that supply the kidney
Resistance arteries	small arteries that contribute to peripheral resistance
Secondary hypertension	high blood pressure due to a known cause

Abstract

Hypertension is a complex, multifactorial and multisystem disorder and a leading cause of morbidity and premature death globally. Major guidelines define it as systolic blood pressure >130 mmHg and/or diastolic blood pressure >80 mmHg. Hypertension is a very common disease with prevalence rates of about 30% in adults worldwide. The incidence of hypertension is age-related. At younger ages, hypertension is more prevalent in males than females, but this trend is reversed by age 65. Gender-related differences in hypertension may relate to cardiovascular effects of sex hormones. The underlying cause of the disease is identified in only ~5% of patients (secondary hypertension), while in 95% of patients, no etiology is found (primary or essential hypertension). Multiple factors including genetics, environmental factors and interacting physiological systems contribute to the pathophysiology of hypertension. High blood pressure is a major preventable risk factor for heart failure, ischemic heart disease, chronic kidney disease, stroke and vascular dementia. The risk of hypertension-related complications and target organ admage increases as blood pressure increases. Hypertension is typically associated with vascular dysfunction, cardiovascular remodelling, renal dysfunction, and stimulation of the sympathetic nervous system. Growing evidence indicates that the immune system is also important and that activated immune cells promote inflammation, fibrosis, and target-organ damage. Common to these processes is oxidative stress, defined as an imbalance between oxidants and antioxidants in favour of the oxidants, which cause disruption of oxidation-reduction (redox) signalling and promotion of molecular and cell damage. This chapter provides a comprehensive review on hypertension and highlights some new concepts on molecular mechanisms and pathophysiological processes

underlying hypertension and approaches to diagnosing and managing hypertension in the clinic.

1. Introduction

Hypertension is a leading cause of premature death worldwide (1). It is a very common disease with prevalence rates from 20-40% of adults globally. The incidence of hypertension is age-related with rates of <10% at age 20 to >75% at age 75 (1-3). Although at younger ages, hypertension is marginally more prevalent in males, this trend is reversed by age 65 (2). High blood pressure remains a leading risk factor for death worldwide and is a key risk factor for older adults (4). It is associated with vascular complications, many of which are used in outcome measures in cerebrovascular disease, coronary artery disease, heart failure, chronic kidney disease, peripheral vascular disease, atrial fibrillation and dementia (4).

The risk of hypertension-related complications increases at systolic blood pressures (SBP) of greater than ~115 mmHg and diastolic blood pressures (DBP) of greater than ~75 mmHg (5). However, the cutoffs for initiation of pharmacological treatment of hypertension are dependent more on the concurrence of other cardiovascular risk factors/co-morbidities than on the blood pressure itself. Thus, for those at the lowest risk (eg. young females with no other risk factors) the threshold for initiation of therapy is higher than those at high risk (eg. patients with pre-existing coronary artery disease, diabetes or age > 75) where the threshold for initiation of treatment is $\geq$ 130 mmHg SBP (4,5).

Primary hypertension (previously called “essential” hypertension) is the most common form of the disease accounting for more than 95% of cases (6). Pathophysiologicaly it involves dysregulation of multiple interconnected physiological systems including neural, anatomical, hemodynamic, endocrine, genetic and adaptive,

which are impacted by environmental factors (6-9). The cause of hypertension is known in only 5% of patients is the cause of hypertension known. This form of hypertension, termed secondary hypertension, is often reversible when the etiological factor is eradicated (8). Common causes of secondary hypertension include renal (eg. chronic kidney disease, polycystic kidney disease), endocrine (catecholamine, cortisol or aldosterone excess) and vascular disease (renovascular stenosis, aortic coarctation) or drugs (chronic non-steroidal anti-inflammatory drugs, amphetamines, antidepressants, oral contraceptives, anti-angiogenic drugs (VEGF inhibitors)) (10).

Regardless of the etiology, hypertension is aggravated by a range of health behaviours including: dietary salt excess, sedentary lifestyle, excess alcohol consumption and dietary deficiencies including diets low in potassium. Further, blood pressure is reduced by reversal of all of the factors as well as by consumption of a diet high in fruits and vegetables (11,12).

The complex etiology of hypertension was best described by Irvine Paige in 1949 in his ‘Mosaic Theory’ when he proposed that high blood pressure involves interplay between many elements including genetic, environmental, anatomic, adaptive, neural, endocrine, humoral and hemodynamics factors (13). Since then there has been enormous progress in discovering molecular and cellular processes that connect the numerous components underlying hypertension (figure 1). More recently the Paige Mosaic Theory has been revisited with additional factors being identified as major drivers coordinating diverse molecular, cellular and systems events in hypertension including new components of the renin angiotensin aldosterone system (RAAS), oxidative stress, inflammation and activation of the immune system (14-19). This chapter provides a comprehensive update on hypertension and highlights some new concepts on molecular mechanisms and pathophysiological

processes underlying hypertension and approaches to evaluating and managing hypertension in the clinic. We also provide an overview of hemodynamic and vascular factors critically involved in hypertension pathophysiology.

2. Hemodynamics in hypertension

The pathophysiology of hypertension, among other players, involves a multifaceted interplay between the heart and blood vessels. The role of the vascular system is to deliver blood to the tissues, and this flow is defined by the pumping actions of the heart, which means that an increase in cardiac output, an increase in total peripheral vascular resistance, or a combination of both cause a rise in blood pressure (20-22). Cardiac output is a result of left ventricular pump function, whereas peripheral vascular resistance is controlled, in large part, by small arteries and arterioles. Changes in small vessel diameter, due to functional, structural and/or mechanical alterations, affect flow and vascular resistance (22,23). Chronic exposure to increased peripheral vascular resistance and increased afterload in the left ventricle are associated with ventricular hypertrophy in hypertension. Rarefaction and remodelling of intramyocardial coronary artery, and left ventricular diastolic dysfunction further contribute to impaired tissue perfusion and susceptibility to ischemia during high oxygen demand (22). These hemodynamic changes, when persistent, cause impairment in target organs through sustained endothelial dysfunction and vasoconstriction (24-27).

2.1. Resistance arteries and peripheral vascular resistance in hypertension

Resistance arteries play a key role in the control of total peripheral vascular resistance in hypertension. Around 45% to 50% of total vascular peripheral resistance is modulated by small arteries (lumen diameter <350 μm) and arterioles (lumen diameter <100 μm), whereas capillaries (≈7 μm lumen diameter) are accountable for 23–30%

(28-30). Alterations in all vessel layers, from the endothelium to the perivascular adipose tissue (PVAT), have been demonstrated (31,32). While endothelial and smooth muscle cell dysfunction are the hallmark of vascular changes in hypertension, other cell types within the vasculature, such as perivascular adipocytes, immune cells, fibroblasts and pericytes are also important (31-34).

2.2. Small vessel dysfunction and remodeling

Vasoconstriction, endothelial dysfunction, eutrophic and/or hypertrophic remodelling, alterations in vascular distensibility, and rarefaction characterize small resistance arteries in patients with essential hypertension (28-30,35). Blood pressure elevation causes an increased load by enhancing vessel wall tension, leading to increased wall stress. To compensate for increased wall stress, an increase in wall thickness or a reduction in lumen diameter, or both, occur. This vascular remodelling is crucial to increased peripheral resistance, which impacts development and sequelae of hypertension. In general, medial hypertrophy associated with hypertension is due to vascular smooth muscle cell hypertrophy (volume increase) and/or hyperplasia (cell proliferation). Inward eutrophic remodelling, mostly observed in patients with primary (essential) hypertension, is characterized by increased media thickness and media-to-lumen ratio, reduced lumen and external diameter and unchanged media cross-sectional area. Inward growth may be associated with peripheral apoptosis, contributing to eutrophic remodelling (36). Chronic vasoconstriction may also result in inward remodelling where remodling of the extracellular matrix and re-arrangement of vascular smooth muscle cells leads to a small lumen (36). Patients with secondary hypertension commonly exhibit hypertrophic remodelling, with marked contribution of cell growth, including VSMCs hypertrophy or hyperplasia (37,38).

The initial adaptative remodelling ultimately becomes nonadaptive and compromises organ function, leading to target organ damage. Endothelial dysfunction, rarefaction, fibrosis and inflammation are important processes that underlie small vessel dysfunction and remodeling and are influenced by many factors including activation of the RAAS, oxidative stress and activation of immune cells (35-38).

3. The renin angiotensin aldosterone system and angiotensin-derived peptides in hypertension

The RAAS is a multiorgan peptidergic system where initially angiotensinogen (AGT) is formed in the liver, released to the circulation, and cleaved to angiotensin I (Ang I) by renin; a protease synthesized and released by the kidneys (19). Ang I undergoes cleavage by angiotensin-converting enzyme (ACE), a zinc metalloproteinase expressed in endothelial and epithelial cells in the lungs, kidneys, and vasculature to generate Ang II (39-41). Ang II plays an important role in blood pressure regulation through cellular effects mediated by binding to the Ang II type 1 receptor (AT1R) leading to coupling of G proteins and activation of myriad signalling pathways that regulate cardiac and vascular contraction, inflammation and fibrosis (40,41). Major molecular systems activated by Ang II/AT1R include mitogen-activated protein kinases (MAPK), Rho kinase, PI3K, Akt, PKC, growth factor receptors, calcium channels, reactive oxygen species production (ROS), immune cell responses and cytokine production (40,41). These injurious actions of Ang II/AT1R are counteracted by the Ang II type 2 receptor (AT2R), where promotes vasodilation and anti-inflammatory/fibrotic effects, processes that are downregulated in hypertension (42,43).

3.1. Novel angiotensin-derived peptides

Ang II is not the only product of the RAAS, as other peptidases (aminopeptidases, carboxypeptidases, and endopeptidases) can further cleave AGT, Ang I and Ang II to generate Ang(1-12), Ang(1-9), Ang(1-7), Ang III and Ang IV (44). All these angiotensin peptides have physiological and pathological effects in the cardiovascular system and influence blood pressure control. Ang(1-12) levels are increased in hypertension and contributes to circulating Ang II via an alternative chymase-dependent pathway (45), while Ang III induces vasopressin expression contributing to blood pressure increase (46). Transgenic animals that chronically release Ang IV are hypertensive and treatment with AT1R blockers decrease blood pressure in these animals. In addition, in AT1R-expressing CHO cells, low concentrations of Ang IV increase calcium mobilization (47). Some of these additional axes of the RAAS have protective effects in the cardiovascular system and are mainly related to the degradation of Ang I or Ang II by ACE2, a homologue of ACE, producing Ang(1-9) and Ang(1-7) (48,49). ACE2 is not the only enzyme capable of generating Ang(1-7). Peptidases such as THOP1 (thimet oligopeptidase), PEP (prolyl oligopeptidase) and NEP (neutral endopeptidase) produce Ang(1-7) from Ang I, while carboxypeptidase A and prolyl carboxypeptidase (PCP) use Ang II as their substrate (49).

Ang-(1-7) and Ang-(1-9) are vasoprotective. Overexpression of Ang(1-7)-producing fusion protein in DOCA-salt rats attenuated hypertension and protected against cardiac dysfunction and fibrosis (51). Acting predominantly via the Mas1 receptor, Ang(1-7) induces vasodilation via nitric oxide (NO) production in endothelial cells, and downregulates inflammation, proliferation, and fibrosis in the cardiovascular system (52). Ang(1-9) is protective against cardiomyocyte death and reduces infarct size through Akt activation in an AT2R-dependent manner (53,54). It also reduced

apoptosis and inflammation in an experimental model of pulmonary arterial hypertension via AT2R activation (55).

3.2. Aldosterone

Hyperaldosteronism is a common cause for secondary hypertension and is prevalent in resistant hypertension (56,57). Aldosterone is produced by cells in the zona glomerulosa of the adrenal gland in response to Ang II and when plasma potassium levels are reduced. Aldosterone binds to the mineralocorticoid receptor (MR), expressed in multiple tissues such as the heart, vessels, kidney, and brain, and cells responsible for blood pressure control such as endothelial, vascular smooth muscle, renal and immune cells (59). Aldosterone acting via the MR regulates ion transport, where it augments Na^+ reabsorption while increasing K^+ and H^+ excretion, via upregulation of the pump Na^+K^+-ATPase and the channel ENaC, which in turn increases blood pressure (60,61). In SHRSP rats, a genetic model of hypertension, plasma aldosterone levels are increased followed by vascular dysfunction and fibrosis, while aldosterone signaling in vascular smooth muscle cells from the same model was exacerbated and due to MR-dependent activation of p66Shc and Nox1-derived ROS generation (61). In vascular cells, aldosterone rapidly increases intracellular calcium and activates signalling proteins critically involved in hypertension and organ damage, such as MAPKs, EGFR, PKC and c-Src (60-62).

4. Sex hormones and hypertension

Hypertension is a disease where sex differences are evident, suggesting a role for sex hormones, such as estrogen (17β-estradiol) and testosterone in the regulation of blood pressure. Estrogen receptors are expressed in endothelial and vascular smooth muscle cells and modulate vascular tone via genomic processes through activation of nuclear receptors (ERα, ERβ), and by non-genomic mechanisms, by activation of

membrane-bound receptors (ERα, Erβ, GPER), leading to activation of signalling pathways associated with NO production and vasodilation (63). By activating ERα, estrogen modulates components of the RAAS, where studies demonstrated that the lack of ERα exacerbates Ang II-induced hypertension (64) and estrogen is capable of increasing ACE2 activity and Ang(1-7) production (65). The estrogen receptor ERβ has also been associated with anti-hypertensive effects. ERβ deficiency leads to dysfunctional cation channel activity and hypertension and, in SHR rats, activation of ERβ receptors decreases blood pressure (66,67). Although estrogen is considered to have protective effects in the maintenance of blood pressure, changes in estrogen metabolism may generate deleterious metabolites that play an important role in the development of some forms of hypertension. In pulmonary arterial hypertension (PAH), dysregulation of estrogen metabolism towards to the metabolite 16α-hydroxyestrone increased ROS production, protein tyrosine phosphatase oxidation and downregulation of Nrf2 and expression of associated antioxidant enzymes leading to pulmonary vascular smooth muscle cell proliferation (68).

Androgens, like testosterone and its metabolite 5α-dihydrotestosterone (DHT), also regulate processes important in blood pressure maintenance by activating the androgen receptor leading to transcription factor function or signalling activation independent of DNA-binding actions. Androgen receptors are expressed in cells of the cardiovascular system such as cardiomyocytes, endothelial cell, VSMCs, fibroblasts and immune cells (69). Due to sex differences in hypertension, where males exhibit higher blood pressure values than premenopausal females, it was assumed that testosterone plays a deleterious role in the cardiovascular system. Studies have demonstrated that androgens are involved with blood pressure increase, sodium and water retention and ROS generation (70). Testosterone regulates RAAS components,

where it increases renin levels and expression of ACE or AT1R (71). In the New Zealand rat model of hypertension, testosterone increased Ang II-induced vascular dysfunction (72), while in androgen receptor knockout mice (ARKO) treated with Ang II, cardiac hypertrophy and fibrosis are decreased due to less ERK1/2 and ERK5 activation and improved left ventricle function (73).

Unlike pre-clinical studies, human studies have demonstrated a protective role for testosterone in the cardiovascular system. This may relate to relative concentrations of testosterone. Low levels of testosterone are associated with endothelial dysfunction while increased levels may be vasoprotective (74). Molecular mechanisms associated with testosterone vascular protective effects, and possible anti-hypertensive actions, involve reduction in calcium influx, production of endothelium-derived relaxing factors such as hydrogen sulphide and NO, reduced ROS generation and anti-calcification actions (75).

5. Oxidative stress and hypertension

ROS are key mediators of cell signalling involved in several cellular events, such as contraction, relaxation, proliferation, migration, differentiation, extracellular matrix deposition and inflammation. However, increased ROS generation and/or impaired antioxidant capacity results in oxidative stress, which is associated with dysregulated redox signalling, protein, lipid, and DNA damage, inflammation and ultimately cell injury (76). Oxidative stress, which is induced by Ang II, is a central process involved in the pathophysiology of hypertension in many systems such as the vasculature, kidneys, heart, and brain (77).

5.1. Generation of ROS in hypertension

Several sources of ROS are upregulated in experimental models of hypertension and in hypertensive patients, including the Nox enzymes (7 isoforms), endoplasmic

reticular (ER) stress and mitochondrial oxidases (figure 2). Of these Noxs are most important ROS-generating oxidases in the cardiovascular system. Upregulation of Nox1, Nox2 and Nox4 have been demonstrated in almost all experimental models of hypertension (77,78). Genetic deletion of Nox1 in mice resulted in reduced vascular ROS (79), while Nox1 overexpression exacerbated Ang II-induced increase in blood pressure and vascular hypertrophy (80). Vascular Nox2 is implicated in vasoconstriction and vascular inflammation (81), while fibroblast Nox2 plays an important role in vascular fibrosis and remodelling (81). Nox4 is one of the main isoforms in the kidney and seems to be important in salt-sensitive hypertension. In this model of hypertension, Nox4 was implicated in renal oxidative stress and injury as well as vascular dysfunction and hypertension (82). Nox5 is also implicated in hypertension as blood pressure is increased in mice expressing Nox5 in kidney cells (83) and mice expressing Nox5 in vascular smooth muscle cells display vascular dysfunction and hyperreactivity (84). In cardiomyocyte-expressing Nox5 mice cardiac dysfunction and myocardial hypertrophy are amplified with cardiac overload (85). Furthermore, high levels of Nox5 were detected in vascular smooth muscle cells and in renal proximal tubule cells from hypertensive patients (86,87).

Another source of ROS that has been implicated in experimental hypertension is endoplasmic reticular (ER) stress. Upregulation of ER stress markers was observed in aorta, mesenteric arteries, heart and brain in hypertensive rats (88,89). Treatment with ER stress inhibitors, 4-PBA and TUDCA, reduced blood pressure and improved vascular function in experimental hypertension (90). ROS generation is induced by ER stress, and we showed important interplay between Nox-derived ROS and ER stress response, where ER stress-regulated Nox-ROS induced vascular dysfunction in VSMC from hypertensive rats (91).

Increased mitochondrial ROS also plays a role in the pathophysiology of hypertension. Treatment with antioxidants targeted to the mitochondria were demonstrated to reduce blood pressure in experimental hypertension (92). In hypertension, mitochondrial oxidative stress is associated with decreased activity of antioxidant systems, such as SOD2 (93). Downregulation of the mitochondrial deacetylase SIRT3 that activates SOD2 is associated with high levels of mitochondrial ROS in hypertension. Genetic manipulation of SIRT3 in animal models showed that SIRT3 silencing exacerbates, while SIRT3 overexpression protects, animals against Ang II-induced hypertension, supporting the importance of mitochondrial ROS in hypertension (93).

5.2. Oxidative stress and cardiovascular function in hypertension

In the cardiovascular and renal systems oxidative stress is associated with remodelling and inflammation (94-96) (figure 3). Increased ROS generation causes inactivation of phosphatase and sustained activation of kinases, such as c-Src, ERK1/2 and p38 MAPK involved in cardiovascular hypertrophy and inflammation (97). In addition, ROS activate Ca^{2+} channels, transcription factors and cytoskeletal proteins leading to altered contraction, migration, apoptosis and rearrangement of the cytoskeleton (97,98). Increased ROS generation in the kidney is associated with vascular and tubular dysfunction in hypertension. Renal oxidative stress is also implicated in activation of renal afferent nerves, renin release, renal vasoconstriction, dysregulation of Na^+ and H_2O homeostasis, glomerular cell dysfunction and proteinuria (99).

Another key redox-regulated mechanism involved in cardiovascular dysfunction associated with hypertension is endothelial dysfunction. Increased generation of superoxide anion (O_2^-) quenches NO, an important endothelial-derived vasodilator

leading to impaired vasorelaxation (94-99). This reaction results in generation of peroxynitrite ($ONOO^-$), a highly reactive nitrogen species involved in protein oxidation and cell damage (100). One of the targets of $ONOO^-$ is tetrahydrobiopterin (BH4), an important endothelial nitric oxide synthase (eNOS) cofactor, that upon oxidation is inactivated further aggravating vascular dysfunction (101). ROS are also involved in endothelial cell activation and recruitment of immune cells to the vascular wall in experimental and human hypertension (102,103).

In addition to peripheral systems, oxidative stress in the central nervous system seems to be important in the pathogenesis of hypertension. ROS plays an important role in sympathetic activation in the subfornical organ, leading to increase in blood pressure (104). Additionally, Ang II-induced hypertension involves increased Nox derived ROS generation in the brain (104,105). Administration of SOD to the subfornical organ prevents Ang II-induced increase in blood pressure supporting the role of oxidative stress in the brain in the development of hypertension.

6. Inflammation and the immune system in hypertension

Oxidative stress and activation of inflammatory processes are hallmarks of cardiovascular damage in experimental and clinical hypertension. Endothelial cells are regulators of the vascular inflammatory response and are the barriers between the vascular space and tissues. Vascular inflammation is triggered by increased expression of endothelial cell adhesion molecules such as P-selectin and E-selectin, and expression of leukocyte-derived ligands including P-selectin ligand-1 (PSGL-1) (106). Leukocyte:endothelial cell interaction facilitates rolling and transmigration of circulating leucocytes to the subendothelial space and vascular media, where they induce an inflammatory response by stimulating local production of cytokines and chemokines (107) (figure 4). Endothelial inflammation is also associated with reduced

eNOS activation, decreased production of the vasodilator NO, increased generation of O_2^- and formation of ONOO-, processes that promote oxidative stress and proinflammatory signalling (108).

Vascular inflammation in hypertension is defined as a low-grade, sub-clinical, chronic event that involves toll-like receptors (TLR) of which there are 10 subtypes (TLR1-10) (109,110). TLR activation induces a potent pro-inflammatory intracellular cascade that involves MyD88 (myeloid differentiation primary response protein 88) or TRIF (Toll/interleukin-1 receptor domain-containing adaptor protein interferon-β) (110). Both pathways induce activation of NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells) and consequent production of pro-inflammatory mediators (TNFα (tumor necrosis factor alpha), IL-6 (interleukin 6)], chemokines (MCP-1 (Monocyte chemoattractant protein-1) , IL-8)). Experimental models indicate that TLR4 and TLR9 are especially important in vascular inflammation in hypertension (111,112).

Inflammasomes are important players of the innate immune system. There are several types of inflammasomes, including NLRP3 (nucleotide-binding and oligomerization domain-like receptor family pyrin domain-containing 3), NLRC4 (NLR family CARD domain-containing protein 4), NLRP6, NLRP9, pyrin, and AIM-2 (absent in melanoma 2) (113). In hypertension, NALP3 is the most studied member of the family. It is expressed in vascular cells and its activation drives the formation of the inflammasome complex that promotes production of pro-inflammatory cytokines IL-1β and IL-18. Activation of the inflammasome pathway has been observed in experimental models of hypertension, such as Ang II- and aldosterone-salt induced hypertension, DOCA-salt hypertension and pulmonary arterial hypertension, and is associated with endothelial dysfunction, vascular remodelling, and target organ

damage (114,115). Genetic studied demonstrated that individuals carrying polymorphisms in the *NLRP3* gene exhibit elevated blood pressure (116).

6.1. Cytokines and inflammatory profile in hypertension

Experimental models of hypertension exhibit increased production of IL1β, IL-6, IL-11 and TNFα. Clinical studies demonstrated that high levels of IL-6 and C-reactive protein (CRP) are associated with increased risk for hypertension. In patients with rheumatoid arthritis, infusion with infliximab, a TNFα inhibitor reduced blood pressure (117,118). In experimental models of hypertension TNFα-deficiency attenuated vascular and renal injury (119). Disruption of TNFα signaling using Etanercep, which blocks effects of the free cytokine, prevented Ang II-induced hypertension and ROS production in mice (120). Endothelial dysfunction in human placental vessels induced by TNFα was reduced by treatment with aspirin, indicating the upstream effects of cyclooxygenases in this pathway (121).

IL-1β is a potent cytokine produced by inflammasome activation and interacts with IL-1R1 and a decoy receptor IL-1R2. While pre-clinical studies suggest that IL-1β may be an attractive therapeutic target in hypertension, data from clinical studies are less convincing. CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), a randomized, double-blind trial involving more than 10 000 patients with low-grade chronic inflammation, demonstrated significantly reduced major adverse cardiovascular event rates by targeting the IL-1β, but without beneficial effects on blood pressure (122). A smaller study in 146 patients demonstrated that IL-1 antagonism decreased blood pressure and increased vasodilation and Ang(1-7) production (123). Further clinical studies are needed to better understand the therapeutic targeting of IL-1β in hypertension.

6.2. Immune cells and cardiovascular damage in hypertension.

Neutrophils, monocytes/macrophages and dendritic are professional phagocytes and important effector cells of the innate immune system. Neutrophils are the most abundant innate immune cells present in the circulation and release pro-inflammatory and pro-oxidant mediators which cause tissue injury. Experimental neutrophil depletion reduced blood pressure and vessel constriction (124).

Monocytes and macrophages. These are highly plastic cells. In the presence of inflammatory stimuli these cells acquire a pro-inflammatory phenotype and contribute to endothelial cell damage (125). In response to Ang II and aldosterone, macrophages produce ROS and pro-inflammatory cytokines including MCP-1, a potent monocyte-attracting chemokine. Macrophage deficiency by genetic mutation or pharmacologic treatment reduced blood pressure and prevented vascular dysfunction, arterial hypertrophy, and oxidative stress in various models of experiemntal hypertension (126,127).

Dendritic cells. Dendritic cells (DCs) are considered professional antigen presenting cells and are at the interface of the innate and adaptive immunity. The main function of DCs is to present antigens to T cells to initiate and regulate the adaptive immune response. The importance of DCs in cardiovascular homeostasis was observed in experimental models of cardiovascular and renal damage induced by aldosterone and salt (128,129). Ablation of DCs prevented blood pressure elevation, fibrosis and inflammation by reducing production of NGAL (neutrophil gelatinase-associated lipocalin) (129). During hypertension development “neoantigens” are formed as a result of ROS production that induce lipid oxidation and formation of gamma ketoaldehydes or isoketals. Isoketals rapidly ligate to protein lysines in the dendritic

cells, forming neoantigens that are presented to T cells leading to their activation/proliferation and cardiovascular damage (130).

Lymphocytes. Activation of T lymphocytes initiate the adaptive immune response following antigen presentation from antigen presenting cells in secondary lymphoid tissues. After activation, T lymphocytes proliferate and differentiate into effector cells. Main populations of T lymphocytes are CD4+ or T helper cells and CD8+ or cytotoxic T cells. Experimental models of hypertension that are deficient in B and T lymphocytes exhibited reduced blood pressure (131). In these models, increased blood pressure was restored after adoptive transfer of T lymphocytes, but not B lymphocytes, thus confirming the pathogenic role of T lymphocytes in hypertension (132). T-lymphocytes express functional receptors for Ang II and AT1R deletion in these cells is associated with reduced blood pressure by mechanisms dependent on ROS production. In models of salt-sensitive hypertension, Th17 and Th1 through the production of IL17A or IFNγ respectively, seems to be responsible for upregulating renal sodium channels, including sodium hydrogen exchanger 3 (NHE), Na-K-2Cl-cotransporter (NKCC2), sodium chloride cotransporter (NCC) and the epithelial sodium channel (ENaC), which may induce sodium retention (133,134). Renal accumulation of $CD8^+$ T lymphocytes is a major source of IFNγ and cytotoxic components in kidney inflammation in hypertension (135).

Regulatory T cell (Treg) have immunosuppressant and tolerogenic characteristics and different from $CD4^+$ Th1 or Th17 and $CD8^+$ T cells, they regulate the immune response and avoid aberrant activation mainly by the production of the anti-inflammatory and tolerogenic cytokine IL-10 (135,136). In animal models, adoptive transfer of Treg lowered blood pressure and ameliorated the cardiovascular and renal injury (136).

6.3. Immune cell activation and vascular inflammation

Immune cells express TLRs, C-type lectin receptors (CLR), RLRs (retinoic acid-inducible gene I -like receptors), NLRs (nucleotide-binding domain, leucine-rich repeat-containing protein receptors) and CD36 (137). Moreover, they express receptors for Ang II, aldosterone and ET-1. Activation of these receptors trigger a complex signalling cascade that ultimately activate different transcription factors including NFκB, AP-1, Elk-1 (ETS domain-containing protein-1), ATF2 (activating transcription factor 2), the phosphoprotein p53 and members of the IRF (interferon-regulatory factor) family (138,139). Activation of these pathways amplify low-grade inflammatory responses and oxidative stress, leading to organ damage.

7. The kidney, salt and hypertension

The kidney plays an important role in arterial blood pressure control in large part via regulation of salt and water excretion and control of peripheral vascular tone. Kidney dysfunction is both a cause and consequence of elevated blood pressure (140). Hypertension is a major risk factor for chronic kidney disease (CKD) and end stage renal disease (ESRD) and is the primary diagnosis in many patients on dialysis (140,141). Pre-clinical studies demonstrated that kidney transplantation from normotensive rats reduces blood pressure in hypertensive animals (143) and in humans, the prevalence of hypertension increases to more than 75% in patients with a low glomerular filtration rate (GFR) (<30 ml/min/1.73 m^2). The kidneys play a pivotal role in blood pressure control through several mechanisms including, control of sodium and water balance, neurohormonal factors such as RAAS and ET-1 and glomerular filtration.

7.1. Control of sodium and water balance

Physiologically, an increase in BP leads to increase in sodium and water excretion, with reduction in the volume of extracellular fluid and a consequent drop in blood pressure. This phenomenon, called pressure natriuresis, is a major homeostatic factor that normally controls blood pressure (143). Impaired pressure diuresis, related to high salt intake and fluid retention contributes to hypertension, especially in salt-sensitive individuals (143,144).

Pressure natriuresis is regulated by multiple factors, including the RAAS, which has an important role in peripheral vasoconstriction. As a compensatory mechanism, an increase in BP causes inhibition of the RAAS, leading to reduced vascular contractility of afferent arterioles, and consequent reduction in solute reabsorption in the proximal and distal tubules. On the order hand, activation of the RAAS increases proximal tubular sodium reabsorption, which reduces GFR and increases total vascular resistance (145,146).

7.2. Salt-sensitive hypertension

Several animal and human studies have demonstrated a direct association between increased salt intake and increased risk for hypertension (147-149), which in turn, predisposes to development of CKD (150,151). For most individuals, the kidney adapts rapidly to an increase in salt intake, with a transient rise in arterial pressure. In some individuals, salt intake causes a disproportionate rise in blood pressure (at least a 10% increase in mean arterial pressure (152). These individuals, defined as salt-sensitive, are especially encouraged to reduce their dietary salt intake for effective blood pressure control (153). Mechanisms underlying salt-sensitivity remain unclear although increased sodium reabsorption may be important since salt-sensitive hypertensive individuals have higher proximal tubular sodium reabsorption. In addition sodium reabsorption is increased in African Americans, who are prone to salt-sensitive

hypertension, via upregulation of the Na, K, 2Cl cotransporter (NKCC2) in the ascending limb (154,155).

7.3. Glomerular function and hypertension

Hypertension causes sclerosis of the glomeruli, which has a negative impact on kidney function largely due to a decrease in nephron number. As a compensatory mechanism, there is an increase in glomerular filtration in undamaged glomeruli. Hyperfiltration is associated with a faster decline in renal function. In humans, excess salt intake results in pressure and volume overload of the kidney, and the resulting glomerular hypertension accelerates the decline in glomerular filtration rate (GFR) (156,157). Reduction in GFR activates receptors in the macula densa to signal cells of the juxtaglomerular apparatus to secrete renin, which promotes an increase in production of angiotensin II (Ang II) and aldosterone important in the pathophysiology of hypertension (158,159).

7.4. The RAAS and endothelin-1 in the kidney

In the kidney, upregulation of the RAAS leads to Ang II-induced vasoconstriction and impaired natriuresis, while hyperaldosteronism causes an increase in tubular sodium and water reabsorption, with consequent blood pressure elevation (160,161). Activation of the endothelin (ET-1) system, through ET_A and ET_B receptors, may also be important in kidney function and blood pressure regulation. ET-1-induced activation of renal ETA receptors causes vasoconstrication and enhances sodium reabsorption, while activation of ET_B receptors inhibits sodium reabsorption in the collecting ducts suggesting a protective effect of ET_B receptor in kidney function. This is corroborated *in vivo*, where ET_B receptor knockout mice develop salt retention and severe hypertension, an effect not observed in ET_A-knockout mice (162,163). In humans with

chronic renal failure, the ET_A receptor antagonist BQ-123 is effective in lowering blood pressure, an effect that is dependent on increased renal blood flow and urinary sodium excretion (164).

7.5. Hypertension and chronic kidney disease

Not only do the kidneys play an important role in regulating blood pressure, but they are a target organ of damage of hypertension (165). Mechanisms underlying hypertension-associated CKD remains elusive but may involve endothelial dysfunction. The endothelium is involved in the regulation of important biological mechanisms, including angiogenesis, inflammatory responses, immunity, and vascular tone and permeability. High dietary salt intake leads to endothelial dysfunction, an effect observed in an early stage of CKD and potentiated as the disease progresses toward ESRD (166,167).

Several mechanisms contribute to endothelial dysfunction in CKD patients, including increased levels of proinflammatory cytokines, advanced glycation end-products (AGEs), oxidative stress, increased activation of NF-κB pathway and low vitamin D (168). In CKD patients, excessive oxidative stress, and chronic inflammation increase the production of AGEs, which in turn promotes CKD-related endothelial dysfunction. Soluble AGE (sRAGE) is a biomarker of inflammation, oxidative stress, and heart failure (169). Via binding to AGE, sRAGE receptor prevents AGEs activation of membrane-RAGE and RAGE-related endothelial dysfunction. Increased levels of sRAGE are observed in CKD patients, which may reflect an exacerbated level of AGEs. In addition to their known role as proinflammatory agents, AGEs increase the expression of FGF-23, a key molecule that impairs endothelium-dependent vasorelaxation by increasing superoxide levels and reducing NO bioavailability (170).

8. The autonomic nervous system and blood pressure control

It is now clear that neurogenic activation influences blood pressure regulation. Neurogenic hypertension is defined as dysegulation of autonomic nervous system (ANS) regulatory systems such as overactivation of sympathetic nerves, loss of parasympathetic and baroreflex homeostasis, excessive cerebral Ang II production, and increased neural ROS generation leading to increased blood pressure (171). The ANS includes the peripheral nervous system (PNS), and comprises two distinct divisions of the the sympathetic nervous system (SNS) and, the parasympathetic nervous system (PSNS), which together function to regulate the cardiovascular demands of peripheral tissues such as the heart, kidney, and lungs. The system is regulated by the neuronal networks of the central nervous systems (CNS), most notably the subfornical organ (SFO), hypothalamus paraventricular nucleus (PVN), nucleus tractus solitarius, and rostral ventral lateral medulla (RVLM), as well as the caudal ventrolateral medulla (CVM) (172,173). The SNS and PSNS influence cardiovascular function via cardiac and vascular sympathetic nerves, the hypothalamic-pituitary-gland axis (HPA), sympathetic juxtaglomerular cell stimulation and activation of the RAAS. Abnormal function of these systems contribute to hypertension pathology.

8.1. The ANS in hypertension pathology

Although the factors that drive ANS dysfunction that lead to hypertension are not fully understood, many pathophysiological mechanisms are involved including the RAAS and networking with the kidney. The brain is highly sensitive to Ang II, especially in regions of the forebrain that lack the blood-brain-barrier, where it induces alterations in neuronal membrane potential and overactivation of neuronal action potential and neuronal firing, particularly in circumventricular organs (CVO) such as the SFO, PVN,

and RVLM (174,175). Increased neuronal firing in these circumventricular pathways leads to increases in neurotransmission of arginine vasopressin (AVP) and corticotrophin-releasing hormones (CRH) and overactivation of SNS, consequently leading to increases in blood pressure (175,176). Furthermore, chronic levels of circulatory and brain-derived Ang II activate neuromodulatory pathways that enhance the AT_1R activation through epithelial sodium channels. As such, stimulus of sodium-sensitive sites in the CNS can cause further excitation of the SNS, which contribute to neurogenic hypertension (177). Long-term overactivation of the SFO-PVN-RVLM pathway may also elicit neural plasticity, whereby the signalling properties of these neuronal pathways maintain an increased level of SNA activity (178).

Under physiological conditions, SNS efferent renal nerves and afferent renal nerves form a bidirectional feedback loop of sympathetic and sensory nerves between the brain and the kidneys. The efferent renal nerves innervate vascular smooth muscle cells of renal arteries and veins and forms the renal nerve plexus, which regulates the renal tubular system and juxtaglomerular cells. Hyperactivation of renal efferent nerves contribute to renal dysfunction, leading to decreased blood flow and increased renal vasoconstriction, renal tubular sodium retention, renal vascular resistance, which promote an increase in aldosterone and renin secretion promoting blood pressure elevation (178,179).

9. Diagnosis and management of hypertension in the clinic

9.1. Blood pressure measurement and diagnosis of hypertension

Blood pressure assessment in the clinical management of human hypertension is almost exclusively done noninvasively using the brachial artery. Traditionally this has utilized sphygmomanometric approaches- initially using mercury and then aneroid technologies (i.e., auscultation-based). However, in current practice semiautomated

and automated devices using oscillometric techniques have become the gold standards (180). Techniques for measuring blood pressure out of office (home blood pressure measurements or 24 hr. ambulatory blood pressure measurements) have been shown to be more predictive of hypertension-related cardiovascular morbidity than office blood pressure assessments and are the gold standard approaches for the diagnosis of hypertension (180,181). Among office blood pressure measurement techniques those devices that perform multiple blood pressure measurements without the requirement for a health care provider to be in the room (automatic/unattended blood pressure measurements- AOBP) have been shown to be more predictive of hypertension related morbidity than other means of non-invasive blood pressure measurement (180,181).

Based on major North American guidelines, hypertension is diagnosed when blood pressure is consistently > 130 and/or > 80 mmHg (182-286). However many patients with hypertension between 130-139/80/89 mmHg (termed stage 1 hypertension) may not require immediate drug therapy, especially if they do not have concomitant risk factors. Modern guidelines now consider absolute cardiovascular risk together with blood pressure levels in the initiation of drug treatment. Antihypertensive therapy should be strated in patients with stage 1 hypertension and who are at high risk (eg. age 65 and older, co-morbidities of diabetes, CKD, or cardiovascular disease). Irrespective of blood pressure threshold for initiation of drug therapy, the ideal target blood pressure is <130/80 mmHg.

9.2. Lifestyle improvement

Extensive research demonstrates that lifestyle improvement is a cornerstone of hypertension prevention and blood pressure control. Modifiable factors such as weight

control, alcohol consumption reduction, increased regular exercise, healthy sleep patterns, reduced dietary salt and sugar intake, healthy diet and smoking cessation not only improve cardiovascular health but reduce blood pressure and improve hypertension control (183-186). Major international hypertension guidelines stress the importance of the implementation of lifestyle modifications (182-187).

Risk factors for hypertension includes environment, lifestyle, genetic factors and the interaction between all these factors. Dietary factors are among the lifestyle factors that most influence the blood pressure, and dietary interventions have been shown to improve blood pressure control and reduce risks of end organ damage associated with hypertension (182-187). The most effective diet associated with beneficial effects in blood pressure reduction include the DASH diet (Dietary Approaches to Stop Hypertension) and Mediterranean diets (188). The DASH diet is a low-salt diet along with high intake of vegetable, whole grains, nuts, low fatty dairy products and low intake of red meat, sugar, saturated fat and cholesterol compared to the standard Western diet (189). In a randomized trial, the DASH diet showed significant effects in lowering blood pressure in men, women, blacks and nonblacks. A diet enriched mostly in fruits and vegetables also reduced blood pressure, but effects were lower than those observed with the DASH diet (190,191). The main differences among these diets are that apart from low salt intake, the DASH diet is also rich in calcium, magnesium and potassium, also called nutraceuticals that may give additional effects on blood pressure control.

9.3. ***Pharmacological therapy of hypertension***

First line therapy of hypertension (in the absence of other comorbidities). Most national and international guidelines have designated those antihypertensive drugs as “first line” that have been shown both to lower blood pressure safely and effectively and

(more importantly) reduce the risk of hypertension-related complications. Conversely, those drugs) that have been shown to be less effective in reducing hypertension-related cardiovascular risk (like α-adrenergic antagonists or for whom their impact on cardiovascular outcomes as a first line drug has yet to be unambiguously demonstrated (like aldosterone antagonists) are designated as second line (or third or fourth line). In the category of first line drugs most national and international guidelines recognize angiotensin converting enzyme inhibitors (ACE-I), angiotensin II subtype 1 receptor blockers (ARBs), calcium channel blockers (CCBs) and thiazide/thiazide type diuretics (Table 1) (182,183,191,192). β-adrenergic antagonists are less consistently recognized as first line and primarily only in younger patients with hypertension.

Single pill combinations as first line therapy. Two-drug combinations have only recently been recognized as a first line therapy and are indicated as initial therapy regardless of the initial extent of elevation in blood pressure. These first line single pill combinations include formulations which include either an ARB or ACEi with a thiazide/thiazide like diuretic or CCB. Notably 3 drug combinations of antihypertensive drugs are increasingly available, although none of these formulations have yet to demonstrate the efficacy data generally required of a first line therapy. The emergence of single pill combinations as an initial therapy reflects the appreciation that especially at lower doses, these combinations are generally more effective (across all ages and races) and with an improved adverse effect profile as compared to a single drug therapy prescribed at a standard dose (193). The superior adverse effect profiles of combination drugs predominantly reflect i) the dose-dependent increase in adverse effects seen for most antihypertensive drugs ii) the lower doses of each individual constituent drug in the combinations and iii) the impact of the individual drugs in the combination in mitigating the adverse effects associated with the companion drug. For

example, the adverse impact of diuretics on insulin resistance is mitigated when combined with an ACE-Inhibitor or Angiotensin receptor blocker. Further, the peripheral edema associated with a dihydropyridine calcium channel blocker is mitigated when it is combined with either an ACE-I or ARB.

Treatment of hypertension in patients with comorbidities. The choice of antihypertensive drug therapy in patients with comorbidities either reflects i) the demonstration of that drug's effectiveness in hypertension management in those specific patient populations or ii) the effectiveness of those drugs in reducing morbidity/mortality in those patient populations regardless of whether or not they also are hypertensive (Table 2).

Treatment of resistant hypertension. Despite optimal pharmacological therapy up to 10% of patients with hypertension remain resistant to therapy as defined by those who do not reach blood pressure targets despite 3 drug therapy generally including a diuretic (194,195). Those patients are more likely to have a secondary form of hypertension, specifically renovascular hypertension, primary aldosteronism and pheochromocytoma. Management of these patients beyond ruling out a secondary form of hypertension includes i) revisiting health behaviours (sodium restriction, adequate potassium intake, reducing alcohol etc.), and eliminating drugs which cause higher blood pressure (like non-steroidal anti-inflammatory drugs, oral contraceptives, cocaine, amphetamines and glucocorticoids). In patients with resistant hypertension aldosterone antagonists (spironolactone, eplerenone) and amiloride are preferred as demonstrated in the PATHWAY trial (196).

10. Conclusions

Hypertension remains a leading cause of premature death on a global basis. The etiology of primary hyprtension, by far the most cause, is multifactorial reflecting a

mosaic of factors including dysregulation of the autonomic nervous system, the renin angiotensin aldosterone system, renal/sodium metabolism, immune function, and oxidative stress pathways. Management of hypertension includes both pharmacological and health behaviour therapies. The firstline choice of antihypertensive therapies reflects the use of those drug classes which have been shown to have both antihypertensive effects and reduce the risk of hypertension-related cardiovascular complications or those effective in patients with selected comorbidities including coronary artery and cerebrovascular disease, heart failure, diabetes and renal disease

Acknowledgements

The authors are funded by grants from the British Heart Foundation (BHF) (RE/13/5/30177; 18/6/34217; CH/12/29762).

Conflicts

There are no conflicts to declare

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Figure legends

Figure 1. **Pathophysiologic mechanisms leading to cardiac and vascular changes in function and structure in hypertension.** Blood pressure (BP) may rise progressively because of genetic and/or epigenetic drive. Either directly or indirectly via the action of increased oxidative and endoplasmic reticulum (ER) stress. Vasoconstriction and smooth muscle SMC growth and apoptosis, low-grade inflammation, and vascular fibrosis can lead to vascular and cardiac remodelling, which can also reflect into BP elevation. Changes in the extracellular matrix components may change the architecture of the vessel wall, and the intracellular signalling, favouring restructuring of SMC cells. Rarefaction and endothelial dysfunction, mainly mediated by reduced NO bioavailability, also contributes to the etiology and cardiovascular complications of hypertension.

Figure 2. ROS production and scavenging. ROS sources include the Nox family of enzymes, endoplasmic reticulum (ER), mitochondria, and the enzymes xanthine oxidase, uncoupled nitric oxide synthase (NOS) cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome P450. Reduction of oxygen in the presence of one free electron results in generation of the free radical superoxide anion ($O_2^{\bullet -}$). In turn, superoxide anion is converted to hydrogen peroxide (H_2O_2) spontaneously or catalysed by the enzyme superoxide dismutase (SOD). Hydrogen peroxide is scavenged by catalase, glutathione peroxidase (GPx) and peroxiredoxin (Prx).

Figure 3. Oxidative stress in hypertension. Increased ROS levels are observed in several systems and organs in hypertension, indicating that oxidative stress is a central process involved in the pathophysiology of hypertension.

Figure 4. Vascular inflammation in hypertension. Schematic demonstrating molecular processes involved in vascular inflammation and endothelail dysfunction in hypertension

Figure 5. Diagram of the efferent sympathetic pathway and baroreflex. Changes in blood pressure (BP) activate the SNS through several CVO neuronal pathways in the brain. The RVLM, however, plays the key functional role in that it not only receives signals to initiate SNS activity (for example, through carotid sinus and baroreceptor responses to BP) but also sends signals to the peripheral vasculature and organs to regulate blood flow. Preganglionic ACh activates muscarinic receptors that initiate post-ganglionic action potential and release the neurotransmitter norepinephrine (NE), leading to physiological changes such as increases in vasoconstriction, cardiac output, and activation of the RAAS system.

Table 1. Major Antihypertensive Drug Classes

	Prototype(s)	Antihypertensive mechanism(s)	Primary adverse effects
Aldosterone antagonists and Na channel blockers	Spironolactone, amiloride	vasodilator	hyperkalemia
Alpha adrenergic blockers	prazosin	vasodilator	postural hypotension, nasal congestion
Beta adrenergic blockers	propranolol	negative cardiac inotrope, renin inhibition	bradycardia, worsening dyslipidemia, insulin resistance, asthma
Centrally acting agents	methyldopa, clonidine	alpha 2 adrenergic agonists, decreased sympathetic nervous system activity, vasodilator	depression, fatigue
Diuretics	hydrochlorothiazide, chlorthalidone, indapamide	acutely: diuresis chronically: vasodilation	hyponatremia, hypokalemia, worsens dyslipidemia, gout, insulin resistance
Direct vasodilators	hydralazine, minoxidil	arterial vasodilator. Inhibition of inositol trisphosphate (IP3)-induced release of calcium (hydralazine); activation of ATP sensitive K channels (minoxidil)	reflex tachycardia, sodium retention. Worsens left ventricular hypertrophy hirsutism (minoxidil)
Calcium channel blockers	diltiazem, verapamil, nifedipine	primarily vasodilator (nifedipine); mixed vasodilator/negative inotrope (verapamil, diltiazem)	worsens heart failure, bradycardia/heart block (verapamil, diltiazem); constipation (verapamil)
Angiotensin Converting Enzyme Inhibitors	captopril	vasodilator	hyperkalemia, worsening renal function. Angioneurotic edema, cough
Angiotensin Receptor Blockers	losartan	vasodilator	hyperkalemia, worsening renal function.

Table 2. Considerations in the individualization of initial antihypertensive drug therapy in adults (adapted from Hypertension Canada Guidelines 2020)

	Initial therapy
Diabetes mellitus	
Diabetes mellitus with microalbuminuria*, kidney disease, cardiovascular disease or additional cardiovascular risk factors	ACE inhibitors or ARBs
Diabetes mellitus not included in the above category	ACE inhibitors, ARBs, dihydropyridine CCBs or Thiazide/thiazide-like diuretics
Cardiovascular disease	
Coronary artery disease	ACE inhibitors or ARBs; β blockers or CCBs for patients with stable angina
Recent myocardial infarction	β blockers and ACE inhibitors/ARBs
Heart failure	ACE inhibitors (ARBs if ACE inhibitor-intolerant) and β blockers. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated BNP or NT-proBNP level, or NYHA Class II to IV symptoms.
Left ventricular hypertrophy	ACE inhibitor, ARB, long acting CCB or thiazide/thiazide-like diuretics.
Past stroke or TIA	ACE inhibitor and a thiazide/thiazide-like diuretic combination. .
Non-diabetic chronic kidney disease	
Non-diabetic chronic kidney disease with proteinuria†	ACE inhibitors (ARBs if ACE inhibitor-intolerant) if there is proteinuria. Diuretics as additive therapy.

*Microalbuminuria is defined as persistent albumin to creatinine ratio >2.0 mg/mmol. †Proteinuria is defined as urinary protein >500 mg/24hr or albumin to creatinine ratio [ACR] >30 mg/mmol in two of three specimens.