Hypertension

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Abstract | Systemic arterial hypertension is the most important modifiable risk factor for all-cause morbidity and mortality worldwide and is associated with an increased risk of cardiovascular disease (CVD). Fewer than half of those with hypertension are aware of their condition, and many others are aware but not treated or inadequately treated, although successful treatment of hypertension reduces the global burden of disease and mortality. The aetiology of hypertension involves the complex interplay of environmental and pathophysiological factors that affect multiple systems, as well as genetic predisposition. The evaluation of patients with hypertension includes accurate standardized blood pressure (BP) measurement, assessment of the patients' predicted risk of atherosclerotic CVD and evidence of target-organ damage, and detection of secondary causes of hypertension and presence of comorbidities (such as CVD and kidney disease). Lifestyle changes, including dietary modifications and increased physical activity, are effective in lowering BP and preventing hypertension and its CVD sequelae. Pharmacological therapy is very effective in lowering BP and in preventing CVD outcomes in most patients; first-line antihypertensive medications include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, dihydropyridine calcium-channel blockers and thiazide diuretics.

Systemic arterial hypertension (hereafter referred to as hypertension) is characterized by persistently high blood pressure (BP) in the systemic arteries. BP is commonly expressed as the ratio of the systolic BP (that is, the pressure that the blood exerts on the arterial walls when the heart contracts) and the diastolic BP (the pressure when the heart relaxes). The BP thresholds that define hypertension depend on the measurement method (TABLE 1). Several aetiologies can underlie hypertension. The majority (90–95%) of patients have a highly heterogeneous essential, or primary, hypertension with a multifactorial gene–environment aetiology. A positive family history is a frequent occurrence in patients with hypertension, with the heritability (a measure of how much of the variation in a trait is due to variation in genetic factors) estimated to be between 35% and 50% in the majority of studies[1,2]. Genome-wide association studies (GWAS) have identified ~120 loci that are associated with BP regulation and together explain 3.5% of the trait variance[3–5]. These findings are becoming increasingly important as we search for new pathways and new biomarkers to develop more-modern omics-driven diagnostic and therapeutic modalities for hypertension in the era of precision medicine[6].

Several rare, monogenic forms of hypertension have been described (for example, Liddle syndrome, glucocorticoid-remediable aldosteronism (a mineralocorticoid excess state) and conditions due to mutations in *PDE3A* (which encodes cGMP-inhibited 3′,5′-cyclic phosphodiesterase A)), in which a single gene mutation fully explains the pathogenesis of hypertension and indicates the best treatment modality[7–9]. If hypertension is caused by another condition (for example, primary aldosteronism, pheochromocytoma (a neuroendocrine tumour of the adrenal glands or other neuroendocrine tissues) or renal artery stenosis), it is referred to as secondary hypertension.

Hypertension is the most common preventable risk factor for cardiovascular disease (CVD; including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation and peripheral artery disease), chronic kidney disease (CKD) and cognitive impairment and is the leading single contributor to all-cause mortality and disability worldwide[10]. The relationship between BP and the increased risk of CVD is graded and continuous, starting at BPs as low as 115/75 mmHg, well within what is considered to be the normotensive range. Successful prevention and treatment of hypertension are key to reducing disease burden and promoting longevity in the world's population. In treating hypertension, it is important to consider a person's predicted atherosclerotic CVD (ASCVD) risk more than the level of BP alone, as persons with high ASCVD risk derive the greatest benefit from BP-lowering treatment[11].

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This Primer discusses the epidemiology and pathophysiology of primary hypertension, prevention strategies for slowing the progression of BP elevation, management strategies (including optimal BP targets) for lowering BP and preventing CVD outcomes in patients with established hypertension and the effects of antihypertensive treatment on quality of life; finally, we explore knowledge gaps, future trends and the outlook for hypertension research and treatment over the next decade.

Epidemiology

In pre-industrial societies, BP levels had narrow distributions with mean values that changed little with age and averaged around 115/75 mmHg (REF. 12), a value that probably represents the normal (or ideal) BP for humans. However, in most contemporary societies, systolic BP levels rise steadily and continuously with age in both men and women. This ubiquitous finding could be explained by the fact that age is a proxy for the probability and duration of exposure to the numerous environmental factors that increase BP gradually over time, such as excessive sodium consumption, insufficient intake of dietary potassium, overweight and obesity, alcohol intake and physical inactivity. Other factors, such as genetic predisposition or adverse intrauterine environment (such as in gestational hypertension or pre-eclampsia), have small but definite associations with high BP levels in adulthood[13]. Even modest rises in the mean population BP lead to large increases in the absolute number of people with hypertension[14].

As economic development progresses, hypertension initially affects those with a high socio-economic status, but at later stages of economic development, the prevalence of hypertension and its consequences is greatest in those with lower socio-economic status; this phenomenon is seen both within and between countries. Further, the speed of change in the prevalence of hypertension from 2000 to 2010 has been much more rapid than in previous epidemiological transitions[15].

Disease burden

Globally, 3.5 billion adults have non-optimal systolic BP levels (that is, >110–115 mmHg), and 874 million adults have a systolic BP of ≥140 mmHg. Thus, approximately one in four adults has hypertension[16]. Between 1990 and 2015, there was a 43% increase in the total global number of healthy life years lost to nonoptimal BP, driven by population increase, population ageing and a 10% increase in the age-standardized prevalence of hypertension[16]. The Global Burden of Disease study has shown that nonoptimal BP continues to be the largest single risk factor contributing to the global burden of disease and to global all-cause mortality, leading to 9.4 million deaths and 212 million lost healthy life years (8.5% of the global total) each year[10].

Cardiovascular disease risk

Prospective observational studies have repeatedly demonstrated a strong, continuous, positive relationship between BP and CVD, with no evidence of a threshold for risk throughout the usual range of BP observed in clinical practice[17–19]. The relationship between BP and CVD applies to both systolic BP and diastolic BP but is somewhat more-robust for systolic BP in adults[19]. It is noted in both sexes, at all ages throughout adulthood and for all major manifestations of CVD, including stroke (ischaemic and haemorrhagic), coronary artery disease, heart failure, peripheral artery disease and end-stage renal disease (although there are variations in the strength of the associations and the slopes of the curves)[17–20] (FIG. 1). The relationship is independent of other CVD risk factors, and the level of BP has proved to be a major component of CVD risk in all prediction models[21]. Approximately two-thirds of all adults who have hypertension or receive treatment with BP-lowering medication at 30 years of age have a ~40% higher risk of experiencing a CVD event than their age-matched and sex-matched counterparts with a lower level of BP[18]. In addition, CVD events in individuals with hypertension tend to manifest about 5 years earlier than in individuals with a lower level of BP[18].

In individuals of 40–69 years of age, a 20 mmHg increase in systolic BP or a 10 mmHg increase in diastolic BP regardless of baseline values is associated with more than a doubling of the risk of stroke or ischaemic heart disease mortality[17], whereas a systolic BP reduction of 5 mmHg can decrease stroke mortality by 14% and CVD mortality by 9%. At older ages (≥80 years), the corresponding relative risk is slightly lower, but the absolute risk is far greater than earlier in life[17]. For example, a 20 mmHg difference in systolic BP between 120 mmHg and 140 mmHg is associated with an annual difference in absolute risk that is nearly ten times larger at ages of 80–89 years than at ages of 50–59 years[17].

Mechanisms/pathophysiology

Blood pressure regulation

BP is determined by several parameters of the cardiovascular system, including blood volume and cardiac output (the amount of blood pumped by the heart per minute), as well as the balance of arterial tone, which is affected by

both intravascular volume and neurohumoral systems (discussed in the following sections). The maintenance of physiological BP levels involves a complex interplay of various elements of an integrated neurohumoral system that includes the renin–angiotensin–aldosterone system (RAAS), the roles of natriuretic peptides and the endothelium, the sympathetic nervous system (SNS) and the immune system (FIG. 2). Malfunction or disruption of factors involved in BP control in any component of this integrated neurohumoral system can directly or indirectly lead to increases in mean BP, BP variability or both, over time resulting in target-organ damage (for example, left ventricular hypertrophy and CKD) and CVD outcomes[22].

The pathophysiological mechanisms responsible for hypertension are complex and act on a genetic background. Primary hypertension involves multiple types of genes; some allelic variants of several genes are associated with an increased risk of developing primary hypertension and are linked in almost all cases to a positive family history (BOX 1). This genetic predisposition, along with a host of environmental factors, such as high sodium intake, poor sleep quality or sleep apnoea, excess alcohol intake and high mental stress, contributes to the development of hypertension[22–24]. Finally, the probability of developing hypertension increases with ageing, owing to progressive stiffening of the arterial vasculature caused by, among other factors, slowly developing changes in vascular collagen and increases in atherosclerosis[25–27]. Immunological factors can also play a major part, especially in the background of infectious or rheumatological diseases such as rheumatoid arthritis. The mosaic theory of hypertension describes its multifaceted pathophysiology[28,29].

Sodium homeostasis regulation

Sodium is a crucial regulator of blood volume: high serum sodium concentration promotes fluid (water) retention, thereby increasing blood volume and BP. When dietary sodium increases in normotensive individuals, compensatory haemodynamic changes occur to maintain constant BP. These changes include reduction in renal and peripheral vascular resistance and increased production of nitric oxide (NO, a vasodilator) from the endothelium. However, if the effect of NO is impaired or absent, an increase in BP occurs. Endothelial dysfunction is a risk factor for the development of salt sensitivity and subsequent hypertension.

Table 1 | **Definitions of hypertension based on the 2013 ESH/ESC guidelines**

Category	Subtype	Systolic BP (mmHg)	Diastolic BP (mmHg)
Office BP	NA	≥140	≥90
Ambulatory BP	Daytime (awake)	≥135	≥85
	Night-time (asleep)	≥120	≥70
	24 h	≥130	≥80
Home BP	NA	≥135	≥85

For the diagnosis of hypertension, systolic blood pressure (BP), diastolic BP or both have to exceed the reported values. ESC, European Society of Cardiology; ESH, European Society of Hypertension; NA, not applicable. Modified from REF. 77.

Salt sensitivity is defined as a marked elevation in BP following a sodium load of ≥5 g and is characterized by an elevation of systolic BP of at least 10 mmHg within a few hours of ingestion. Individuals who are salt-sensitive have underlying endothelial dysfunction due to genetic or environmental influences. In response to a high salt load, these individuals generally manifest overproduction of transforming growth factor-β (TGFβ), which increases the risk of fibrosis, and oxidative stress and have limited bioavailable NO. Chronic high salt ingestion can result in endothelial dysfunction, even in individuals who are not salt-sensitive[30], and also affects the gut microbiota, with resultant changes that contribute to increased salt sensitivity and the development of hypertension[31]. High salt intake also seems to drive autoimmunity by inducing T helper 17 (T_H17) cells[31]. High salt intake in mice has been shown to deplete *Lactobacillus murinus* in the gut microbiota. Treatment of mice with *L. murinus* prevented salt-induced exacerbation of salt-sensitive hypertension by modulating T_H17 cells[31]. In line with these findings, a moderate high-salt challenge in a pilot study in humans reduced intestinal survival of *Lactobacillus* spp., increased the number of T_H17 cells and increased BP[31]. Thus, the gut microbiota seems to contribute to salt sensitivity of BP and the pathogenesis of hypertension.

Renin–angiotensin–aldosterone system

The RAAS has wide-ranging effects on BP regulation, mediating sodium retention, pressure natriuresis (that is, the mechanism whereby increases in renal perfusion pressure (the gradient between renal arterial and venous BP) lead to decreased sodium reabsorption and increased sodium excretion), salt sensitivity, vasoconstriction, endothelial dysfunction and vascular injury and plays an important part in the pathogenesis of hypertension[22] (FIG. 2). The RAAS is present at the cellular level in many organs, but its most crucial role is to help regulate pressure–volume homeostasis in the kidney, where it maintains perfusion in volume-depleted states (that is, when there is a reduction in extracellular fluid volume as a result of sodium and fluid loss) and is suppressed in volume-expanded (fluid overload) conditions. Renin and its precursor, prorenin, are synthesized and stored in the juxtaglomerular cells of the kidney and are released in response to various stimuli (FIG. 3). The main function of renin is to cleave angiotensinogen to form angiotensin I. Angiotensin-converting enzyme (ACE) cleaves angiotensin I to form angiotensin II, which is at the centre of the pathogenetic role of the RAAS in hypertension[32] (FIG. 3).

Angiotensin II enhances sodium reabsorption in the proximal tubule by increasing the activity of the sodium/hydrogen exchanger 3, electrogenic sodium bicarbonate cotransporter 1 and Na^+/K^+-ATPase and by inducing aldosterone synthesis and release from the adrenal glomerulosa[22]. Angiotensin II is also associated with endothelial dysfunction and has profibrotic and pro-inflammatory effects, mediated in large part by increased oxidative stress, resulting in renal, cardiac and vascular injury. Angiotensin II is tightly linked to target-organ damage in hypertension via these mechanisms[22].

ACE2 has emerged as an important modulator in the pathophysiology of hypertension, CVD and renal disease, owing to its role in metabolizing angiotensin II into angiotensin (1–7)[33]. Angiotensin (1–7) induces systemic and regional vasodilation, diuresis and natriuresis and exerts antiproliferative and antigrowth effects on vascular smooth muscle cells, cardiac myocytes and fibroblasts as well as on glomerular and proximal tubular cells[33]. Angiotensin (1–7) also has cardiorenal protective effects that are mediated by the proto-oncogene Mas receptor through signalling pathways that include mitogen-activated protein kinases (MAPKs), PI3K–AKT (phosphoinositide 3-kinase–RAC serine/threonine-protein kinase), NADPH oxidase, TGFβ1, the epidermal growth factor (EGF) receptor and nuclear factor-κB (NF-κB) activity[33–35].

Aldosterone plays a crucial part in hypertension. By binding to the mineralocorticoid receptor, it induces nongenomic effects (that is, without directly modifying gene expression) that include activation of the amiloride-sensitive sodium channel, commonly known as the epithelial sodium channel (ENaC), and result in the stimulation of renal sodium reabsorption in the cortical collecting duct[36]. Aldosterone also has many nonepithelial effects that contribute to endothelial dysfunction, vasoconstriction and hypertension[36,37]. These include vascular smooth muscle cell proliferation, vascular extracellular matrix deposition, vascular remodelling, fibrosis and increased oxidative stress[36,37].

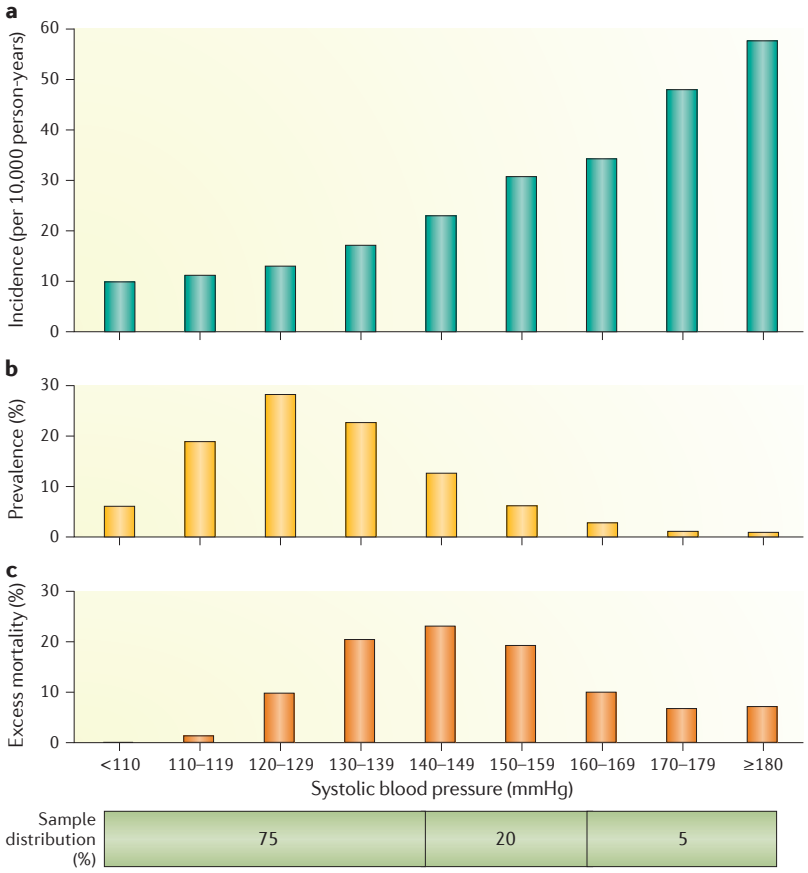

Figure 1 | **Association between systolic blood pressure and coronary heart disease mortality.** The relationship of systolic blood pressure (BP) to subsequent risk of coronary heart disease mortality was evaluated in >340,000 US men of 35–57 years of age at the beginning of the study and followed up for an average of 11.6 years. **a** | Distribution of the incidence of coronary heart disease mortality, adjusted for age, race, total serum cholesterol level, cigarettes smoked per day, use of medication for diabetes mellitus and income. Individuals with the highest levels of BP were at greatest risk of cardiovascular disease (CVD) mortality. **b** | Prevalence of coronary heart disease mortality. Only a minority of the men examined were exposed to the high risk associated with hypertension (≥140 mmHg for systolic BP, as per office BP measurement). However, a much larger number of individuals, who had BP in the nonhypertensive range, were exposed to the more-modest but still important increases in CVD risk. **c** | Estimation of the per cent of excess coronary heart disease mortality occurring in each category of systolic BP using individuals with a systolic BP of <110 mmHg as the reference group. About two-thirds of the overall burden of BP-related coronary heart disease mortality occurred in men who had a systolic BP of ≥140 mmHg (25% of the sample). However, about two-thirds of the remaining disease burden could be attributed to the approximately 20% of adults who had a systolic BP in the high-normal range (systolic BP 130–139 mmHg)[203]. Data from (REF. 19).

Natriuretic peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) play an important part in salt sensitivity and hypertension (FIG. 2). They have important natriuretic and vasodilator properties that enable the maintenance of sodium balance and BP during sodium loading[38,39]. Upon administration of a sodium load, atrial and ventricular stretch leads to the release of ANP and BNP, respectively, which leads to systemic vasodilation and decreased plasma volume (owing to fluid shifts from the intravascular to the interstitial compartment) and results in BP lowering[40]. Natriuretic peptides increase glomerular filtration rate via an increase in efferent arteriolar tone in volume-expanded states and inhibit renal sodium reabsorption through both direct and indirect effects. Direct effects include decreased activity of Na^+/K^+-ATPase and the sodium-glucose cotransporter in the proximal tubule and inhibition of the ENaC in the distal nephron. Indirect effects include inhibition of renin and aldosterone release[39].

Natriuretic peptide deficiency promotes hypertension. Corin (also known as atrial natriuretic peptide-converting enzyme) is a serine protease that is largely expressed in the heart and converts the ANP and BNP precursors pro-ANP and pro-BNP to their active forms. Corin deficiency has been associated with volume overload, heart failure and salt-sensitive hypertension[41]. Natriuretic peptide deficiency also predisposes to insulin resistance and type 2 diabetes mellitus. Obesity is associated with natriuretic peptide deficiency, probably through upregulation of the atrial natriuretic peptide receptor 3 in adipose tissue[42]. Natriuretic peptides have therapeutic potential for the metabolic syndrome — a cluster of conditions (including high BP, high fasting glucose levels, abdominal obesity, high triglycerides and microalbuminuria) that occur together, increasing the risk of CVD and diabetes mellitus[42].

Endothelium

The endothelium is a major regulator of vascular tone and a major contributor to salt sensitivity through NO (FIG. 2). Endothelial cells produce a host of vasoactive substances, of which NO is the most important in BP

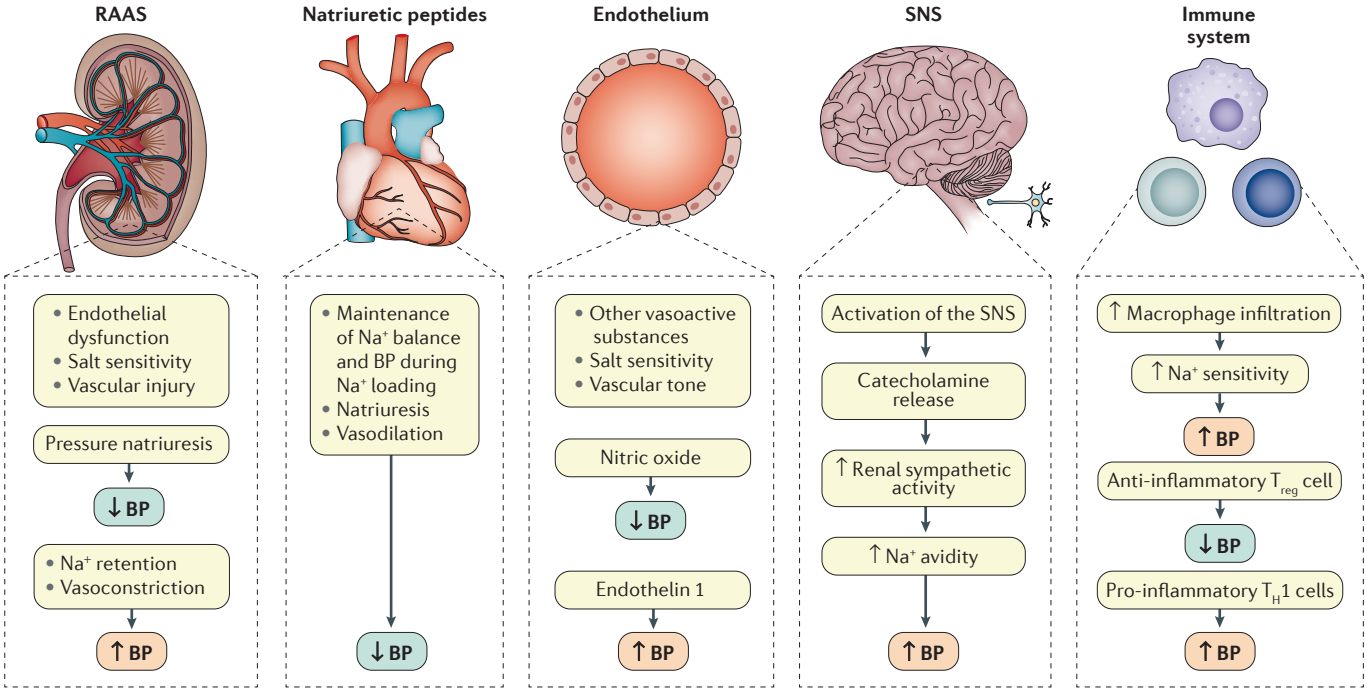

Figure 2 | **The major neuroendocrine systems involved in the regulation of blood pressure.** Neurohumoral, immune and organ systems involved in the maintenance of blood pressure (BP). Na^+, sodium; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; T_{reg}, regulatory T.

regulation[43,44]. NO is continuously released by endothelial cells in response to flow-induced shear stress, leading to vascular smooth muscle relaxation through activation of guanylate cyclase and generation of intracellular cyclic GMP[45]. Interruption of NO production via inhibition of constitutively expressed endothelial NO synthase (eNOS) causes BP elevation and development of hypertension in animals and humans[46]. Studies to evaluate NO activity in humans have demonstrated decreased whole-body production of NO in patients with hypertension compared with normotensive controls[46,47].

Endothelial cells also secrete a variety of other vasoregulatory substances, including vasodilators, such as prostacyclin and endothelium-derived hyperpolarizing factors, and vasoconstrictors, such as endothelin 1 (ET1), locally generated angiotensin II and the prostanoids thromboxane A2 and prostaglandin A2. ET1 is a potent vasoconstrictor that activates ET1 receptor (ETA) in vascular smooth muscle[48]. Other vasodilating substances secreted by a variety of cell types, such as calcitonin gene-related peptides, adrenomedullin and substance P, act primarily through increases in NO release from endothelial cells[49,50]. The glucose-regulating gut hormone glucagon-like peptide 1 also has vasodilating properties[51]. The balance between these factors, along with NO and ET1, determines the final effect of the endothelium on vascular tone[48,51–53]. Circulating ET1 levels are not consistently increased in hypertension, but there is a trend towards increased sensitivity to the vasoconstrictor and hypertensive effects of ET1 in individuals with hypertension[53]. ETA antagonists attenuate or abolish hypertension in a variety of experimental models and are effective in lowering BP in humans[48,53].

Endothelial dysfunction plays a seminal part in the pathogenesis of hypertension. Normotensive offspring of parents with hypertension often have impaired endothelium-dependent vasodilation, which implies a genetic component in the development of endothelial dysfunction[47]. Endothelial dysfunction in the setting of chronic hypertension is related to a combination of direct pressure-induced injury and increased oxidative stress. Several enzyme systems, including NADPH oxidase, xanthine oxidase and cyclooxygenase, as well as decreased activity of superoxide dismutase, generate reactive oxygen species[47,54]. Excess superoxide anions bind to NO, decreasing NO bioavailability and generating the pro-inflammatory oxidant peroxynitrite. Decreased NO bioavailability is the central factor that links oxidative stress to endothelial dysfunction and hypertension[47]. Individuals who are salt-sensitive might be very sensitive to the haemodynamic stress of increased blood volume, leading to overproduction of TGFβ and oxidative stress and limiting bioavailable NO[30]. Angiotensin II, along with other factors, including cyclic vascular stretch as a result of BP changes, ET1, uric acid, systemic inflammation, noradrenaline, free fatty acids and tobacco smoking, increases NADPH oxidase activity and plays a central part in the generation of oxidative stress in hypertension[52].

Sympathetic nervous system

Baroreceptors, mechanoreceptors that sense pressure changes in the circulatory system, are housed in various locations in the arterial tree, a key place being the carotid sinus, a dilated area at the base of the internal carotid artery just superior to the bifurcation of the common

Box 1 | **Genetic predisposition to hypertension**

A large genome-wide association study of 2.5 million genotyped single nucleotide polymorphisms (SNPs) in >69,000 individuals of European ancestry from 29 studies demonstrated that most SNPs related to blood pressure (BP) regulation and cardiovascular disease (CVD) risk involved natriuretic peptides[196]. SNPs in genes that encode precursors for atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) had been previously identified[197], and two other loci containing genes involved in natriuretic peptides and nitric oxide (NO) signalling pathways were identified in this study. Both of these pathways regulate cyclic GMP, which promotes vasodilation. A 2016 study identified 66 BP-associated loci, which were enriched for *cis*-regulatory elements in vascular endothelial cells, consistent with a role in BP control through modulation of vascular tone. This information prompted the development of a genetic risk score to predict target-organ damage[4].

Gene deletion studies in rodent models have evaluated cardiac ANP and BNP as paracrine regulators of vascular regeneration. Deletion of the genes encoding ANP and BNP exaggerates cardiac fibrosis and increases adverse left ventricular (LV) remodelling[38], and atrial natriuretic peptide receptor 1 (NPR1) deficiency leads to increased BP, cardiac fibrosis and LV dysfunction. Further, deletion of the gene encoding the endothelial guanylyl cyclase-A receptor, a cell surface receptor for natriuretic peptides, leads to diminished vascular regeneration and angiogenesis in response to critical hindlimb ischaemia, as well as cardiac fibrosis and diastolic dysfunction.

Finally, clinical studies have observed an association between certain *CORIN* polymorphisms and risk of pre-eclampsia and hypertension, particularly among African-American populations but not among Chinese populations[198].

carotid artery. When this artery is stretched by elevated BP, nerve bundles projecting from the baroreceptors in the carotid sinus send messages to the brain to reduce sympathetic outflow of nerve impulses (nerve traffic) and, thereby, BP[55–57]. The SNS is generally more activated in persons with hypertension than in normotensive individuals[58,59]. SNS activity is also greater in individuals with obesity, in men than in women, in younger than in older persons and in those with advanced kidney disease[60,61]. Many patients with hypertension are in a state of autonomic imbalance with increased sympathetic activity and decreased parasympathetic activity[59,62]. SNS hyperactivity is relevant to both the generation and maintenance of hypertension (FIG. 2). Studies in humans have also identified markers (such as increased systemic catecholamine spillover (the amount of catecholamines released from sympathetic nerves innervating blood vessels that enter the bloodstream) and sural nerve activity assessed by microneurography) of sympathetic overactivity in normotensive individuals with a family history of hypertension[63]. Among patients with hypertension, increasing severity of hypertension is associated with increasing levels of sympathetic activity measured by microneurography[64,65]. Plasma catecholamine levels, microneurographic recordings and systemic catecholamine spillover studies have provided evidence of increased sympathetic activity in patients with hypertension who have obesity, in those with the metabolic syndrome and in those whose hypertension is complicated by heart failure or kidney disease[65].

The importance of the SNS in the pathogenesis of hypertension has been defined in a variety of experimental models. Models of obesity-related hypertension demonstrate that increased renal sympathetic nerve activity and its attendant increase in renal sodium reabsorption are key factors in the maintenance of sustained hypertension[62]. In another animal model, rats that received daily infusions of phenylephrine for 8 weeks developed hypertension during the infusions; their BP normalized under a low-salt diet after discontinuation of phenylephrine, but once rechallenged with a high-salt diet, the animals became hypertensive again[30]. The degree of BP elevation on the high-salt diet was directly related to the degree of renal tubulo-interstitial fibrosis and decrease in glomerular filtration rate, suggesting that catecholamine-induced hypertension causes renal interstitial injury and a salt-sensitive phenotype that persists even after sympathetic overactivity is no longer present. In addition, increased SNS activity results in α-1 adrenergic receptor-mediated endothelial dysfunction, vasoconstriction, vascular smooth muscle proliferation and increased arterial stiffness, which contribute to the development and maintenance of hypertension[66]. Finally, there is evidence that sympathetic overactivity enhances salt sensitivity owing to a reduction in activity of *WNK4*, encoding serine/threonine kinase WNK4, which inhibits the thiazide-sensitive Na-Cl cotransporter, resulting in increased distal tubular sodium retention[67]. These mechanisms have been reviewed recently[66].

Inflammation and the immune system

Inflammation makes an important contribution to the genesis of hypertension and related target-organ damage. Inflammation is associated with increased vascular permeability and release of potent mediators, such as reactive oxygen species, NO, cytokines and metalloproteinases. Cytokines mediate the formation of neointima (a new or thickened layer of arterial intima), thereby decreasing the lumen diameter of resistance vessels (small arteries and arterioles that are highly innervated by autonomic nerves and the primary vessels involved in the regulation of BP) and promoting vascular fibrosis, leading to increased vascular resistance and stiffness. Cytokines also affect renal tubular function by increasing local synthesis of angiotensinogen and angiotensin II, as well as promoting sodium and volume retention in hypertension[68]. Matrix metalloproteinases stimulate the degradation of the extracellular matrix, enabling infiltration of immune cells through the vessel wall into the interstitium of the affected organs, promoting apoptosis and enhancing collagen synthesis and matrix deposition, leading to target-organ damage[68].

Whereas animal data are clear about the relationship between inflammation and hypertension, the data in humans are limited. There are associations between C-reactive protein, tumour necrosis factor and various interleukins and hypertension, but no direct link[68]. GWAS have identified a single nucleotide polymorphism (SNP) of *SH2B3* (SNP rs3184504), which results in an amino acid substitution in SH2B adaptor protein 3 (a protein involved in T cell receptor activation and signalling) that is associated with many autoimmune and cardiovascular disorders, including hypertension[69]. Further, drugs that are used to treat inflammation, such as NSAIDs and cyclosporine, raise rather than lower BP in individuals with hypertension, highlighting the complex nature of the relationship between inflammation and hypertension[69].

Both innate and adaptive immune responses participate in the generation of reactive oxygen species and inflammatory changes in the kidneys, blood vessels and brain in hypertension[68,70] (FIG. 2). Innate immune responses, especially those mediated by macrophages, have been linked to hypertension induced by angiotensin II, aldosterone and NO antagonism[68,70]. Reductions in macrophage infiltration of the kidney or the perivascular space of the aorta and medium-sized arteries lead to reductions in BP and salt sensitivity[68]. Adaptive immune responses via T cells have also been linked to the genesis of hypertension and its target-organ damage. T cells express type 1 angiotensin II receptor (AT1) and mediate angiotensin II-dependent hypertension[70]; of note, depletion of mature lymphocytes ameliorated hypertension and kidney injury resulting from a high-salt diet in the Dahl Salt Sensitive rat model[71]. Thus, a balance between pro-inflammatory T cell reactivity and inflammatory suppression induced by regulatory T cells determines the development of hypertension, as demonstrated by the amelioration of hypertension with the adoptive transfer of regulatory T cells in several animal models of hypertension[68–70]. Abnormalities in both pro-inflammatory T cells and anti-inflammatory regulatory T cells are implicated in hypertension-induced target-organ damage, as these cells regulate the inflammatory processes in the kidney and vasculature that underlie hypertension-induced kidney disease[68,70,71].

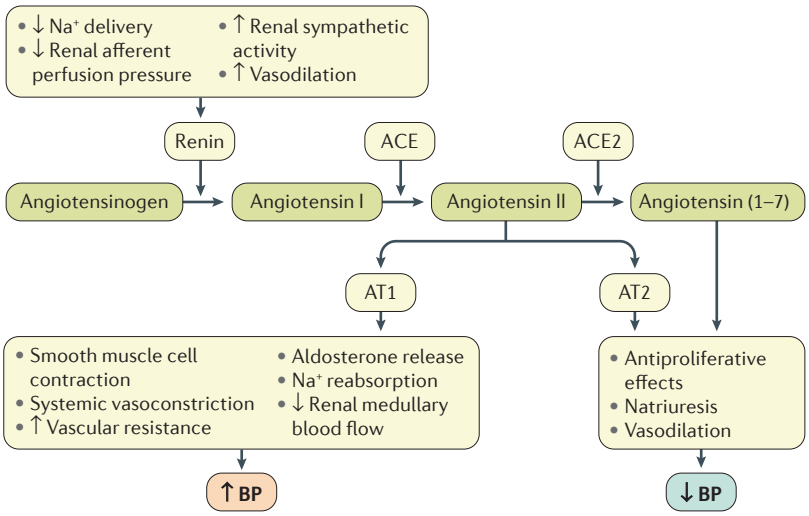

Figure 3 | **Role of the renin–angiotensin–aldosterone system in the regulation of blood pressure.** Decreased renal afferent arteriolar perfusion pressure, reduced sodium (Na^+) delivery to the macula densa (an area lining the wall of the distal convoluted tubule in contact with the glomerulus), activation of renal sympathetic nerves (via β_1 adrenergic receptor stimulation) and a variety of vasodilators, including prostaglandin E2, stimulate the release of renin. Angiotensin II activates the type 1 angiotensin II receptor (AT1), triggering smooth muscle cell contraction, systemic vasoconstriction, increased renovascular resistance and decreased renal medullary blood flow, a mediator of salt sensitivity. Stimulation of the AT2 has opposite effects, resulting in vasodilation, natriuresis and antiproliferative actions. Cross-transplantation studies using wild-type mice and mice lacking the AT1 have shown that both systemic and renal actions of angiotensin II are relevant to physiological blood pressure (BP) regulation but that the detrimental effects of angiotensin II in hypertension are mediated mainly via the kidneys[204,205]. Angiotensin-converting enzyme (ACE) inhibitors and AT1 antagonists have been shown to increase angiotensin (1–7) levels in the plasma and urine of normotensive animals and to enhance renal ACE2 activity[33]. Studies in rodents and humans with diabetic kidney disease suggest that upregulation of *ACE2* delays progression of kidney disease[206].

Diagnosis, screening and prevention

Diagnosis and screening

Primary hypertension is usually asymptomatic; thus, in clinical practice, all adults should have their BP measured at regular office visits. Hypertension is most commonly diagnosed based on repeated BP measurements in a clinical office setting. Accurate measurement and recording of BP are essential to categorize the level of BP, ascertain BP-related CVD risk and guide management. Since 2010, methods to measure out-of-office BP have been increasingly introduced to guide diagnosis and treatment of hypertension[72,73] (TABLE 1). These include home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM). HBPM refers to the measurement of BP at regular intervals by an individual at their home or elsewhere outside the clinic setting. ABPM consists of measuring and recording the BP at regular intervals (usually every 20–30 minutes), typically for a 24-hour period and while individuals go about their daily activities. The ability to measure out-of-office BP has enabled the identification of distinct BP phenotypes, including white-coat or isolated clinic hypertension and masked or isolated ambulatory hypertension[74,75]. White-coat hypertension is characterized by elevated office BP but normal ABPM or HBPM readings. By contrast, masked hypertension is characterized by normal office readings but elevated out-of-office readings (ABPM and HBPM)[74,75].

Diagnosis. The evaluation of a patient with elevated BP requires more than the diagnosis of hypertension. It should also include the assessment of the CVD risk, target-organ damage and concomitant clinical conditions that could affect the BP or related target-organ damage, as well as recognition of features suggestive of secondary hypertension. Some of these investigations are routine tests necessary in all patients, but others are necessary only in specific patient groups identified by history, clinical examination and routine tests. In rare, inherited forms of hypertension, a single gene mutation explains the pathogenesis of hypertension[7–9] (FIG. 4). A small proportion of patients have a potentially reversible cause of hypertension, and a correct diagnosis might lead to a cure or a substantial improvement in BP control with a reduction of CVD risk. Thus, it is appropriate to implement a simple screening for secondary hypertension in all patients. The screening is based on clinical history, physical examination and routine laboratory investigations (BOXES 2,3). Secondary hypertension should also be considered in cases of a sudden worsening of hypertension, poor BP response to drug treatment or severe target-organ damage that is out of proportion to the duration and severity of hypertension. In these cases, specific diagnostic tests are indicated (TABLE 2).

The medical history has to address the time of the first diagnosis of hypertension, current and past BP measurements and antihypertensive medications. A history

of pregnancy-related hypertension is an important factor in the assessment of women with hypertension. Hypertension results in an increased risk of CVD complications and CKD. Thus, a careful medical history should be taken in all patients to enable assessment of global CVD risk, with special emphasis on current and past smoking habits and evidence of dyslipidaemia and diabetes mellitus. CVD risk should be estimated using an established calculator (for example, the American College of Cardiology ASCVD Risk Estimator). Adults at high risk of CVD have a high probability to benefit from antihypertensive drug therapy in addition to lifestyle changes[76].

The physical examination aims to establish the diagnosis of hypertension and screen for target-organ damage and secondary causes (BOX 2). The patient should sit quietly for 5 minutes before a BP reading is taken, and the BP cuff should be at heart level. An average of 2–3 BP measurements obtained on 2–3 separate occasions provides an accurate basis for estimation of BP[77,78]. At least once, BP should be measured on both arms, and differences in systolic BP of >20 mmHg and/or in diastolic BP of >10 mmHg should initiate investigations of vascular abnormalities[77]. Careful attention should be paid to choosing an appropriately sized cuff, particularly for the increasing number of patients with obesity.

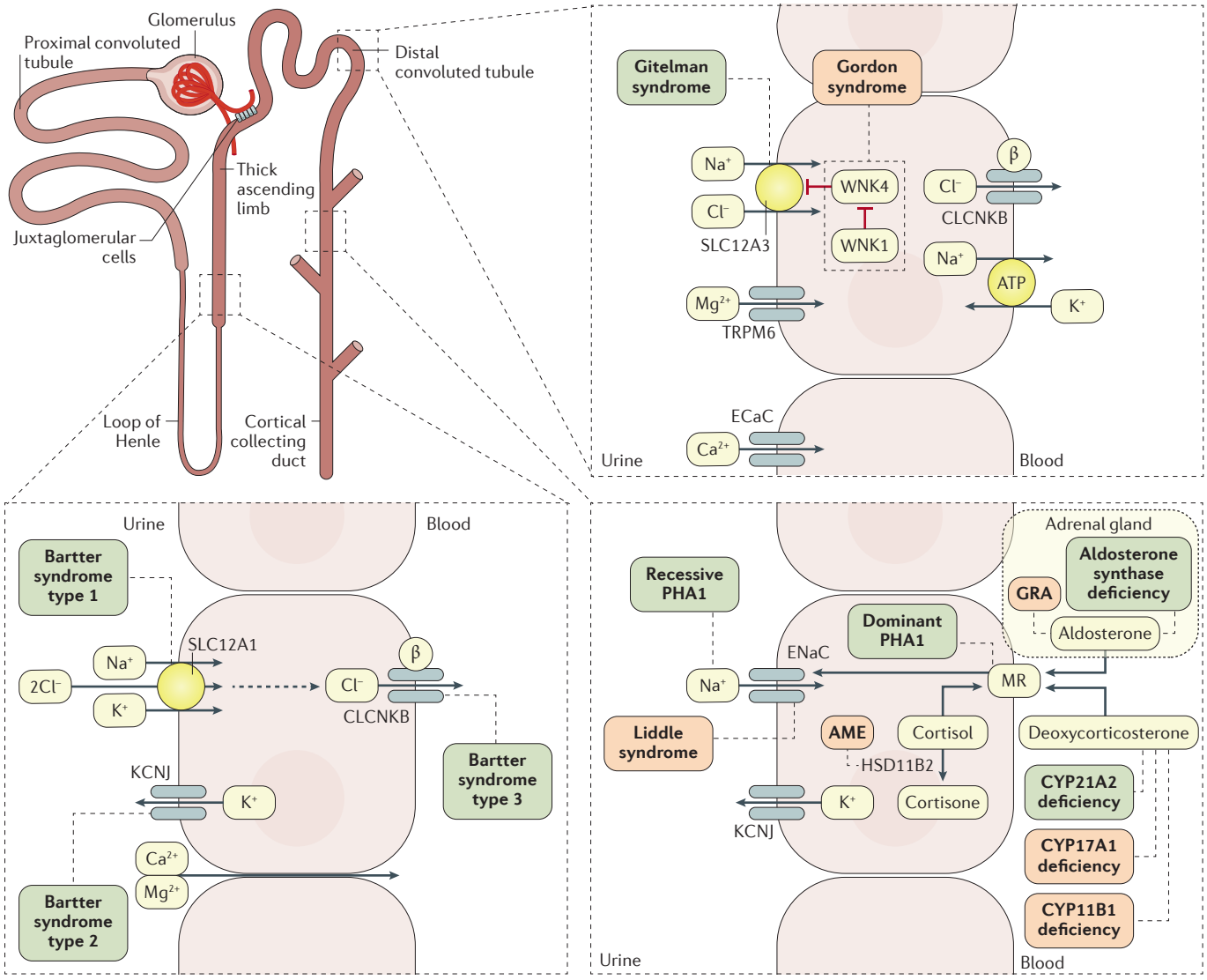

Figure 4 | **Pathways affected in single gene, Mendelian hypertension and hypotension syndromes.** Some inherited diseases can affect the renal–angiotensin–aldosterone system pathways and, therefore, blood pressure (BP); hypertensive disorders are listed in orange boxes and hypotensive disorders in green boxes. AME, apparent mineralocorticoid excess; Ca^{2+}, calcium; Cl^-, chloride; CLCNKB, chloride channel protein ClC-Kb; CYP11B1, cytochrome P450 11B1, mitochondrial; CYP17A1, steroid 17-α-hydroxylase/17,20 lyase; CYP21A2, steroid 21-hydroxylase; ECaC, epithelial calcium channel; ENaC; epithelial sodium channel; GRA, glucocorticoid-remediable aldosteronism; HSD11B2, corticosteroid 11-β-dehydrogenase isozyme 2; K^+, potassium; KCNJ, inward rectifier potassium channel; Mg^{2+}, magnesium; MR, mineralocorticoid receptor; Na^+, sodium; PHA1, pseudohypoaldosteronism, type 1; SLC12A1, solute carrier family 12 member 1; SLC12A3, solute carrier family 12 member 3; TRPM6, transient receptor potential cation channel subfamily M member 6; WNK1, serine/threonine-protein kinase WNK1; WNK4, serine/threonine-protein kinase WNK4. Adapted with permission from REF. 7, LWW.

Box 2 | **Physical examination for patients with hypertension**

Signs suggestive of secondary hypertension

- Features of Cushing syndrome
- Neurofibromatosis (pheochromocytoma)
- Enlarged kidneys (polycystic kidney)
- Abdominal bruits (abnormal sound) (renovascular hypertension)
- Precordial murmurs (sounds audible via the stethoscope) (aortic coarctation and aortic disease)

Signs of target-organ damage

- Brain: motor or sensory deficit
- Retina: hypertensive retinopathy
- Heart: atrial fibrillation, arrhythmias, pulmonary congestion and peripheral oedema
- Peripheral arteries: absent, reduced or asymmetrical pulses and ischaemic skin lesions
- Carotid arteries: murmurs

Evidence of obesity

- BMI (body weight/height^2) of >30 kg/m^2
- Waist circumference* of >102 cm in men and of >88 cm in women

BMI, body mass index. *Values might need to be adjusted on the basis of ethnicity or other factors.

Further, BP should be measured in both sitting and standing positions to rule out orthostatic hypotension (a sudden drop in the BP when a person stands up from a lying or sitting position). This is particularly important in elderly individuals.

All patients should undergo auscultation of the carotid arteries, heart and renal arteries. Detection of murmurs (sounds audible via the stethoscope) should lead to further investigations, including carotid ultrasonography, echocardiography and renal ultrasonography. An irregular pulse frequently indicates atrial fibrillation, which should be confirmed by an electrocardiogram (EKG). Laboratory investigations are used to detect additional risk factors, to confirm or exclude secondary hypertension, to detect clinical or subclinical target-organ damage and to estimate global CVD risk (BOX 3).

Screening. Despite overwhelming evidence that hypertension is a major treatable CVD risk factor, studies across the world show that a large proportion of individuals with hypertension are either unaware of their high BP or aware but not treated or inadequately treated[15,79]. Thus, there is a strong indication to screen middle-aged or younger persons to detect and treat more patients with hypertension. The most serious attempt by a health care system to improve the diagnostic aspects of hypertension has been done in the United Kingdom, based on the pay-for-performance principle, that is, to give incentives to general practitioners (primary care physicians) for the appropriate diagnosis and treatment of chronic diseases, including hypertension. Early reports[80,81] showed that this initiative was associated with an increased rate of BP monitoring and better BP control, but a later report suggested that this was not a sustained improvement[82]. It is possible that the initiative championed by the International Society of Hypertension (ISH) and many national societies, which targeted entire populations by screening for hypertension in public places over the entire month of May 2017, might have better and more-sustained results[83].

Prevention

The association between BP and CVD risk highlights the importance of treating hypertension, especially when severe. Further, it also underscores the importance of strategies to reduce BP-related CVD risk in those whose BP level is higher than normal (average systolic BP 120–129 mmHg) but below the hypertension threshold. Reducing BP in adults with a high normal BP (referred to as elevated BP in the 2017 ACC/AHA BP Guideline) provides the potential to directly reduce CVD risk and to prevent or at least slow the age-related tendency for individuals to develop hypertension.

In most countries, there is a strong tendency for BP, especially systolic BP, and the prevalence of hypertension to increase progressively from childhood until late in life[79]. However, studies in isolated societies that have limited contact with the outside world[84,85] indicate that high BP is not an inevitable consequence of ageing and that the rise in BP associated with local migration by members of isolated societies is related to changes in diet, decreased physical activity and consumption of alcohol[84,86,87]. These reports underscore the logic of efforts to prevent high BP in settings where an age-related increase in BP is common.

Lifestyle changes. A variety of nonpharmacological interventions are effective in lowering BP and preventing hypertension. The most effective interventions are weight loss[88–90], reduced sodium intake[88–91], increased potassium intake[92,93], increased physical activity[94], reduced consumption of alcohol[95,96] and diets, such as the dietary approaches to stop hypertension (DASH) diet[97], that combine several elements that favourably affect BP[98,99] (TABLE 3). The DASH diet is especially successful when combined with other effective BP-lowering interventions, such as a reduced intake of dietary sodium[91]. Lifestyle changes are the best way for the individual to implement these interventions. Even small improvements in an individual's lifestyle can be valuable. The websites of several government agencies and professional societies provide helpful tips for lifestyle changes and monitoring of BP. Careful monitoring of BP is essential because the beneficial effects of lifestyle changes are predicated on maintenance of the intervention[100].

Two complementary strategies aimed at achieving a small population-wide reduction in BP or a larger reduction in those who are at higher risk of developing hypertension can be employed to implement hypertension prevention interventions[98,99,101]. Modelling studies suggest that a downward shift of as little as 2 mmHg in the population distribution of diastolic BP would result in a 17% reduction in the incidence of hypertension, a 14% reduction in the risk of stroke and transient ischaemic attacks and a 6% reduction in the risk of coronary heart disease[102]. Public health interventions focused on dietary improvements and increases

Box 3 | **Laboratory investigations in the diagnosis of hypertension**

Routine tests

- Haemoglobin and haematocrit
- Fasting plasma glucose
- Serum total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol
- Fasting serum triglycerides
- Serum potassium and sodium
- Serum uric acid
- Serum creatinine
- Estimated glomerular filtration rate (eGFR)
- Urine analysis including a test for microalbuminuria
- 12-lead electrocardiogram (EKG)

Additional tests based on history, clinical examination and routine tests

- Haemoglobin A_{1c}
- Quantitative proteinuria
- Out-of-office BP measurements*
- Echocardiography
- Holter monitoring
- Carotid ultrasonography
- Abdominal ultrasonography
- Pulse wave velocity
- Ankle-brachial index
- Further specialist tests for secondary hypertension (renin, aldosterone, catecholamines and their metabolites)

*Ambulatory blood pressure (BP) monitoring (ABPM) is the preferred method for measurement of out-of-office BP to confirm high BP and to diagnose masked hypertension. Careful home BP monitoring (HBPM) is acceptable when ABPM is not feasible.

in physical activity that are known to lower BP provide the basis for population-wide strategies. Diet in the general population can be favourably influenced by means of public health education campaigns, food products labelling and collaborations with food manufacturers to reduce the calorie and sodium content of their products, as well as with fast-food companies and restaurants to reduce portion size and to promote healthier food preparation and promotion practices. Physical activity can be increased by making it easier for members of the community to engage in exercise on a routine basis.

Pharmacological interventions. Low-dose pharmacological therapy has also been effective in lowering BP and preventing hypertension in three randomized controlled trials conducted in adults with high normal BP[103–105]. The Brazilian multicentre PREVER-Prevention Trial compared treatment with the low-dose, long-acting, thiazide-like diuretic chlorthalidone in combination with the potassium-sparing agent amiloride with placebo treatment[105]. Treatment with the low-dose chlorthalidone and amiloride combination resulted in both a decrement in BP and prevention of hypertension and a reduction in left ventricular mass. Although a drug intervention is easier to implement and to maintain than a lifestyle change intervention, there is a natural reluctance to recommend a lifetime of pharmaceutical therapy for the prevention of hypertension. Consideration of low-dose pharmacotherapy should be restricted to those who are at high risk of developing hypertension despite energetic efforts to lower BP by means of one or more nonpharmacological interventions[105].

Management

BP treatment thresholds and targets

Until 2015, most guidelines recommended a target BP of <140/90 mmHg for most patients and of <150/90 mmHg for elderly patients (defined as of >60 years of age or of >80 years of age)[77,106] (TABLE 4). However, after the publication of the results of the Systolic Blood Pressure Intervention Trial (SPRINT)[107], target systolic BP values have been frequently debated. SPRINT was a randomized, open-label, controlled trial that enrolled 9,361 participants without diabetes mellitus but with increased CVD risk. Patients with a history of stroke were excluded. Participants were randomized to a standard systolic BP target of <140 mmHg or intensive systolic BP target of <120 mmHg. Intensive BP treatment in SPRINT resulted in a significantly greater (25%) reduction in the primary end point (first occurrence of myocardial infarction, acute coronary syndrome, stroke or heart failure or death from cardiovascular causes) compared with standard treatment. Office BP measurement in SPRINT was performed with an automated device timed to start measurement after 5 minutes of rest in an effort to standardize measurements in the various clinics and to minimize the white-coat effect[108]. Because large differences had been observed between automated office BP measurement and conventional auscultatory measurements (with the automated technique showing lower values)[109], some groups have questioned the applicability of the SPRINT intensive systolic BP target of <120 mmHg to ordinary office practice[110]. Both the appropriate methods of measuring office BP (automated versus manual; unattended versus attended) and the appropriate BP targets for antihypertensive treatment are currently topics of vigorous debate. In summary, newer guidelines published after SPRINT generally have more-aggressive goals, at least for individuals at high CVD risk (TABLE 4).

The patient's global CVD risk and comorbidities should be considered in determining the need for pharmacological antihypertensive treatment. The 2017 US ACC/AHA BP Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults[111] recommends the use of antihypertensive medication in patients with pre-existing CVD and those without a CVD event but an estimated 10-year ASCVD risk of ≥10% at BP levels of ≥130/80 mmHg. In individuals without CVD and with 10-year ASCVD risk of <10%, antihypertensive medication should be initiated at BP of ≥140/90 mmHg. (FIG. 5; TABLE 4).

Nonpharmacological management

Lifestyle advice is recommended for all patients with hypertension. The most effective interventions are the same as those used for the prevention of hypertension. Targeted dietary approaches can reduce the systolic BP in individuals with hypertension. For example, reducing

sodium intake (ideally to <2.3 g per day or <1.5 g per day in those most susceptible to the effects of sodium on BP, but reduction by at least 1.0 g per day is desirable) can lower the systolic BP by 2–4 mmHg (REFS 111–113). A similar reduction can be expected by increasing potassium intake to 3.5–5.0 g per day[92].

Reduced salt intake. For metabolic balance, the amount of salt consumed must be equal to that lost. Thus, under normal living conditions and physical activity levels, an intake of 5 g of salt per day is considered sufficient, in line with the WHO recommendation (<5 g per day)[114]. By contrast, the currently estimated dietary intake of salt is about 9–12 g per day in most countries. The current recommendations of the American Heart Association (AHA)[115] are stricter than the European guidelines, recommending lowering salt intake to 2.3 g per day, whereas the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommend 5–6 g of salt per day[77].

Randomized controlled trials carried out in persons with hypertension have consistently shown that reduced sodium intake is associated with BP reduction[116]. The most convincing evidence is provided by the DASH-sodium trial[91], in which the effects of three different sodium intakes were tested separately in combination with two diets: the DASH diet, which is rich in fruit, vegetables and low-fat dairy products and reduced in saturated fat and cholesterol, and a control diet consisting of what many people in the United States typically eat. Reduction of sodium intake by ~0.9 g per day induced a greater BP reduction when the starting sodium intake was <2.3 g per day, which corresponds to ~6.0 g of salt per day. Of note, sodium reduction reduced BP in individuals without hypertension on both diets. Reduced sodium intake can also prevent hypertension (relative risk reduction of ~20% with or without concomitant weight loss)[90], improve hypertension control[117] and, therefore, possibly reduce the need for antihypertensive medication[100]. In the Intersalt

Table 2 | **Diagnostics of secondary hypertension**

Possible causes	Clinical indications			Diagnostics	
	Clinical history	Physical examination	Laboratory investigations	First-line tests	Additional confirmatory tests
Common causes					
Renal parenchymal disease	• History of urinary tract infection or obstruction, haematuria (blood in the urine) or analgesic abuse • Family history of polycystic kidney disease	Abdominal masses (in case of polycystic kidney disease)	• Presence of protein, erythrocytes or leukocytes in the urine • Decreased GFR	Renal ultrasonography	Detailed workup for kidney disease
Renal artery stenosis	• Fibromuscular dysplasia: early-onset hypertension (especially in women) • Atherosclerotic stenosis: hypertension of abrupt onset, worsening or increasingly difficult to treat or flash pulmonary oedema	Abdominal bruit (abnormal sound)	• Difference of >1.5 cm in length between the two kidneys (renal ultrasonography) • Rapid deterioration in renal function (spontaneous or in response to RAAS blockers)	Renal duplex Doppler ultrasonography	• Magnetic resonance angiography • Spiral CT • Intra-arterial digital subtraction angiography
Primary aldosteronism	• Muscle weakness • Family history of early-onset hypertension and cerebrovascular events at <40 years of age	Arrhythmias (in case of severe hypokalaemia)	• Hypokalaemia (spontaneous or diuretic-induced) • Incidental discovery of adrenal masses	Aldosterone:renin ratio under standardized conditions (corrected hypokalaemia and withdrawal of drugs affecting the RAAS)	• Confirmatory tests (oral sodium loading, saline infusion, fludrocortisone suppression or captopril test) • Adrenal CT scan • Adrenal vein sampling
Uncommon causes					
Pheochromocytoma	• Paroxysmal hypertension or a crisis superimposed to sustained hypertension • Headache, sweating, palpitations and pallor • Positive family history of pheochromocytoma	Skin stigmata of neurofibromatosis (café-au-lait spots and neurofibromas)	Incidental discovery of adrenal (or, in some cases, extra-adrenal) masses	Measurement of urinary fractionated metanephrines or plasma-free metanephrines	• CT or MRI of the abdomen and pelvis • ^{123}I-labelled meta-iodobenzyl-guanidine scanning • Genetic screening for pathogenetic mutations
Cushing syndrome	• Rapid weight gain • Polyuria (excessive production of urine) • Polydipsia (excessive thirst) • Psychological disturbances	Typical body habitus (central obesity, moon-face, buffalo hump, red striae (stretch marks) and hirsutism)	Hyperglycaemia	24 h urinary cortisol excretion	Dexamethasone-suppression test

GFR, glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system. Modified from REF. 77.

Table 3 | **Dietary approaches to stop hypertension (DASH) eating plan**

Food group	Servings*	Examples of a serving
Whole grains	6–8 per day	1 slice of whole grain bread
Vegetables	4–5 per day	1 cup of raw leafy vegetables
Fruits	4–5 per day	1 medium-sized fruit
Dairy products (low-fat or fat-free)	2–3 per day	1 cup of milk or yogurt
Fats and oils	2–3 per day	• 1 teaspoon of margarine or vegetable oil or • 1 tablespoon of mayonnaise or • 2 tablespoons of salad dressing
Lean meat, poultry and fish	2–3 per day	2 ounces of cooked meats, chicken or fish
Nuts, seeds and legumes	4–5 per week	• 1/3 cup of nuts or • 2 tablespoons of peanut butter or • 2 tablespoons of seeds or • 1/2 cup of cooked peas or beans
Candy and added sugars	≤5 per week	• 1 tablespoon of sugar, jelly or jam or • 1 cup of lemonade

*Recommended frequency of servings for a 2,000-calorie-per-day diet.

study[118], lower sodium intake was associated with a blunted age-related rise in systolic BP.

There is strong evidence to support population-wide recommendations to lower salt intake[119,120]. As more than 75% of dietary salt comes from processed foods (in Western countries), any population strategy to reduce salt intake must involve food manufacturers and restaurants to progressively reduce salt added to foods. So far, only three countries (Japan, Finland and the United Kingdom) have successfully reduced population salt intake[121].

Increased potassium intake. Healthy individuals with normal kidney function usually have a potassium intake of 4.7 g per day; a higher intake is not associated with increased risk because potassium is readily excreted in persons who do not have CKD. Increased potassium intake is associated with reduced BP in individuals with low as well as high baseline potassium intake[92,93]. Of note, potassium reduces BP to a greater extent in black individuals than in white individuals[122]. The effect of potassium on BP is dependent on salt intake. There is a greater BP reduction with increased potassium intake in the context of lower salt intake[123]. Thus, the best strategy is to increase potassium intake and reduce sodium intake at the same time. The preferred strategy to increase potassium intake is to increase consumption of fruits and vegetables that are rich in potassium rather than using supplements. In individuals with impaired urinary potassium excretion, a potassium intake of <4.7 g per day is recommended[124].

Moderate alcohol consumption. Keeping alcohol intake ≤2 standard drinks (~3.5 alcohol units) per day for men and ≤1 standard drink (~1.75 alcohol units) per day for women can also contribute to a 2–4 mmHg BP reduction[95,96].

Physical activity. Regular physical activity reduces BP in individuals with hypertension. Endurance training (aerobic exercise) reduces BP more in persons with hypertension than in individuals with normal BP. A narrative review of 27 randomized clinical trials in individuals with hypertension showed that regular medium-intensity to high-intensity aerobic activity reduced BP by a mean of 11/5 mmHg (REF. 125). Sessions lasting 40–60 minutes performed at least three times a week had the greatest effect on BP. Three randomized controlled trials of isometric exercise (strength training) showed a BP reduction of similar magnitude to that induced by aerobic exercise in individuals with hypertension[125]. A meta-analysis of 64 controlled studies of the efficacy of dynamic resistance training (strength training) as stand-alone antihypertensive therapy showed BP reductions comparable to or greater than those achieved with aerobic exercise training[126]. Greater BP reductions occurred in individuals with higher resting BP (~6/5 mmHg for individuals with hypertension and 3/3 mmHg for individuals with prehypertension) and in non-white individuals[126].

Weight loss. Excess adiposity generally raises BP in susceptible individuals, and patients with hypertension who also have obesity require more antihypertensive medications to control their BP and are more likely to be resistant to treatment[127]. A meta-analysis showed that any reduction in body weight lowered systolic BP by an average of 2.7 mmHg and diastolic BP by an average of 1.3 mmHg (REF. 128). However, the response varies substantially between individuals. Lifestyle interventions, including hypocaloric diets and physical exercise, are commonly recommended for patients with obesity and hypertension; however, the average weight loss is modest, and most patients regain weight[129] (BOX 4).

Antihypertensive pharmacotherapy

Antihypertensive pharmacotherapy has evolved over several decades, driven by the development of various antihypertensive medication classes and large-scale outcome trials proving their benefits on CVD morbidity and mortality[130]. Clinicians are now faced with a plethora of antihypertensive medications of different drug classes and a variety of fixed-dose combinations. Typically, antihypertensive pharmacotherapy begins with first-line antihypertensive medications either in monotherapy or in combination[131]. Combination therapy might be preferable in patients with higher levels of pretreatment BP. First-line antihypertensive medications include ACE inhibitors, angiotensin II receptor blockers (also known as sartans), dihydropyridine calcium-channel blockers and thiazide diuretics[106]. β-Adrenoreceptor blockers are also indicated in patients with heart failure with reduced left ventricular ejection fraction or post-myocardial infarction, and some guidelines recommend β-adrenoreceptor blockers as first-line antihypertensive medications[77,132]. The choice should be based on individual efficacy and tolerability. Ethnicity affects the response to antihypertensive medications, and it has been suggested that calcium-channel blockers and diuretics are the first choice in black individuals[106,133]. Further, in specific clinical situations, for example, hypertension in pregnant women, other medications such as α-methyldopa (an agonist of α-adrenoreceptors in the central nervous system

that inhibits the SNS) or labetalol (an α-β-adrenergic antagonist) are preferable, whereas some first-line antihypertensives, for example, ACE inhibitors and angiotensin II receptor blockers, are contraindicated because of increased risk of renal teratogenicity. Divided dosing of antihypertensive drugs tends to decrease adherence and should be avoided when possible[134].

BP cannot be controlled with monotherapy in many patients, particularly those with severe hypertension. When combining antihypertensive medications, it is important to consider whether the drugs have additive effects on BP or adverse effects and whether the patient has comorbidities that mandate particular drug choices[77]. ACE inhibitors or angiotensin II receptor

Table 4 | **Blood pressure targets recommended by various guidelines**

Guideline	Population	Goal BP (mmHg)
2010 Chinese guidelines[207]	Adults <65 years	<140/90
	Adults ≥65 years	<150/90 (<140/90 if tolerated)
	Adults with diabetes mellitus, CHD or renal disease	<130/80
2013 ESH/ESC[77]	Non-frail adults <80 years	<140/90
	Adults >80 years	<150/90
	Adults with diabetes mellitus	<140/85
	Adults with CKD without proteinuria	<140/90
	Adults with CKD with overt proteinuria	<130/90
	Adults with CHD	<140/90
2013 ASH and ISH*[208]	Adults 55–80 years	<140/90
	Young adults	<130/80
	Adults >80 years	<150/90
2014 Hypertension guideline[106] (formerly known as JNC 8)	Adults <60 years	<140/90
	Adults ≥60 years	<150/90
	Adults with diabetes mellitus	<140/90
	Adults with CKD	<140/90
2014 South African guidelines[209]	Most adults	<140/90
	Adults >80 years	140–150‡
2014 JSH[210]	Most adults	<140/90
	Patients 75–89 years	<150/90 (<140/90 if tolerated)
	Adults with diabetes mellitus or CKD	<130/80
	Adults with CHD or CVD	<140/90
2016 CHEP[211]	Adults <80 years	<140/90
	Adults ≥80 years	<150‡
	High-risk adults ≥50 years	≤120‡§
2016 Australian guidelines[212]	Adults at high CVD risk without diabetes mellitus, including patients with CKD and those >75 years	<120‡
	Adults with diabetes mellitus in whom prevention of stroke is a priority	<120‡
2017 ADA[213]	Adults with diabetes mellitus	<140/90
	Adults with diabetes mellitus and high CVD risk	<130/80
2017 ACC/AHA BP Guideline[111]	Adults with known CVD or 10-year ASCVD event risk of ≥10%	<130/80
	Adults with no clinical CVD and 10-year ASCVD risk of < 10%	<130/80
	Adults of ≥65 years of age, noninstitutionalized and ambulatory	<130‡
	Adults of ≥65 years of age, with comorbidities and limited life expectancy	Individualized goal based on clinical judgement and patient preference

ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ASH, American Society of Hypertension; BP, blood pressure; CHD, coronary heart disease; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISH, International Society of Hypertension; JNC 8, Eighth Joint National Committee; JSH, Japanese Society of Hypertension. *The 2013 ASH and ISH guidelines were written to provide information for practitioners in low-income and middle-income countries as well as in developed countries. ‡Systolic blood pressure. §Should be guided by automated office BP measurement.

blockers, thiazide diuretics and dihydropyridine calcium-channel blockers are additive in lowering BP and can be combined as double or triple combination therapies. By contrast, combining ACE inhibitors and angiotensin II receptor blockers adds little BP-lowering effects while increasing the risk of renal dysfunction and hyperkalaemia (high blood potassium levels, which can lead to cardiac arrhythmias). Similarly, combining RAAS inhibitors with β-adrenoreceptor blockers adds little BP reduction, but this combination is indicated in patients following acute myocardial infarction or heart failure with reduced left ventricular ejection fraction for reasons beyond BP reduction.

ACE inhibitors and angiotensin II receptor blockers. Among medications that inhibit components of the RAAS, ACE inhibitors and angiotensin II receptor blockers are considered first-line antihypertensives, whereas other antihypertensive medications targeting the RAAS, including direct renin inhibitors and mineralocorticoid receptor antagonists, are usually considered reserve medications because there is less clinical trial evidence supporting their use as first-line antihypertensive therapy. ACE inhibitors and angiotensin II receptor blockers have been tested extensively in large-scale hypertension trials[135]. In patients with heart failure with reduced left ventricular ejection fraction or with diabetic nephropathy, both drug classes improved outcomes, making them particularly good choices in these populations. Both classes seem to be comparable in reducing CVD risk[136] and tend to improve glucose metabolism and, therefore, could be preferable in younger patients and in patients with conditions predisposing to type 2 diabetes mellitus, including obesity and the metabolic syndrome[137]. ACE inhibitors are generally well tolerated, but reductions in kidney function, hyperkalaemia, cough and — less commonly — angioedema (swelling caused by fluid accumulation) could occur with their use. The risk of angioedema, which can be life threatening, is substantially increased in black individuals[138] as well as in patients treated with both ACE inhibitors and dipeptidyl peptidase 4 inhibitors (used in the treatment of diabetes mellitus, examples of which include sitagliptin, vildagliptin, saxagliptin and linagliptin)[139]. ACE inhibitors that can be dosed once daily are preferred. Angiotensin II receptor blockers can also elicit hyperkalaemia and worsening of kidney function but do not usually cause cough or angioedema[136].

Dihydropyridine calcium-channel blockers. Dihydropyridine calcium-channel blockers elicit vasodilation by blocking vascular smooth muscle L-type calcium channels. They are effective antihypertensive drugs with

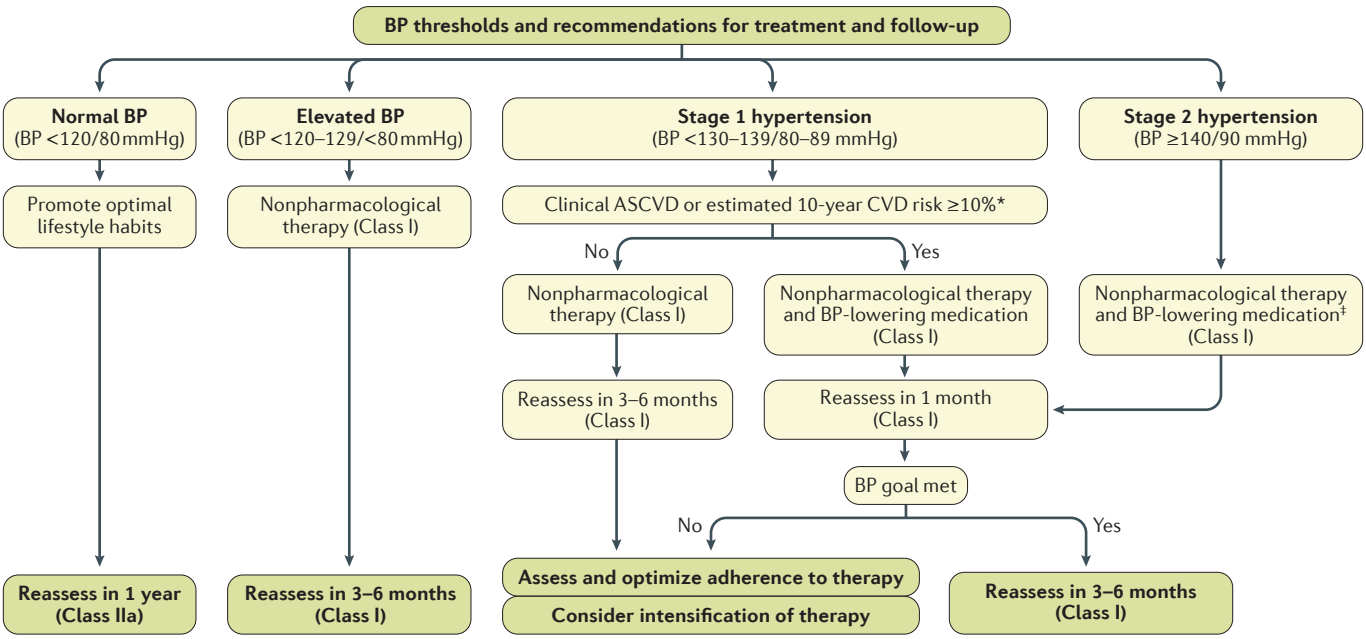

Figure 5 | **Algorithm for the management of hypertension.** Guidelines for the treatment of hypertension. ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease. *Using the American College of Cardiology–American Heart Association Pooled Cohort Equations. Note that patients with diabetes mellitus or chronic kidney disease are automatically placed in the high-risk category. For the initiation of renin–angiotensin–aldosterone system inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2–4 weeks after initiating therapy. ‡Consider initiation of pharmacological therapy for stage 2 hypertension with two antihypertensive agents of different classes. Patients with stage 2 hypertension and blood pressure (BP) of ≥160/100 mmHg should be promptly treated, carefully monitored and receive upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (for example, elderly individuals or those with postural symptoms), identification of white-coat hypertension or a white-coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment and assistance with treatment to achieve BP target. Class of recommendation: Class I, strong; Class IIa, moderate. Reprinted with permission *Hypertension*. 2017;HYP.0000000000000065 © 2017 American Heart Association, Inc. (REF. 111).

extensive experience in large clinical trials[135]. A practical advantage of this drug class is that it can be combined with all other first-line antihypertensive drugs. Peripheral oedema, which is explained by peripheral arterial vasodilation rather than worsening heart failure or kidney dysfunction, is a common adverse effect, particularly in individuals with obesity. Non-dihydropyridine calcium-channel blockers, especially verapamil, also inhibit cardiac calcium channels, an effect that can reduce heart rate and cardiac contractility[140]. Calcium-channel blockers can induce or worsen constipation, especially in institutionalized older persons[141]. All calcium-channel blockers modestly inhibit the drug metabolizing enzyme cytochrome P450 3A4 and, therefore, could elicit important drug–drug interactions[142].

Thiazide-type and thiazide-like diuretics. Thiazide-type diuretics (for example, hydrochlorothiazide) have a benzothiadiazine ring, whereas thiazide-like diuretics (for example, chlorthalidone, metolazone and indapamide) lack the benzothiadiazine structure. Both subclasses of thiazide diuretics inhibit sodium and chloride co-transporters in renal tubules, thereby promoting natriuresis, and have been an important component of pharmacological hypertension management ever since the first trials showing morbidity benefits of antihypertensive therapy[143]. Over the years, diuretic doses have been substantially reduced to attain better risk–benefit profiles. Thiazide-type and thiazide-like diuretics can worsen glucose metabolism, increasing the risk of new-onset diabetes mellitus, but whether or not this metabolic action translates into long-term increases in CVD risk has been called into question[144]. Hydrochlorothiazide, the most commonly prescribed thiazide-type diuretic worldwide, might be less effective in mitigating CVD risk compared with chlorthalidone or indapamide[145,146]. Drug-related electrolyte disturbances, including hypokalaemia and hyponatraemia (low blood potassium and sodium levels, respectively), are particularly important adverse effects; hypokalaemia can lead to cardiac arrhythmias and muscle weakness, and hyponatraemia can cause confusion, seizures and coma. The risk of hypokalaemia is reduced when thiazide-type and thiazide-like diuretics are combined with potassium supplements or potassium-sparing agents, such as ACE inhibitors, angiotensin II receptor blockers or potassium-sparing diuretics. Hyponatraemia is a potentially life-threatening adverse effect, particularly in elderly persons.

β-Adrenoreceptor blockers. β-Adrenoreceptor blockers lower BP by reducing cardiac output, heart rate, renin release and SNS activity[147]. They improve outcomes following acute myocardial infarction and in patients with heart failure with reduced left ventricular ejection fraction; however, in the absence of these comorbidities, β-adrenoreceptor blockers are inferior to other first-line antihypertensives in reducing CVD morbidity and mortality[148]. This effect has been attributed to lesser reductions in aortic BP[149] and adverse effects on body weight[150] and on glucose metabolism with β-adrenoreceptor blockade. Some of these disadvantages might be mitigated with newer vasodilator β-adrenoreceptor blockers, such as nebivolol and carvedilol[151]. However, there are no large-scale antihypertensive trials demonstrating that this difference translates into better clinical outcomes. β-Adrenoreceptor blockers might promote bronchial obstruction in patients with asthma and should not be combined with non-dihydropyridine calcium-channel blockers (such as verapamil) that also lower sinus node rate or atrioventricular conduction.

Newer pharmacological agents. Overall, the interest of the pharmaceutical industry in developing new antihypertensive medications has been limited in recent years. Moreover, most antihypertensive drugs are out of patent and, therefore, available as relatively inexpensive generics. Further, some of the currently approved drugs, such as angiotensin II receptor blockers, have placebo-like tolerability. Newer pharmacological agents approved for other indications, including combined angiotensin II receptor and neprilysin inhibitors[152] (for heart failure), soluble guanylyl cyclase modulating drugs[153] (for pulmonary hypertension) and sodium-glucose cotransporter 2 (encoded by *SLC5A2,* also known as *SGLT2*) inhibitors[154] (for type 2 diabetes mellitus), could also be useful in treating hypertension. Other pharmacological agents, such as newer mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, activators of the ACE2–angiotensin (1–7)–MAS receptor axis and natriuretic peptide receptor agonists, are in various stages of preclinical or clinical development[155], often for indications other than hypertension. Drugs addressing novel pressor mechanisms could be useful in patients with treatment-resistant hypertension, particularly those not responding to or not tolerating mineralocorticoid receptor antagonists.

Box 4 | **Hypertension and obesity**

Weight loss is recommended for individuals with obesity and can be particularly important if these patients also have hypertension. Medications have been developed for the treatment of obesity, but their approval status differs between the United States and Europe: some drugs are only approved in the United States (for example, lorcaserin and phentermine/topiramate), whereas others are approved only in Europe. Blood pressure (BP) reductions in patients with hypertension have been reported for some weight loss medications[199], but their specific pharmacological actions might attenuate the positive influences of weight loss on BP and cardiovascular disease outcomes[200]. Bariatric surgery is very effective in reducing body weight, and the risk of hypertension is substantially reduced up to 5 years following bariatric surgery[201]. However, large and sustained body weight reductions are needed to substantially reduce BP following bariatric surgery[202], and there are no large clinical trials specifically testing the effects of weight loss medications or bariatric surgery on hypertension control.

Moreover, drugs with actions in addition to BP reduction could prove clinically useful. For example, combined angiotensin II receptor blockade and neprilysin inhibition has been shown to ameliorate insulin resistance in patients with obesity and hypertension[156] and decrease the progression to type 2 diabetes mellitus in patients with heart failure[157].

Treatment-resistant hypertension

Treatment-resistant hypertension is commonly diagnosed when office BP is >140/90 mmHg, despite treatment with ≥3 properly dosed antihypertensive drugs, including a diuretic, and secondary hypertension has been ruled out[158]. Poor treatment adherence is a common cause of apparent treatment-resistant hypertension. The true prevalence of treatment-resistant hypertension is unknown, but an estimated 12.8% of all individuals with hypertension in the United States and 15.3% of those treated with antihypertensive drugs fulfil the criteria for treatment-resistant hypertension[159]. Adding a fourth or fifth drug to the treatment regimen could lead to satisfactory BP control in these patients. The PATHWAY trial rotated patients with treatment-resistant hypertension through different add-on drugs or placebo in a randomized fashion[160]. All patients received a standardized antihypertensive regimen comprising three drugs, including a diuretic. Compared with α-adrenoreceptor or β-adrenoreceptor blockade, the mineralocorticoid receptor antagonist spironolactone was the most effective fourth antihypertensive drug. In another study in patients whose BP was uncontrolled despite receiving three drugs, sequential addition of a mineralocorticoid receptor antagonist followed by a loop diuretic (which acts at the ascending limb of the loop of Henle in the kidney) was more effective than adding an ACE inhibitor followed by a β-adrenoreceptor blocker[161]. Overall, mineralocorticoid receptor antagonism is a reasonable choice in patients with difficult-to-control hypertension. Given the risk of inducing hyperkalaemia[162], serum potassium concentrations should be monitored.

Device-based treatments. Device-based treatments have been primarily developed for patients with severe resistant hypertension whose BP cannot be controlled with antihypertensive drugs[155]. Catheter-based renal nerve ablation[163,164], electrical carotid sinus stimulation[165,166], modulation of baroreflex transduction with a dedicated carotid stent[167], carotid body denervation[168] and deep-brain stimulation[169] are thought to lower BP through SNS inhibition. Creation of a defined arteriovenous stent with a coupler device lowers BP by reducing peripheral vascular resistance[170]. These treatments are in various stages of clinical development, with the most extensive data available on renal nerve ablation and electrical carotid sinus stimulation. No treatment has yet been proved efficacious in lowering BP in randomized sham-controlled clinical trials[164,166], because either the primary end point was not achieved or no trials have been conducted. Finally, trials with hard clinical end points do not exist.

Quality of life

Health-related quality of life (HRQOL) is a multidimensional concept that includes domains related to physical, mental, emotional and social functioning; studies demonstrate that each additional disease, as well as the severity of these diseases, is associated with declines in HRQOL[171]. Population-based studies have consistently shown that being diagnosed with hypertension is associated with worsening of HRQOL even after adjusting for other comorbidities[172,173]. Altered HRQOL in persons with hypertension has been attributed to a variety of factors, including the diagnosis, treatment and effects of alterations (both elevations and reductions) in BP[172].

Labelling someone as having hypertension can result in worsening of self-perceived health status[174]. This was well demonstrated in a classic study of otherwise healthy Canadian steelworkers identified as having hypertension as part of a screening programme. In the year following diagnosis, absenteeism from work owing to illness more than tripled in those made newly aware of their hypertension, whereas it increased only slightly in those previously aware of their hypertension[175]. This finding could not be explained by hypertension treatment or BP level and was believed to be a direct consequence of people adopting a 'sick role'. These findings have been replicated in studies carried out in diverse settings and using different measures of physical and mental health[174].

Antihypertensive medication use is associated with a variety of symptoms that could lower HRQOL[176]. Observational studies showed an association between the number of antihypertensive medications prescribed and worsening of HRQOL[177]. Some classes of antihypertensive medications (for example, ACE inhibitors) are better tolerated than others (for example, β-adrenoreceptor blockers and centrally acting agents, such as α-methyldopa) and result in significantly better scores on measures of general well-being[178]. Further, small differences in HRQOL have even been reported among medications of the same class, for example, between enalapril and captopril[179]. However, clinical trials with newer antihypertensive agents have generally indicated that they are extremely well tolerated and can enhance the effects of nonpharmacological treatment on HRQOL[176,180]. In the Treatment of Mild Hypertension Study (TOMHS), the combination of lifestyle modifications with any of five different antihypertensive medication classes resulted in greater improvements in HRQOL than lifestyle modifications plus placebo[180].

Treatment-related reductions in BP could have a negative effect on HRQOL, particularly in older and more-frail patients at high risk of hypotension. Clinical trials performed in the 1990s that evaluated patients with very high baseline BP, for example, the Systolic Hypertension in the Elderly Program Trial (SHEP) and the Systolic Hypertension in Europe Trial (Syst-Eur), generally found minimal effects of BP reductions on HRQOL[181,182]. Two more-recent clinical trials have targeted lower BPs (intensive systolic BP target

Box 5 | **Outstanding research questions**

Measurement issues

- Is hypertension management improved by basing treatment strategies on unattended office blood pressure (BP) measurements, out-of-office (home or ambulatory) BP measurements or central BP measurements?
- How should BP be measured in patients with atrial fibrillation?

Treatment issues

- Should salt restriction at the population level continue to be recommended at current targets?
- To what extent should age, estimated cardiovascular disease (CVD) risk and concomitant conditions influence treatment thresholds?
- Should white-coat hypertension be treated?
- If management strategy is to be influenced by central or out-of-office BP levels, what treatment thresholds and targets should be used?
- Should reducing 24-hour and long-term BP variability be a consideration in the selection of drug treatment for optimal CVD protection?
- What combinations of antihypertensive agents give optimal CVD protection, stratified by age and ethnicity?
- What is the optimal BP treatment target stratified by age, CVD risk and concomitant disease status?
- What is the optimal management of treatment-resistant hypertension that is resistant to four agents, including spironolactone?
- If treatment thresholds are to be driven by estimated CVD risk, at what level should antihypertensive drug treatment be initiated and what other CVD protective agents should be considered?
- Is initiating drug therapy with two hypertensive agents more effective than initiating with monotherapy for optimal CVD prevention?

of <120 mmHg versus standard systolic BP target of <140 mmHg). It had been postulated that this lower BP might be expected to cause cerebral hypoperfusion, resulting in falls, dizziness and cognitive impairment[183,184,107]. In a substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, HRQOL was evaluated in 1,028 participants randomized to either intensive or standard therapy. No differences in mental function were noted between treatment groups, but intensive therapy was associated with a small, not clinically significant, decrease in physical function[184]. In SPRINT, targeting systolic BP of <120 mmHg required one additional antihypertensive medication compared with standard treatment to target systolic BP of <140 mmHg and was generally safe and well tolerated[107,185]. Compared with standard treatment, intensive treatment did not affect the perceived HRQOL of SPRINT participants, measured by patient-reported outcomes of physical and mental health, self-reported satisfaction with care and medication adherence, even when stratifying by age and comorbidities[185]. Almost 90% of participants in both treatment groups reported satisfaction with their BP care, and more than one-third described improvement in satisfaction over baseline levels.

Quality of life concerns remain an important aspect of hypertension management. SPRINT has demonstrated that with careful clinical management, lower BP can be targeted without concern of worsening physical and mental function. Clinicians must seek the optimal balance of reducing CVD morbidity and mortality while maximizing well-being for each individual patient.

Outlook

Although there is regional variability in the outlook for hypertension over the next 5 to 10 years, it is clear overall that the prevalence of hypertension and, therefore, the associated global burden attributable to hypertension will increase[186]. Global population growth and ageing will largely contribute to this increase — 1.5 billion people are expected to be affected by 2025 (REF. 187) — which will be focused in low-income and middle-income countries[186]. However, these adverse trends in disease burden will be variably offset by improvements in prevention, awareness and treatment. The size of improvements in each of these three areas will vary from nonexistent (hypertension prevention could even worsen in some parts of the world, as exposure to factors that promote raised BP increases) to substantially large and important elsewhere in the world.

Overall, prevention will probably contribute least to any improvement in BP-associated disease burden. This is because 80% of the world is in the process of developing, which hitherto has inevitably been associated with increased exposure to the main environmental determinants of raised BP, such as excess intake of calories, alcohol and salt. Food and drink industries, governments and education systems would be required to cooperate to reverse this pattern.

Implementation of preventive strategies has largely been limited to high-income countries. Despite reasonably compelling evidence to the contrary[112], recommendations that the general population should restrict salt intake have been questioned on the basis of largely suboptimal observational data[188]. Such confusion worsens an already very difficult public health challenge. Data show that only approximately half of people with hypertension are aware of their condition[189], and the Lancet Commission on hypertension identified that improving awareness of hypertension is a crucial action needed to improve the current disease burden[190,191]. The global BP awareness campaign promoted by the ISH, whereby World Hypertension Day was extended to become May Measurement Month (MMM) in 2017, could contribute substantially to improving rates of routine BP screening around the world[83]. Over 1.2 million adults (of ≥18 years of age) from >100 countries were screened as part of MMM, and the ensuing data allied to health-economic analyses will be used to persuade policymakers in each country that improved local BP screening and treatment facilities are wise financial investments.

Improving the efficacy of drug treatment also holds great promise for reducing hypertension-associated disease burden. Rather than focusing on rare secondary causes of hypertension or on the optimal management of treatment-resistant hypertension[164], the greatest effect could be achieved by the delivery and distribution of affordable, effective single-pill combinations of two or three drugs to low-income and middle-income countries where the burden of hypertension is considerable and where any such therapies are currently either largely unavailable or unaffordable[192]. Unfortunately, optimal combinations of two antihypertensive agents have not been identified for the majority of the world's

hypertensive population: no such data are available for black, South Asian or East Asian patients[193]. However, the first in a series of trials in these ethnic groups is underway in sub-Saharan Africa (N.R.P. *et al.*, unpublished data).

Meanwhile, single-pill formulations of the drug combinations most commonly recommended in current guidelines (calcium-channel blocker plus a diuretic, calcium-channel blocker plus an RAAS-blocker or diuretic plus an RAAS-blocker) are readily available and have low production costs. In addition, a three-drug combination of a calcium-channel blocker, a diuretic and an RAAS blocker[132] should also be produced for more-severe hypertension, with low-dose spironolactone available as a fourth-line agent[160]. Hence, one or two tablets will be able to control BP in all but a small proportion of patients with hypertension.

These formulations should be made available and affordable in all countries of the world[190]. Additional local obstacles to the distribution and delivery of these agents to patients with hypertension within each country will also have to be overcome — among which the lack of effective screening programmes is crucial[190].

Antihypertensive medications are prescribed by different health professionals in different countries. However, even in high-income countries, much of the routine uncomplicated hypertension management could, and probably should, be carried out by nurse practitioners or other nonphysician health workers. In more-remote parts of the world, the use of e-health-care techniques[194] should be increased to facilitate task shifting or task sharing by nonphysician health workers where doctors are unavailable[195].

In summary, although there are many interesting unanswered scientific research questions in the field of hypertension (BOX 5), perhaps the most pressing need to reduce the disease burden is to evaluate the best ways, at a local level, to screen routinely for raised BP and then to deliver the best, most affordable, evidence-based combination of antihypertensive agents. Meanwhile, efforts to drive public health policy towards encouraging more-healthy diets and lifestyles from a BP and CVD viewpoint should be encouraged, and basic scientific research that might allow precision medicine to be applied to patients with hypertension must also continue.

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Author contributions
Introduction (M.C.A. and S.O.); Epidemiology (A.R. and P.K.W.); Mechanisms/pathophysiology (G.L.B. and G.G.); Diagnosis, screening and prevention (A.F.D. and P.K.W.); Management (J.J. and R.C.); Quality of life (D.R.B.); Outlook (N.R.P.); Overview of Primer (S.O.).

Competing interests
S.O. (in the previous 24 months) has received research grant support or reimbursement for travel to meetings or other nonfinancial support from Actelion Clinical Research/George Clinical, AstraZeneca AB, Bayer, Lundbeck, Novartis, Novo Nordisk and ROX Medical, has consulted for Actelion/George Clinical, Lundbeck, Novo Nordisk and ROX Medical and has served as director and/or principal investigator for SPRINT University of Alabama at Birmingham (UAB) Clinical Center Network (CCN) and sub-investigator for the UAB CCN clinical site, for which Takeda and Arbor Pharmaceuticals donated 5% of medication used. G.L.B. served as a consultant for AbbVie, Bayer, Janssen, Merck, Relypsa and Vascular Dynamics, serves or has served as principal investigator for the FIDELIO trial (Bayer) and is a steering committee member for CALM-2-Vascular Dynamics, (CREDENCE)-Janssen and SONAR-AbbVie. G.G. has received lecture fees from Astra Zeneca and Merck. J.J. served as a consultant for Boehringer-Ingelheim, Novartis, Novo-Nordisc, Orexigen, Riemser, Sanofi, Theravance and Vivus and is cofounder of Eternygen GmbH. N.R.P. served as advisory board member (ad hoc) for Medtronic, MSD, Pfizer, Servier and Takeda (companies producing blood pressure-lowering agents and devices), received speaker honoraria from AstraZeneca, Menarini, Napi Labs and Servier, received research funding from Menarini, Pfizer and Servier, and is the president of the International Society of Hypertension. George Health Enterprises, the social enterprise arm of The George Institute for Global Health, has applied for a patent in the area of low-dose combinations on which A.R. is listed as an inventor and has received investment capital to develop fixed-dose combinations containing aspirin, statin and blood pressure-lowering drugs. A.R. is an investigator on grants for several trials of blood pressure-lowering interventions. M.C.A., D.R.B., R.C., A.F.D. and P.K.W. declare no competing interests.

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