Hypertension

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Competing interests

G.B. served as Consultant for Janssen, Bayer, AbbVie, Vascular Dynamics, Relypsa, Merck, Medtronic; served/serves as Principal Investigator for FIDELIO trial (Bayer), Steering Committee member (CREDENCE)-Janssen, SONAR-AbbVie, and CALM-2-Vascular Dynamics. J.J. served as consultant for Novartis, Novo-Nordisc, Boehringer-Ingelheim, Sanofi, Orexigen, Riemser, Theravance, Vivus; and is cofounder of Eternygen GmbH. S.O. (in the previous 24 months) has received research grant support or reimbursement for travel to meetings or other, non-financial support from Actelion Clinical Research/George Clinical; AstraZeneca AB; Bayer; Lundbeck; Novartis; Novo Nordisk; Rox Medical; has consulted for Actelion/George Clinical, Lundbeck, Novo Nordisk and ROX Medical; served as Director/Principal Investigator, SPRINT University of Alabama at Birmingham (UAB) Clinical Center Network (CCN); and sub-investigator UAB CCN clinical site; for which Takeda and Arbor Pharmaceuticals donated 5% of medication used. N.R.P. served as advisory board member (ad hoc) for Pfizer, Takeda, MSD, Servier, and Medtronic (companies producing blood pressure lowering agents/devices); received speaker honoraria from Servier, AstraZeneca, Napi Labs, and Menarini; and received research funding from Servier, Pfizer and Menarini. 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 to develop fixed-dose combinations containing aspirin, statin and BP lowering drugs. AR is an investigator on grants for several trials of blood pressure lowering interventions. M.C.A., R.C., A.F.D., G.G. and P.K.W. declare no competing interests. Editor's note: D.R.B. has chosen not to declare any competing interests, but may do so later.

Author contributions

Introduction (M.C.A., and S.O.); Epidemiology (A.R.); Mechanisms/pathophysiology (G.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.).

ABSTRACT

Systemic hypertension is the most important modifiable risk factor for all-cause morbidity and mortality worldwide. Less than half of hypertensive persons are aware of their condition, and many others are aware but not treated, or inadequately treated. Successful treatment of hypertension reduces the global burden of disease and mortality. The etiology of hypertension involves the complex interplay of pathophysiologic and environmental factors that act on a genetic background. Evaluation of patients with hypertension includes accurate standardized blood pressure (BP) measurement, assessing patients' predicted risk of atherosclerotic cardiovascular disease (ASCVD), evidence of target organ damage, detection of secondary causes of hypertension, and presence of comorbidities, including CVD and kidney disease. New paradigms for hypertension treatment consider predicted ASCVD risk rather than BP values alone, since persons at high-risk for CVD are most likely to benefit from treatment. Nonpharmacological interventions 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 preventing CVD outcomes in most persons with hypertension.

[H1] INTRODUCTION

Systemic arterial hypertension is persistently high BP in the systemic arteries. Several aetiologies can underlie hypertension. A positive family history is a frequent occurrence in hypertensive patients, with the heritability estimated to vary between 35% and 50% in the majority of studies[1,2]. Several rare, monogenic forms of hypertension have been described, e.g., the Liddle's syndrome, glucocorticoid-remediable aldosteronism and PDE 3A mutations, where a single gene mutation fully explains the pathogenesis of hypertension and dictates the best treatment modality[3,4,5]. If hypertension is caused by another condition (such as aldosteronism, pheochromocytoma or renal artery stenosis), it is referred to as secondary hypertension.

The great majority of patients suffer from a highly heterogeneous "essential" or primary hypertension with a multifactorial gene-environment etiology. Genome-wide association studies (GWAS) have identified approximately 120 loci which are associated with BP regulation and together explain 3.5% of the trait variance[6,7,8]. 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[9].

Hypertension is the most common preventable risk factor for heart failure, stroke, myocardial infarction, atrial fibrillation, chronic kidney disease (CKD), and cognitive impairment, and is the leading single contributor to all-cause death and disability worldwide. The relationship between BP and the risk of CVD is graded and continuous, with no evidence of a threshold, down to a BP of 115/75 mmHg, well within what is considered to be the normotensive range. The probability of dying from ischemic heart disease or stroke is doubled for every 20 mmHg rise in systolic BP (that is, the pressure that the blood exerts on the arterial walls when the heart contracts) or 10 mmHg elevation in diastolic BP (the pressure when the heart relaxes) in middle aged and elderly persons[10], and a systolic BP reduction of 5 mmHg in the population can decrease stroke mortality by 14% and CVD mortality by 9%. Successful prevention and treatment of hypertension are key in reducing disease burden and promoting longevity in the world's population.

BP is regulated by a complex interplay of various elements of the cardiovascular, endocrine, renal and neural systems, and compensatory mechanisms arising from elevated BP result in target organ damage, for example, left ventricular hypertrophy and CKD and CVD outcomes, such as stroke and heart failure. It is important to consider a person's predicted ASCVD risk, more than the level of BP alone, in treating hypertension, since persons with high CVD risk derive the greatest benefit from BP lowering treatment. This Primer will discuss the epidemiology and pathophysiology of hypertension, strategies for preventing and slowing the progression of BP elevation, best strategies (including optimal BP targets) for lowering BP and preventing CVD outcomes in patients with established hypertension, effects of antihypertensive treatment on quality of life, and explore knowledge gaps, future trends and outlook for hypertension research and treatment over the next decade.

[H1] EPIDEMIOLOGY

In pre-industrial societies, BP levels had narrow distributions with mean values that changed little with age and averaged around 115/75 mmHg[11], likely representing normal (or ideal) BP for our species. In most contemporary societies, systolic BP levels rise steadily and continuously with age in both men and women. This ubiquitous finding arises because age is a proxy for likelihood and duration of exposure to the numerous environmental factors that increase BP gradually over time, such as excessive sodium consumption, overweight and obesity, alcohol intake and physical inactivity. Other factors, such as genetic predisposition or adverse intrauterine environment, have small but definite associations with high levels of adult BP[12]. Even modest rises in mean population BP lead to large increases in the absolute number of people with hypertension[13].

As economic development progresses, high BP initially affects higher socioeconomic groups and later disproportionately affects those with lower socioeconomic status. This phenomenon is seen

both within and between countries – for example, North America and Sub-Saharan Africa have had opposite trends of BP levels in recent decades[14] Further, the speed of change in recent decades has been much more rapid than in previous epidemiological transitions. Over the last several decades age-standardized mean adult BP levels have increased steadily in South America, sub-Saharan Africa, South Asia and South East Asia, while they have fallen in other regions, most notably Western Europe and North America[14]. Adult age-standardized BP levels are now highest in Russia, Eastern Europe, Central Asia and much of sub-Saharan Africa, with mean adult systolic BP levels over 130mmHg in these areas. BP levels are now lowest in North America, following a gradual decline in recent decades[14]. Globally, 3.5 billion adults now have non-optimal systolic BP levels (i.e. above 110 to 115 mmHg) and 874 million adults have systolic BP ≥140 mmHg. Thus, approximately one in four adults has hypertension. Between 1990 and 2015 there was a 43% increase in the total global number of healthy life years lost to non-optimal BP, driven by population increase, population aging, and a 10% increase in the age-standardized rate of high BP [14].

Multiple prospective observational studies have shown a positive association between BP levels and coronary heart disease, ischemic stroke, hemorrhagic stroke and most major subtypes of CVD[10,15].These associations have generally been direct and continuous from the lowest levels of BP, although there are variations in the strength of the associations and the slopes of the lines relating systolic, diastolic and other indices of BP with CVD. The Global Burden of Disease project has shown that non-optimal BP continues to be the biggest 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[16]. (**Figure 1**)

[H2] Hypertension is a risk factor for CVD

Observational studies have repeatedly demonstrated a strong, continuous relationship between BP and CVD, with no evidence of a threshold for risk throughout the usual range of BP in clinical practice[10,15,17].The relationship applies to both systolic BP and diastolic BP, but is somewhat more robust for systolic BP in adults[17]. It is noted in both sexes, is seen at all ages throughout adulthood, and is apparent for all major manifestations of CVD, including stroke, coronary artery disease, heart failure, peripheral vascular disease, and end stage renal disease[10,15,17,18]. The relationship is independent of other CVD risk factors, and level of BP has proven to be a major component of all CVD risk prediction models. Approximately two-thirds of all adults who have hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or treatment with BP lowering medication) at 30 years of age are likely to experience a CVD event during their lifetime, which is about 40 % higher than the corresponding risk

for their counterparts with a lower level of BP[15]. In addition, CVD events in those with hypertension are likely to manifest about five years earlier than in those with a lower level of BP[15].

At ages 40-69 years, a 20 mmHg higher level of systolic BP or a 10 mmHg higher level of diastolic BP at any point in the distribution is associated with more than a doubling of the risk for stroke mortality[10]. At older ages, the corresponding relative risk is slightly less but the absolute risk is far greater than earlier in life[10]. Figure 2 displays the relationship between systolic BP and a specific CVD outcome, coronary heart disease (CHD) mortality, during an average of 11.1 years of follow-up in 347,978 adults[17]. Those with the highest BPs were at greatest risk for CVD mortality (Figure 2A). Figure 2B demonstrates that only a minority of the sample was exposed to the high risk associated with hypertension (≥140 mmHg for systolic BP). However, a much larger number of them were exposed to the more modest but still important increases in CVD risk within the non-hypertensive range of BP. Combining information about incidence (Figure 2A) and prevalence (Figure 2B) allows for estimation of the excess risk that results from each category of BP. This suggests that about 25% of the overall burden of BP-related CHD mortality occurred in approximately 5% of adults who had a systolic BP ≥160 mmHg, whereas almost 45% occurred in the approximately 20% who had a systolic BP ≥ 140 mmHg but <160 mmHg, and >30% occurred in the approximately 75% of adults with a systolic BP <140 mmHg. About two-thirds of the latter could be attributed to the approximately 20% of adults who had a systolic BP in the high-normal range (systolic BP 130-139 mmHg)[19].

[H1] MECHANISMS/PATHOPHYSIOLOGY

[H2] BP regulation

BP is determined by several factors, including blood volume and cardiac output (the amount of blood pumped by the heart per minute). Moreover, maintenance of BP involves an integrated neurohumoral system that includes the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), release of nitric oxide (NO) from the endothelium and central mechanisms from relay centers the brain. Malfunction or disruption in any of these systems will result in either increases in mean BP or increased BP variability or both. Sodium (Na^+) is a crucial regulator or blood volume: high serum Na^+ concentration promotes fluid (water) retention, thereby increasing blood volume and BP. Natriuresis (the excretion of Na^+ in the urine) is controlled by the kidneys. Salt sensitivity is defined as a marked elevation in BP following a Na^+ load of 5 or more grams and is characterized by an elevation of systolic BP of at least 10 mmHg within a few hours of ingestion.

The pathophysiological mechanisms responsible for systemic hypertension are complex. Functional alterations of several factors involved in BP control have been shown to favor BP elevation directly or indirectly and thus, to act as promoters of hypertension. These factors, which include the

RAAS, SNS, NO, inflammation, and in some circumstances, vasopressin and endothelin, appear to 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. This predisposition to develop the disorder, along with a host of environmental factors, such as high Na^+ intake, poor sleep quality or sleep apnoea, excess alcohol intake, and high mental stress, contribute to the development of hypertension. Aging is major determinant of hypertension development due to slowly developing changes in vascular collagen that support the arterial structure, increases in atherosclerosis and other related factors that lead to vascular stiffening with age. Immunologic factors can also play a major part, especially on the background of infectious or rheumatologic diseases such as rheumatoid arthritis. The mosaic theory of hypertension describes its multifaceted pathophysiology[20] . An updated version of this theory is provided in Figure 3, which illustrates the major mechanisms participating in the pathogenesis of chronic hypertension in humans[21].

[H2] Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS has wide-ranging effects on BP regulation, mediating Na^+ retention, pressure natriuresis (i.e., the mechanism whereby increases in renal perfusion pressure lead to decreased Na^+ reabsorption and increased Na^+ excretion), salt sensitivity, vasoconstriction, endothelial dysfunction, and vascular injury, and plays an important role in the pathogenesis of hypertension. Renin and pro-renin are synthesized and stored in the juxtaglomerular cells of the kidney and are released in response to decreased renal afferent perfusion pressure, reduced Na^+ delivery to the macula densa, activation of renal sympathetic nerves (via β_1 adrenergic receptor stimulation), and a variety of vasodilators, including prostaglandin E2 (Figure 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 center of the pathogenetic role of the RAAS in hypertension. Angiotensin II activates the AT1 receptor, triggering smooth muscle cell contraction, systemic vasoconstriction, increased renovascular resistance and decreased renal medullary blood flow, a mediator of salt sensitivity. Salt sensitivity is defined clinically by BP increases in response to increased Na^+ intake (Figure 4).

Angiotensin II enhances Na^+ reabsorption in the proximal tubule by increasing the activity of the sodium-hydrogen exchanger (NHE3), sodium-bicarbonate exchanger, and sodium-potassium ATPase, and by inducing aldosterone synthesis and release from the adrenal glomerulosa. Angiotensin II is also associated with endothelial dysfunction and has pro-fibrotic and pro-inflammatory effects, largely

mediated 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]. Stimulation of the AT2 receptor has opposite effects, resulting in vasodilation, natriuresis and anti-proliferative actions. Cross-transplantation studies using wild-type mice and mice lacking the AT1 receptor have shown that both systemic and renal actions of angiotensin II are relevant to physiologic BP regulation, but that the detrimental effects of angiotensin II in hypertension are mediated mainly via the kidney[23,24].

Angiotensin-converting enzyme 2 (ACE2) has recently emerged as a key player in the pathophysiology of hypertension and CV and renal disease due to its role in metabolizing angiotensin II into angiotensin-(1-7).[i] Ang-(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 glomerular and proximal tubular cells. Ang-(1-7) also has cardiorenal protective effects that are mediated by the mas receptor through signaling pathways that include mitogen-activated protein kinases (MAPK), PI3K-AKT, NADPH oxidase, TGF-β1, the EGF receptor, and NF-κB activity. ACE inhibitors and AT1 receptor antagonists have been shown to increase Ang-(1-7) levels in plasma and urine of normotensive animals and enhance renal ACE2 activity. (Varagic et al ref). Studies in rodents and humans with non-diabetic kidney disease suggest that upregulation of ACE2 may delay progression of kidney disease.[iii]

Aldosterone plays a critical role in hypertension through stimulation of renal Na^+ reabsorption mediated by non-genomic effects through the mineralocorticoid receptor, leading to increased expression of ENaC[25]. Aldosterone also has many non-epithelial effects that contribute to endothelial dysfunction, vasoconstriction and hypertension[25,26]. These include vascular smooth muscle cell proliferation, vascular extracellular matrix deposition, vascular remodeling, fibrosis, and increased oxidative stress.

[H2] Natriuretic Peptides

Natriuretic peptides (atrial [ANP], brain [BNP] and urodilatin) play an important part in salt sensitivity and hypertension. They have important natriuretic and vasodilator properties that allow maintenance of Na^+ balance and BP during Na^+ loading. Upon administration of a Na^+ load, atrial and ventricular stretch leads to release of ANP and BNP, respectively, resulting in BP lowering due to systemic vasodilation and decreased plasma volume, the latter caused by fluid shifts from the intravascular to the interstitial compartment[27]. Natriuretic peptides increase glomerular filtration rate via an increase in efferent arteriolar tone in volume-expanded states and inhibit renal Na^+ reabsorption through both direct and indirect effects. Direct effects include decreased activity of the Na+-ATPase

and the sodium-glucose co-transporter in the proximal tubule and inhibition of the epithelial sodium channel in the distal nephron. Indirect effects include inhibition of renin and aldosterone release. In addition to promoting hypertension, natriuretic peptide deficiency predisposes to insulin resistance and type 2 diabetes mellitus. Obesity is associated with relative natriuretic peptide deficiency, likely through upregulation of the natriuretic peptide scavenger receptor NPR-C in adipose tissue. The metabolic effects of natriuretic peptides and their therapeutic potential for the metabolic syndrome have been reviewed recently[28].

A large GWAS of 2.5 million genotyped or imputed single nucleotide polymorphisms (SNPs) in 69395 individuals of European ancestry from 29 studies demonstrated that most SNPs related to BP regulation and CVD risk involved natriuretic peptides[29]. Genes that encode precursors for ANP and BNP were noted and correlated with previous work that identified SNPs at this locus. Two other loci identified in this study contain genes involved in natriuretic peptide and related NO signaling pathways, both of which regulate cyclic guanosine monophosphate. A more recent study analyzed 128,272 SNPs from targeted and genome-wide arrays in 201,529 individuals of European ancestry, and genotypes from an additional 140,886 individuals were used for validation[7]. The 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 development of a genetic risk score to predict target organ damage[7].

Gene deletion studies in rodent models have evaluated cardiac ANP and BNP as paracrine regulators of vascular regeneration. Mice with systemic deletion of the endothelial guanylyl cyclase-A (GC-A) receptor gene exhibit diminished vascular regeneration and angiogenesis in response to critical hind limb ischemia, and cardiac tissue in these animals shows fibrosis, diastolic dysfunction and diminished angiogenesis. In contrast, smooth muscle cell-restricted GC-A ablation did not affect ischemic neovascularization, suggesting that cardiac BNP regulates endothelial regeneration via GC-A.[i]

A case control study in Malaysia found a significant association between I/D polymorphisms of the ANP gene in hypertensive patients without diabetes, yet no association between G191A polymorphisms of ANP in hypertensive individuals was found.[ii] Together, these data suggest that ANP gene polymorphisms may affect hypertension, but the data are not definitive.

Corin is a serine protease that is largely expressed in the heart and converts pro-ANP and pro-BNP to their active forms. Corin deficiency has been associated with Na^+ overload, heart failure and salt-sensitive hypertension[30]. Further, clinical studies have observed an association between certain

corin gene polymorphisms and risk of pre-eclampsia and hypertension, particularly among African-American but not Chinese populations[31].

[H2] The Endothelium

The endothelium is a major regulator of vascular tone and major contributor to salt sensitivity through NO. Endothelial cells produce a host of vasoactive substances, of which NO is the most important in BP regulation. 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 guanosine monophosphate[32]. Interruption of NO production via inhibition of constitutively expressed endothelial NO synthase (eNOS) causes BP elevation and development of hypertension in animals and humans. Studies using brachial artery flow-mediated vasodilation and measurement of urinary excretion of NO metabolites to evaluate NO activity in humans have demonstrated decreased whole-body production of NO in patients with hypertension compared with normotensive controls[33],[34] .

Endothelial dysfunction plays a seminal role in the pathogenesis of hypertension. Normotensive offspring of hypertensive parents have impaired endothelium-dependent vasodilation, suggesting a genetic component in the development of endothelial dysfunction[34]. 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.[34,35]. 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[36]. Recent studies documented that salt-sensitive subjects may be very sensitive to the hemodynamic stress of increased effective blood volume, leading to overproduction of TGF-beta, oxidative stress, and limiting bioavailable NO[37]. Angiotensin II, along with other factors, including cyclic vascular stretch, endothelin-1 (ET-1), uric acid, systemic inflammation, norepinephrine, free fatty acids, and tobacco smoking, enhances NADPH oxidase activity and plays a central role in the generation of oxidative stress in hypertension[38].

Endothelial cells also secrete a variety of other vasoregulatory substances, including vasodilators such as prostacyclin and endothelium-derived hyperpolarizing factors, and vasoconstrictors such as locally generated angiotensin II and the prostanoids thromboxane A2 and prostaglandin A2. Other vasodilating substances such as calcitonin gene related peptide,

adrenomedullin and substance P act primarily through increases in NO release from endothelial cells. The glucose-regulating gut hormone glucagon-like peptide-1 (GLP-1) also has vasodilating properties[41]. The balance between these factors, along with NO and ET-1, determines the final impact of the endothelium on vascular tone[38,39,40,41].

ET-1 is a potent vasoconstrictor that activates ET-A receptors in vascular smooth muscle[39]. Circulating ET-1 levels are not consistently increased in hypertension, but there is a trend toward increased sensitivity to the vasoconstrictor effects of ET-1 in hypertensive subjects[40]. ET-1 is a mediator of BP elevation, and ET-A and ET-B receptor antagonists attenuate or abolish hypertension in a variety of experimental models (angiotensin II-mediated hypertension, DOCA-salt hypertension, and Dahl salt sensitive rats) and are effective in lowering BP in humans[39,40].

[H2] Sympathetic Nervous System (SNS)

Baroreceptors, the rheostats of the circulatory system, are housed in various locations in the arterial tree, a key place being the bifurcation of the common carotid artery. When the artery is stretched by elevated BP, nerve bundles projecting from the carotid sinus baroreceptor send messages to the brain to reduce sympathetic outflow and, thereby, BP. The SNS is generally more activated in hypertensive persons compared with normotensive individuals.[42] SNS activity is also greater in obese persons, in men than in women, in younger than in older persons, and in those with advanced kidney disease.[46 47] Many hypertensive patients are in a state of autonomic imbalance with increased sympathetic and decreased parasympathetic activity[43,44]. SNS hyperactivity is relevant to both the generation and maintenance of hypertension. Studies in humans have identified markers of sympathetic overactivity in normotensive individuals with a family history of hypertension[45]. Among hypertensive patients, increasing severity of hypertension is associated with increasing levels of sympathetic activity measured by microneurography[48,49]. Plasma catecholamine levels, microneurographic recordings and systemic catecholamine spillover studies have given evidence of increased sympathetic activity in hypertensive patients who are obese, in those with the metabolic syndrome, and in those whose hypertension is complicated by heart failure or kidney disease[49].

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 sodium avidity are key factors in the maintenance of sustained hypertension[44] 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 re-challenged with a high salt diet, the animals became hypertensive again[37]. 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, enhanced SNS activity results in alpha-1 adrenergic receptor mediated endothelial dysfunction, vasoconstriction, vascular smooth muscle proliferation and increased arterial stiffness, which contribute to the development and maintenance of hypertension. Finally, there is evidence that sympathetic overactivity enhances salt-sensitivity due to a reduction in the activity of the With-no lysine kinase 4 (WNK4) gene, resulting in increased sodium avidity through the thiazide-sensitive Na-Cl co-transporter[50]. These mechanisms have been reviewed recently[51].

[H2] Inflammation and The Immune System

Inflammation, the biologic response to invading organisms, irritants or injury, makes an important contribution to the genesis of hypertension and 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 neo-intima formation, thus decreasing the lumen diameter of resistance vessels, and promote vascular fibrosis, leading to increased vascular resistance and stiffness. Cytokines affect renal tubular function by increasing renal angiotensinogen production and tissue angiotensin II and promote sodium and volume retention in hypertension.[iv] Matrix metalloproteinases stimulate the degradation of the extracellular matrix, allowing infiltration of immune cells through the vessel wall into the interstitium of the affected organs, and activate other enzymes, promote apoptosis and enhance collagen synthesis and matrix deposition, leading to target organ damage.

While animal data are clear about the relationship between inflammation and hypertension, the data in humans are limited. There are associations between C-reactive protein, TNF-alpha and various interleukins and hypertension, but no direct link. GWAS have identified a single nucleotide polymorphism of SH2B3 at position 262 (R262W) of LNK (SNP rs3184504) associated with many autoimmune and cardiovascular disorders, including hypertension.[v] Further, drugs that are used to treat inflammation, such as non-steroidal anti-inflammatory drugs and cyclosporine, raise rather than lower BP in hypertensive individuals, highlighting the complex nature of the relationship between inflammation and hypertension.

The immune system and the inflammatory response intensify the dysfunction of the kidney, vasculature and central nervous system as outlined above and promote hypertension and target-organ damage seen in hypertensive individuals, particularly if the inflammatory response is persistent or excessive. 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[52,53]. Innate immune responses, especially those mediated by macrophages, have been linked to hypertension induced by angiotensin II, aldosterone and NO antagonism. Reductions in macrophage infiltration of the kidney or the peri-adventitial space of the aorta and medium sized arteries lead to reductions in BP and salt-sensitivity[52]. Adaptive immune responses via T cells have also been linked to the genesis of hypertension and its target organ damage. T cells express AT1 receptors and mediate angiotensin II-dependent hypertension,[53] and it has been shown that depletion of mature lymphocytes ameliorated hypertension and kidney injury resulting from a high-salt diet in the Dahl SS rat[54]. Thus, a balance between proinflammatory T cell reactivity and inflammatory suppression induced by T regulatory cells determines the development of hypertension, as demonstrated by the amelioration of hypertension with the adoptive transfer of T regulatory cells in several animal models of hypertension[52-53]. Abnormalities in both pro-inflammatory T cells and regulatory T cells are implicated in hypertension-induced target organ damage, as they regulate the inflammatory processes in the kidney and vasculature that underlie hypertension-induced kidney disease[52,53,54.]

[H1] DIAGNOSIS, SCREENING AND PREVENTION

[H2] Diagnosis and screening

Essential or primary hypertension is usually asymptomatic, thus the description of a silent killer and the recommendation to screen all subjects over 45 years of age has been suggested by many public health guidelines. Hypertension is most commonly diagnosed based on repeated BP measurements in an office setting. Accurate measurement and recording of BP is essential to categorize the level of BP, ascertain BP-related CVD risk and guide management. In the last decade, methods to measure out-of-office BP have been increasingly introduced to guide diagnosis and treatment of hypertension[55 56]. These include home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM). HBPM refers to the regular measurement of BP by an individual at their home or elsewhere outside the clinic setting. ABPM supplements BP readings in office settings, typically for the 24-hour period and while individuals go about their daily activities. Table 1 illustrates definitions of hypertension by office and out-of-office BP levels. The ability to measure out-of-office BP has allowed us to identify distinct BP phenotypes, including white coat or isolated clinic hypertension and masked or isolated ambulatory hypertension[57,58]. White coat hypertension is characterised by elevated office BP but normal readings

when measured using either ABPM or HBPM. In contrast, masked hypertension is characterised by normal office readings but out –of-office readings (ABPM and HBPM) are consistently above normal[57],[58].

The evaluation of a patient with hypertension requires more that the diagnosis of high BP. It should also include assessment of the CV risk, target organ damage and any concomitant clinical conditions as well as recognition of features suggestive of secondary hypertension. Some of these investigations are necessary in all patients, but others only in specific patient groups. The medical history has to address the time of the first diagnosis of hypertension, current and past BP measurements and any antihypertensive medication. A history of pregnancy-related hypertension in women is an important factor. Hypertension translates into an increased risk of CV complications such as coronary heart disease, heart failure, atrial fibrillation, stroke and peripheral arterial disease, as well as chronic kidney disease. Therefore, a careful medical history should be taken in all patients to allow for assessment of global CV risk with a special emphasis on the current and past smoking habit and evidence of dyslipidaemia and diabetes. CVD risk should be estimated using an established calculator (e.g. http://ASCVD-Risk-Estimator/). Adults at high risk for CVD are the most likely to benefit from treatment and usually benefit from antihypertensive drug therapy in addition to lifestyle change[61].

A positive family history is a frequent feature in hypertensive patients, with the heritability estimated to vary between 35% and 50% in the majority of studies[1],[2]. Several rare, monogenic forms of hypertension have been described, e.g., the Liddle's syndrome or glucocorticoid-remediable aldosteronism, where a single gene mutation fully explains the pathogenesis of hypertension and dictates the best treatment modality[3],[4]. However, the great majority of patients suffer from a highly heterogeneous "essential" or primary hypertension with a multifactorial gene-environment aetiology. Several GWAS have identified a large number of loci which are associated with BP regulation and together explain 3.5% of the trait variance[6],[7],[8], [29]. 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[9]. Some of the most important environmental factors leading to high BP include overweight and obesity, excessive consumption of dietary sodium, insufficient intake of dietary potassium, physical inactivity and excessive intake of alcohol.

The physical examination aims to establish the diagnosis of hypertension, screen for secondary causes and estimate the global CV risk (box 1). The patient should sit quietly for 5 minutes before a reading is taken and BP cuff should be at heart level. An average of 2 to 3 BP measurements obtained at 2 to 3 separate occasions provide an accurate basis for estimation of BP[59],[60]. At least once, BP should be measured on both arms, and differences in SBP > 20 mmHg and/or in DBP >10mmHg should initiate

investigations of vascular abnormalities[59].Careful attention should be paid to choosing appropriately sized cuff, particularly for the increasing number of obese patients. Further, BP should be measured in both sitting and standing positions to rule out orthostatic hypotension. This is particularly important in older individuals.

All patients should undergo auscultation of the carotid arteries, heart and renal arteries. Detection of murmurs should lead to further investigations: carotid ultrasound, echocardiography and renal ultrasound, respectively. 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 and to detect clinical or sub-clinical target organ damage as illustrated in box 2.

A small proportion of patients with hypertension have a potentially reversible cause of high BP, and a correct diagnosis might lead to a cure or a significant improvement in BP control with a reduction of CV risk. It is therefore 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 (see above and Box 1 and 2). Secondary hypertension should also be considered in cases of a sudden worsening of hypertension, poor BP response to drug treatment and severe target organ damage, which is out of proportion to the duration and severity of hypertension. In these cases, specific diagnostic tests are indicated as described in Table 2.

Despite overwhelming evidence that hypertension is a major treatable CV risk factor, studies across the world show that a large proportion of hypertensive subjects are either unaware of their high BP or aware but not treated or inadequately treated[62,63]. Thus, there is a strong indication to screen middle-aged or younger persons in order to detect and treat more patients with hypertension. The most serious attempt by a healthcare system to improve the diagnostic aspects of hypertension has been done in the UK, based on pay-for-performance principle, i.e., to give incentives to general practitioners (primary care physicians) for the appropriate diagnosis and treatment of chronic diseases, including hypertension. An early report[64,65] showed that this initiative was associated with an increased rate of BP monitoring and better BP control, but later reports suggested that this was not a sustained improvement[66]. It is possible that the recent initiative championed by the International Society of Hypertension 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.

[H2] Prevention

The association between hypertension and increased risk of CVD highlights the importance of treating hypertension, especially when severe. However, it also underscores the importance of strategies to reduce BP-related CVD risk in those who have a high normal level of BP. Reducing BP in adults with a high normal BP (referred to as elevated BP in the 2017 US guidelines) provides the potential to directly reduce CVD risk and to prevent or at least slow the age-related tendency for individuals to move into the much higher risk category of 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[62]. However, studies in isolated societies indicate that high BP is not an inevitable consequence of aging 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[67,68,69]. These reports underscore the logic of efforts to prevent high BP in settings where an age-related increase in BP is common. A variety of nonpharmacological interventions have been shown to be effective in lowering BP and preventing hypertension. The most effective interventions are weight loss[70,71,72], reduced Na^+ intake[70,71,72,73], increased potassium intake[74,75], increased physical activity[76], reduced consumption of alcohol[77,78] and diets like the Dietary Approaches to Stop Hypertension (DASH) diet[79] that combine several elements which favorably affect BP[80,81] . The DASH diet is especially successful when combined with other effective BP lowering interventions such as a reduced intake of dietary sodium[73]. Lifestyle change is the best way for the individual to implement these interventions. Government agency and professional society websites provide helpful tips for lifestyle change and monitoring of BP. Even small improvements in an individual's lifestyle can be valuable. Careful monitoring of BP is essential because the beneficial effects of lifestyle change are predicated on maintenance of the intervention[82].

Low-dose pharmacological therapy has also been shown to be effective in lowering BP and preventing hypertension in three randomized controlled trials conducted in adults with high normal BP[83,84,85]. The most recent of these, the Brazilian multi-center PREVER-Prevention Trial, compared treatment with the low-dose long-acting thiazide-like diuretic chlorthalidone (12.5 mg/day), in combination with the potassium sparing agent amiloride (2.5 mg/day) to treatment with placebo[85]. Treatment with the low-dose chlorthalidone/amiloride combination resulted in both a decrement in BP and prevention of hypertension and a reduction in left ventricular mass. A drug intervention is easier to implement and maintain than a lifestyle change intervention but there is a natural reluctance to recommend a lifetime of pharmaceutical therapy for 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.

Two complementary strategies aimed at achieving a small population-wide reduction in BP or a larger reduction in those who are at higher risk to develop hypertension can be employed to implement hypertension prevention interventions[80,81,86]. Modeling 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 ischemic attacks, and a 6% reduction in the risk of coronary heart disease[87]. Public health interventions focused on dietary improvements and increases in physical activity that are known to lower BP provide the basis for the population-wide strategy. Diet in the general population can be favorably influenced by means of public health education campaigns, food product labeling, 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 enhanced by making it easier for members of the community to engage in exercise on a routine basis.

[H1] MANAGEMENT

[H2] Treatment goals

Following the publication of the Systolic blood PRessure Intervention Trial (SPRINT)[88], target systolic BP values have been frequently debated. Before publication of SPRINT, most guidelines recommended a target BP < 140/90 mmHg for most hypertensive patients and < 150/90 mmHg for elderly patients over 60 or 80 years (Table 3)[59,89]. SPRINT was a randomized, open-label controlled trial that enrolled 9361 participants without diabetes but with increased CVD risk. Patients with a history of stroke were excluded. Participants were randomized to a standard systolic BP target < 140 mmHg or intensive systolic BP target < 120 mmHg. Intensive BP treatment in SPRINT resulted in a significantly greater (25%) reduction in the primary endpoint (first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes), compared to 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 minimize the white coat effect. Some observers have found large differences between automated office BP measurement and conventional auscultatory measurements (with the former technique showing lower values)[90] and have on that basis questioned the applicability of the SPRINT intensive systolic BP target of < 120 mmHg to ordinary office practice[91].

Both the appropriate method(s) of measuring office BP (automated versus manual; unattended versus attended) and the appropriate BP targets for antihypertensive treatment are currently topics of vigorous debate. The 2016 Canadian Hypertension Education Program Guidelines recommend

intensive BP treatment with a target SBP ≤ 120 mmHg for selected high-risk patients based on automated office BP measurements[92]. The 2016 Australian guidelines recommend a target SBP < 120 mmHg for selected high CV risk patients (without diabetes, including CKD patients and those >75 years)(Table 3)[93]. The recently released US ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults[93a] reassessed the issue of appropriate BP targets to recommend values < 130/80 mmHg for most patients. Individual goals based on clinical judgement and patient preference are suggested for older adults (≥ 65 years of age) with comorbidities and limited life expectancy. The 2013 ASH/ISH guidelines written to provide information for practitioners in low- and middle-income countries as well as in developed countries are more conservative, suggesting a goal of < 130/80 mmHg only for young adults and < 140/90 mmHg for the majority of hypertensive patients aged 55–80 years[59a]. Current ESH/ESC guidelines recommend a BP target of < 140/90 mmHg for the general population of adults with hypertension and a variety of comorbidities[59] but a new version is expected in 2018. The recent American Diabetes Association (ADA) guidelines recommend a target of < 140/90 mmHg for the general population of adults with diabetes and a lower target (< 130/80 mmHg) for adults with diabetes who are at high risk for CVD and stroke[94]. In summary, newer guidelines published after the SPRINT trial seem to have more aggressive goals, at least for individuals < 65 years of age.

[H2] Treatment thresholds

Patient's global CV risk and comorbidities should be considered in determining the need for pharmacologic antihypertensive treatment. This approach is used by the recent US ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults[93a]. Use of antihypertensive medication is recommended in patients with pre-existing CVD and those without an event but an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher at BP levels ≥ 130/80 mmHg. In individuals without CVD and with 10-year ASCVD risk < 10%, antihypertensive medication should be initiated at BP ≥ 140/90 mmHg. For details, see Figure to be reproduced from reference 93a – Fig 4 page 73-74 (new Figure 5).

[H2] Non-Pharmacological Management of Hypertension

Lifestyle advice is recommended in all patients with hypertension. The most effective interventions are the same as for prevention of hypertension. Targeted dietary approaches can contribute to reduce the systolic BP in hypertensive individuals. Reducing sodium intake (ideally to

<2,300 mg/d, or <1,500 mg/d in those most susceptible to the effects of sodium on BP, but reduction by at least 1,000 mg/d is desirable) can lower the systolic BP by 2-4 mmHg, and a similar reduction can be expected with a potassium intake of 3,500 – 5,000 mg/d. Keeping alcohol intake ≤2 standard drinks/d for men and ≤1 standard drink/d for women can also contribute to a 2-4 mmHg BP reduction.

[H3] Reduced salt intake

Randomized controlled trials carried out in hypertensive persons have consistently shown that reduced sodium intake is associated with reduction of BP[95]. The most convincing evidence is provided by the Dietary Approaches to Stop Hypertension (DASH-sodium) trial[73], in which the effects of three different sodium intakes were tested separately in combination with two diets: the DASH diet, rich in fruit, vegetables, low-fat dairy products and reduced in saturated fat and cholesterol, and the 'usual American diet'. Reduction of sodium intake by approx. 0.9 g/day (40 mmol/day) induced a greater BP reduction when the starting sodium intake was <100 mmol/day. Of note, sodium reduction reduced BP in non-hypertensive individuals on both diets. DASH also provides evidence that increased potassium intake is associated with BP reduction. Reduced sodium intake can also prevent hypertension (relative risk reduction of about 20% with or without concomitant weight loss)[72], improve hypertension control[96] and thus, possibly, reduce need for antihypertensive medication[82]. In the Intersalt study[97], lower sodium intake was associated with a blunted age-related rise in systolic BP.

The current recommendations of the American Heart Association[98] and American Society of Hypertension[99] are stricter than the European guidelines, recommending lowering intake to 3.8 g/day salt, whereas the 2013 ESH/ESC guidelines recommend 5–6 g of salt per day[59]. There is strong evidence to support population-wide recommendations to lower salt intake[100],[101] . As more than 75% of dietary salt comes from processed foods, any population strategy to reduce salt intake must involve food manufacturers and restaurants, in order to progressively reduce salt added to foods. So far, only 3 countries (Japan, Finland, and the UK) have successfully reduced population salt intake[102].

[H3] Increased potassium intake

High potassium intake is associated with reduced BP in individuals with low as well as high baseline potassium intake[74]. 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. Therefore, the best strategy is to increase potassium intake and reduce sodium intake at the same time. Potassium reduces BP to a greater extent in blacks than in whites[103]. The preferred strategy to increase potassium intake is to increase consumption of fruits and vegetables that are rich in potassium rather than using supplements[99]. In individuals with impaired urinary potassium excretion, a potassium intake < 4.7 g/d (120 mmol/d) is recommended.

[H3] Moderate alcohol consumption

Keeping alcohol intake ≤2 standard drinks/d for men and ≤1 standard drink/d for women can also contribute to a 2-4 mmHg BP reduction. [77]

[H3] Physical activity

Regular physical activity reduces BP in hypertensive individuals. A recent narrative review of 27 randomized clinical trials in hypertensives showed that regular medium- to high-intensity aerobic activity reduced BP by a mean of 11/5 mmHg[104]. 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 showed a BP reduction of similar magnitude in hypertensives[104]. A meta-analysis of 64 controlled studies of the efficacy of dynamic resistance training as stand-alone antihypertensive therapy showed BP reductions comparable with or greater than those with aerobic exercise training. Greater BP reductions occurred in individuals with higher resting BP (approx. 6/5 mmHg for hypertension and 3/3 mmHg for pre-hypertension) and in non-white individuals[105].

[H3] The Role of Weight Loss

Excess adiposity generally raises BP in susceptible individuals, and obese hypertensive patients require more antihypertensive medications to control their BP and are more likely to be treatment resistant[106]. Modest reductions in body weight lower systolic BP by on average 2-4 mmHg, however, the response varies substantially between individuals. Lifestyle interventions, including hypocaloric diets and physical exercise, are commonly recommended for patients with obesity and hypertension, yet average weight loss is modest and most patients regain weight[107]. Medications have been developed for the treatment of obesity, but their approval status differs between the U.S. and Europe: some drugs are only approved in the U.S. (e.g., lorcaserin and topiramate/phentermine), while others are approved in Europe only. BP reductions in patients with hypertension have been reported for some weight loss medications[108], but drug-specific actions may attenuate the positive influences of weight loss on BP and CVD outcomes[109]. Bariatric surgery is very effective in reducing body weight, and the risk for arterial hypertension is substantially reduced up to five years following bariatric surgery[110]. However, large and sustained body weight reductions are needed to significantly reduce BP following bariatric surgery[111] and there are no large clinical trials specifically testing the effects of weight loss medications or bariatric surgery on hypertension control.

[H2] Antihypertensive Pharmacotherapy

Antihypertensive pharmacotherapy has evolved over several decades driven by development of various antihypertensive medication classes and large-scale outcomes trials proving their benefits on CV morbidity and mortality[112]. Clinicians are now faced with a plethora of antihypertensive medications

of different drug classes and a variety of fixed dose combinations. Typically, antihypertensive pharmacotherapy is begun with first line antihypertensive medications either in monotherapy or in combination[113]. Combination therapy may be preferable in patients with higher levels of pretreatment BP. First line antihypertensive medications include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers ("sartans"), dihydropyridine calcium channel blockers, and thiazide diuretics[89]. Beta-blockers are also indicated in patients with heart failure and reduced left ventricular ejection fraction or post MI, and some guidelines recommend beta-blockers as first line antihypertensive medications [59,114]. The choice should be based on individual efficacyand tolerability. Ethnicity affects the response to antihypertensive medications, and it has been suggested that calcium channel blockers and diuretics may be the first choice in blacks[109,115]. Further, in specific clinical situations, e.g. hypertension in pregnant women, other medications are preferable, while some first line antihypertensives, e.g. angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are contraindicated because of increased risk for renal teratogenicity. Divided dosing of antihypertensive drugs tends to decrease adherence and should be avoided when possible[116].

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 side effects, and whether the patient has comorbidities that mandate particular drug choices[59]. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, thiazide diuretics and dihydropyridine calcium channel blockers are additive in lowering BP and can be combined as double or triple combination therapies. In contrast, combining angiotensin-converting enzyme inhibitors and angiotensin receptor blockers adds little BP lowering while increasing the risk for hyperkalemia and renal dysfunction. Similarly, combining RAAS inhibitors with beta-adrenoreceptor blockers adds little BP reduction. This combination is indicated in patients following acute myocardial infarction or heart failure with reduced left ventricular ejection fraction for reasons beyond BP reduction

[H3] Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have been tested extensively in large-scale hypertension trials[117]. In patients with heart failure with reduced left ventricular ejection fraction or with with diabetic nephropathy, both drug classes improved outcomes, making them particularly good choices in these populations. Both classes appear to be comparable in reducing CVD risk[118]. and also tend to improve glucose metabolism and thus may be preferable in younger patients and in patients with conditions predisposing to type 2 diabetes, including obesity and the metabolic syndrome[119]. Angiotensin-converting enzyme inhibitors are generally well tolerated, but

reductions in kidney function, hyperkalemia, cough, and – less commonly – angioedema may occur with their use. The risk for angioedema, which can be life threatening, is substantially increased in blacks[120] and modestly increased in dipeptidyl peptidase-IV inhibitor (an antidiabetic drug) treated patients[121]. Angiotensin-converting enzyme inhibitors that can be dosed once daily are preferred. Angiotensin receptor blockers may also elicit hyperkalemia and worsening of kidney function, but are not likely to cause cough or angioedema[118].

[H3] Dihydropyridine calcium channel blockers.

Dihydropyridine calcium channel blockers, which lower BP by blocking vascular L-type calcium channels, are effective antihypertensive drugs with extensive experience in large clinical trials[117]. A practical advantage of this drug class is that it can be combined with all other first-line antihypertensives. Peripheral edema, which is explained by peripheral arterial vasodilation rather than worsening heart failure or kidney dysfunction, is a common side effect, particularly in obese individuals. Non-dihydropyridine calcium channel blockers, especially verapamil, can induce or worsen constipation, especially in institutionalized older persons. Calcium channel blockers modestly inhibit the drug metabolizing enzyme cytochrome P450 3A4, and thus may elicit important drug-interactions[122].

[H3] Thiazide and thiazide-like diuretics.

The thiazide/thiazide-type diuretics (hydrochlorothiazide and chlorothiazide) have a benzothiadiazine ring, while the thiazide-like diuretics (chlorthalidone, metolazone and indapamide) lack the benzothiadiazine structure. Both subclasses of diuretics inhibit Na^+ and chloride co-transporters in renal tubules and have been an important component of pharmacological hypertension management ever since the first trials showing morbidity benefits of antihypertensive therapy[123]. Over the years, diuretic doses have been substantially reduced to attain better risk-benefit profiles. Thiazide diuretics may worsen glucose metabolism, but whether or not this metabolic action translates into long-term increases in CVD risk is unclear. Hydrochlorothiazide, the most commonly prescribed thiazide diuretic worldwide, may be less effective in mitigating CVD risk compared to chlorthalidone or indapamide[124,125]. Drug-related electrolyte disturbances, including hypokalemia and hyponatremia, are particularly important adverse effects. The risk for hypokalemia is reduced when thiazide diuretics are combined with potassium-sparing agents, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or potassium-sparing diuretics. Hyponatremia is a potentially life threatening side effect, particularly in elderly persons.

[H3] Beta-adrenoreceptor blockers.

Beta-adrenoreceptor blockers are thought to lower BP by inhibiting beta-adrenergic transmission in the kidney and the heart. They improve outcomes following acute myocardial infarction and in patients with heart failure with reduced left ventricular ejection fraction, but, in the absence of these comorbidities, beta-adrenoreceptor blockers appear to be inferior to other first line antihypertensives in reducing CVD morbidity and mortality[126]. This effect has been attributed to lesser reductions in central BP[127] and adverse effects on body weight[128] and glucose metabolism with beta-adrenoreceptor blockade. Some of these disadvantages may be mitigated with newer vasodilator beta-adrenoreceptor blockers, such as nebivolol and carvedilol[129]. However, there is no evidence from large-scale antihypertensive trials that this difference translates into better clinical outcomes. Beta-adrenoreceptor blockers may promote bronchial obstruction is patients with asthma and should not be combined with non-dihydropyridine calcium channel blockers such as verapamil that lower sinus node rate or atrioventricular conduction.

[H3] Newer Pharmacological Agents

Overall, the interest of pharmaceutical industry in developing new antihypertensive medications has been limited in recent years. Some of the currently approved drugs, such as angiotensin receptor blockers, have placebo-like tolerability. Moreover, most antihypertensive drugs are out of patent and, therefore, available as relatively inexpensive generics. Novel pharmacological approaches approved for other indications, including combined angiotensin receptor and neprilysin inhibitors[130], soluble guanylyl cyclase modulating drugs[131], and sodium-glucose cotransporter 2 (SGLT2) inhibitors[132] may be useful in treating hypertension. Other pharmacological approaches, such as novel mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, activators of the angiotensin-converting enzyme 2/ angiotensin (1–7)/ MAS receptor axis, and natriuretic peptide receptor agonists, are in various stages of preclinical or clinical development[133], often for indications other than hypertension. Drugs addressing novel mechanisms could be useful in patients with treatment resistant hypertension, particularly those not responding to or not tolerating mineralocorticoid receptor antagonists. Moreover, drugs with actions in addition to BP reduction could prove clinically useful. For example, combined angiotensin receptor blockade and neprilysin inhibition has been shown to ameliorate insulin resistance in obese hypertensive patients[134] and decrease the progression to type 2 diabetes mellitus in heart failure patients[135].

[H2] Treatment Resistant Hypertension

Treatment resistant hypertension is commonly diagnosed when office BP is >140/90 mmHg despite treatment with three or more properly dosed antihypertensive drugs including a diuretic. Secondary causes of the hypertension have to be ruled out in order to make the diagnosis[136]. 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 antihypertensives fulfill the criteria for treatment resistant hypertension[137]. Adding a fourth or a fifth drug may lead to satisfactory BP control in these patients. The PATHWAY trial rotated patients with resistant hypertension through different add on drugs or placebo in a randomized fashion[138]. All patients received a standardized antihypertensive regimen comprising three drugs, including a diuretic. Compared with alpha- or beta-adrenoreceptor blockade, the mineralocorticoid receptor antagonist spironolactone was the most effective fourth antihypertensive drug. In another study in patients uncontrolled on three drugs, sequential addition of a mineralocorticoid receptor antagonist followed by a loop diuretic was more effective than adding an ACE inhibitor followed by a beta-adrenoreceptor blocker[139]. Overall, mineralocorticoid antagonism is a reasonable choice in patients with difficult to control hypertension. Given the risk of inducing hyperkalemia[140], serum potassium concentrations should be monitored.

[H3] Device-based Treatments

Device-based treatments have been primarily developed for patients with severe resistant hypertension whose BP cannot be controlled with antihypertensive drugs[133]. Catheter-based renal nerve ablation[141,142], electrical carotid sinus stimulation[143,144], modulation of baroreflex transduction with a dedicated carotid stent[145], carotid body denervation[146], and deep brain stimulation[147] 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[148]. These treatments are in various stages of clinical development, with the most extensive data available on renal nerve ablation and electrical carotid sinus stimulation. None has yet been proven efficacious in lowering BP in randomized sham-controlled clinical trials, and trials with hard clinical endpoints do not exist.

[H1] QUALITY OF LIFE

Health-related quality of life (HRQoL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning. Measurement of HRQoL is based on patient-self-report, yet has been extensively validated by studies demonstrating that each additional disease, as well as the severity of these diseases, is associated with declines in function[149]. Population-

based studies have consistently shown that being diagnosed with hypertension is associated with worsening of HRQoL even after adjusting for other comorbidities[150,151]. 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.

The process of labeling someone as having hypertension can result in worsening of self-perceived health status[152]. This was well-demonstrated in a classic study of otherwise healthy Canadian steelworkers identified as having hypertension as part of a screening program. In the year following diagnosis, absenteeism from work due to illness more than tripled in those made newly aware of their hypertension, while it increased only slightly in those previously aware of their hypertension[153]. 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 from diverse settings and using different measures of physical and mental health[152].

Antihypertensive medication use is associated with a variety of symptoms that could lower HRQoL[154]. In observational studies, being on more antihypertensive medications is associated with worse HRQoL[155]. Some classes of antihypertensive medications, e.g. angiotensin-converting enzyme inhibitors, are better tolerated than others, e.g. beta blockers and centrally acting agents, and result in significantly better scores on measures of general well-being[156]. Further, small differences in HRQoL have even been reported among medications of the same class, e.g., enalapril vs. captopril[157]. However, clinical trials with newer antihypertensive agents have generally indicated that they are extremely well-tolerated and can enhance the effects of non-pharmacologic treatment on HRQoL. In the Treatment of Mild Hypertension Study (TOMHS), combining lifestyle modifications with any of five different antihypertensive medication classes resulted in greater improvements in HRQoL than lifestyle modifications plus placebo[158].

Treatment-related reductions in BP may have a negative effect on HRQoL, particularly in older and more frail patients at high risk of hypotension. Older clinical trials evaluating patients with very high baseline BP, e.g., the Systolic Hypertension in the Elderly Program Trial (SHEP) and the Systolic Hypertension in Europe Trial (Syst-Eur), generally found minimal impact of BP reductions on HRQoL[159,160]. Two more recent clinical trials have targeted lower BPs (intensive systolic BP target < 120 mmHg versus standard systolic BP target < 140 mmHg), and it had been postulated that this lower BP might be expected to cause cerebral hypoperfusion, resulting in falls, dizziness, and cognitive impairment[161,162,163]. 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[162]. In the Systolic Blood Pressure Intervention Trial (SPRINT), targeting systolic BP <120 mmHg required 1 additional antihypertensive medication compared to standard treatment to target systolic BP < 140 mmHg and was generally safe and well tolerated[164]. Compared to standard treatment, intensive treatment did not affect the perceived heath status of SPRINT participants, measured by patient reported outcomes of physical and mental health, self-reported satisfaction with care and medication adherence, even when stratifying on age and comorbidities[164] . Almost 90% of participants in both treatment groups reported satisfaction with their BP care, and more than 1/3 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 CV morbidity and mortality while maximizing well-being for each individual patient.

[H1] OUTLOOK

The outlook for hypertension over the next 5 to 10 years is very variable, depending on where around the world you look. It is clear overall that the prevalence of hypertension and therefore the associated global burden attributable to hypertension, will increase[165]. This increase – 1.5 billion people are expected to be affected by 2025 (Ref. [166]) – is largely due to global population growth and aging and will be focused in low and middle income countries[165]. 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 3 areas will vary from non-existent (in the case of prevention, a worsening in some parts of the world) to significantly large and important elsewhere.

Overall, it is likely that prevention will contribute least to any improvement in BP-associated disease burden. That 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. To reverse this pattern requires the “buy-in” of the food and drink industries, governments, and education systems.

Whilst moves in the right direction have taken place in relation to some of these preventive strategies, they have largely been limited to high income countries. It is also worrisome that despite reasonably compelling evidence to the contrary[167], recommendations that the general population should restrict salt intake have been questioned on the basis of largely suboptimal observational data[168]. Such confusion worsens an already very difficult public health challenge. A lack of awareness of raised BP

status provides a great opportunity for reducing BP-associated health burden since recent data show that only approximately half of people with hypertension are aware of their condition[169]. Both the World Heart Foundation in their Roadmap for reducing CV mortality via lowering raised BP[170], and the Lancet Commission on hypertension[171] identified improved awareness of hypertension as a critical action needed to improve the current disease burden due to raised BP. It is hoped that the global BP awareness campaign instigated by the International Society of Hypertension whereby World Hypertension Day was extended to become May Measurement Month (MMM) in 2017 will contribute significantly to improving rates of routine BP screening around the world[172]. Over 1.25 million adults (≥18 years) from >100 countries were screened as part of MMM and it is hoped that the ensuing data allied to health-economic analyses will be used to persuade policy makers in each country that it makes clear financial sense to enhance local BP screening and treatment facilities.

Improving the efficacy of drug treatment also holds great promise for reducing BP-associated disease burden. However, - rather than focusing on rare secondary causes of hypertension or the optimal management of "resistant hypertension"[142] the biggest impact is likely to be achieved by the delivery and distribution of cheap, effective single-pill combinations of 2 or 3 drugs to low and middle income countries where most hypertension exists and where any such therapies are currently either largely unavailable or unaffordable[173.]

Optimal combinations of 2 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[174]. The first in a series of trials in these ethnic groups is underway in Sub-Saharan Africa. Meanwhile, single-pill combinations of the 3 drugs most commonly recommended in current guidelines (calcium channel blocker plus a diuretic, or calcium channel blocker plus a RAAS-blocker or diuretic plus a RAAS-blocker) are readily available and can be made very cheaply. In addition, a 3-drug combination of a calcium channel blocker, a diuretic and a RAAS-blocker[114] should also be produced for more severe hypertension, with low dose spironolactone available as a fourth-line agent[138]. Hence, 1 or 2 tablets will be able to control BPs of all but a small proportion of hypertensive patients.

Means of making these formulations available cheaply to all countries of the world should be sought[170]. Distribution and delivery of these agents to hypertensive patients within each country also requires further circumnavigation of local obstacles[170] – among which, the lack of an effective screening programme is critical.

Those responsible for prescribing antihypertensive medications are likely to differ around the world. However, even in the higher income countries it is possible and certainly feasible that much of the "routine" uncomplicated hypertension management can, and probably should be carried out by nurse practitioners or other non-physician health workers. In more remote parts of the world, the use of

e-healthcare techniques[175] should be increasingly used to facilitate task-shifting or task sharing by non-physician health-workers where doctors are unavailable[176].

In summary, whilst there are many outstanding and interesting scientific research questions in the field of hypertension (Box 3), perhaps the most urgently needed and important research required to reduce the BP-associated health burden is that which will evaluate the best way(s), at a local level, to screen routinely for raised BP and then to deliver the best, cheap, evidence-based combination of agents to those in need. Meanwhile, efforts to drive public health policy towards encouraging more healthy diets and lifestyle from a BP and CV viewpoint should be encouraged. More basic scientific research which might allow precision medicine to be applied to hypertension must also continue, whilst recognizing the larger and more pressing needs of implementing what is already known.

Box 1 – Physical examination for secondary hypertension, organ damage and obesity

<u>Signs suggestive of secondary hypertension</u>

- Features of Cushing's syndrome
- Neurofibromatosis (pheochromocytoma)
- Enlarged kidneys (polycystic kidney)
- Abdominal murmurs (renovascular hypertension)
- Precordial murmurs (aortic coarctation, aortic disease)

<u>Signs of target organ damage</u>

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

<u>Evidence of obesity</u>

- Weight and height
- Calculate BMI: body weight/height^2
- Waist circumference

Box 2 – Laboratory investigations

Routine tests

- Haemoglobin and haematocrit
- Fasting plasma glucose
- Serum total cholesterol, low-density lipoprotein cholesterol, 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 EKG

Additional tests based on history, clinical examination and routine tests

- Haemoglobin A1c
- Quantitative proteinuria
- Out-of-office BP measurements*
- Echocardiogram
- Holter monitoring
- Carotid ultrasound
- Abdominal ultrasound
- Pulse wave velocity
- Ankle-brachial index
- Further specialist tests for secondary hypertension (renin, aldosterone, catecholamines and their metabolites etc)

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

Box 3 Outstanding Research Questions:

1. Measurement Issues:
    - Is hypertension management improved by basing treatment strategies on serial unattended BP measurements or, out of office (home or ambulatory) or central BP measurements?
    - How should BP be measured in patients with atrial fibrillation?
2. Treatment Issues:
    - Should salt restriction at the population level continue to be recommended at current targets?
    - How far should age, estimated 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 longer-term BP variability be a consideration in the selection of drug treatment for optimal CV protection?
    - What combinations of antihypertensive agents give optimal CV protection, stratified by age and ethnicity?
    - What is the optimal BP treatment target stratified by age, CV risk and concomitant disease status?
    - What is the optimal management of hypertension, truly resistant to 4 agents including Spironolactone.?
    - If treatment thresholds are to be driven by estimated CV risk at what level should antihypertensive drug treatment be initiated and what other CV protective agents should be considered?
    - Is initiating drug therapy with 2 hypertensive agents more effective than initiating with monotherapy for optimal CV prevention?

Figure 1: Map of age-standardized mean systolic blood pressure

Reproduced from Ref. [14]

Figure 2. Systolic blood pressure and coronary heart disease

Relationship of systolic BP to subsequent risk of coronary heart disease mortality during an average follow-up of 11.6 years in 347,978 US men aged 35-57 years at baseline. A | rates of coronary heart disease mortality per 10,000 person-years, adjusted for age, race, serum cholesterol, cigarettes smoked per day, use of medication for diabetes, and income for nine categories of baseline systolic BP. B | distribution of the sample by category of systolic BP. C | Estimation of the percent of excess coronary heart disease deaths occurring in each category of systolic BP ≥110 mm Hg, using those with a systolic BP <100 mm Hg as the reference group. Adapted, with permission, from Ref.[17].

Figure 3. Schematic drawing of the modern Page mosaic theory of hypertension. BP: Blood pressure, RAAS: renin-angiotensin-aldosterone system.

Figure 4 Effects of chronic high salt intake

The hemodynamic effects of chronic high salt intake differed between salt sensitive (SS) and salt resistant (SR) volunteers. Despite similar increases in cardiac output (row 3) and cumulative sodium balance (row 4), SS but not SR patients manifest salt-induced increases in mean arterial pressure (row 1). Adapted *from reference* [37]*.*

Figure 5 Pathways affected in monogenic hypertensive disease.

Thick ascending limb of the loop of Henle (TAL), distal convoluted tubule (DCT), and the cortical collecting tubule (CCT) are indicated, along with the pathway of the renin-angiotensin system, the major regulator of renal salt reabsorption. Inherited diseases affecting these pathways are indicated, with hypertensive disorders in red and hypotensive disorders in blue. Abbreviations: AI, angiotensin I; ACE, angiotensin converting enzyme; AII, angiotensin II (AII); MR, mineralocorticoid receptor; GRA, glucocorticoid-remediable aldosteronism; PHA1, pseudohypoaldosteronism, type-1; AME, apparent mineralocorticoid excess; 11 bHSD2, 11b-hydroxysteroid dehydrogenase-2; DOC, deoxycorticosterone; PT, proximal tubule and WNK, Serine/threonine-protein kinase. *Modified from Ref*[3]

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Table 1 - Current definitions of hypertension by office and out-of-office BP levels

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥ 140	and/or	≥ 90
Ambulatory BP			
Daytime (awake)	≥ 135	and/or	≥ 85
Night time (asleep)	≥ 120	and/or	≥ 70
24hr	≥ 130	and/or	≥ 80
Home BP	≥ 135	and/or	≥ 85

Modified from Ref[59]*.*

966 **Table 2 – Diagnostics of secondary hypertension**

967 **Clinical indications and diagnostics of secondary hypertension**

	Clinical indications			Diagnostics	
Common causes	**Clinical history**	**Physical examination**	**Laboratory investigations**	**First-line test(s)**	**Additional/confirmatory test(s)**
Renal parenchymal disease	History of urinary tract infection or obstruction, haematuria, analgesic abuse; family history of polycystic kidney disease	Abdominal masses (in case of polycystic kidney disease)	Presence of protein, erythrocytes, or leucocytes in the urine, decreased GFR	Renal ultrasound	Detailed work-up 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; flash pulmonary oedema	Abdominal bruit	Difference of >1.5 cm in length between the two kidneys (renal ultrasound), rapid deterioration in renal function (spontaneous or in response to RAA blockers)	Renal Duplex Doppler ultrasonography	Magnetic resonance angiography, spiral computed tomography, intra-arterial digital subtraction angiography
Primary aldosteronism	Muscle weakness; family history of early onset hypertension and cerebrovascular events at age <40 years	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 RAA system)	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, 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 pathogenic mutations
Cushing's syndrome	Rapid weight gain, polyuria, polydipsia, psychological disturbances	Typical body habitus (central obesity, moon-face, buffalo hump, red striae, hirsutism)	Hyperglycaemia	24-h urinary cortisol excretion	Dexamethasone-suppression tests

CT, computed tomography; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; RAA, renin–angiotensin–aldosterone

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969 Modified from Ref[59].

970

971 **Table 3. Blood pressure targets recommended by various guidelines**

Guideline	Population	Goal BP (mmHg)
2013 ESH/ESC[59]	Non frail adults < 80 years	< 140/90
	Adults > 80 years	< 150/90
	Adults with diabetes	< 140/85
	Adults with CKD without proteinuria	< 140/90
	Adults with CKD with overt proteinuria	< 130/90
	Adults with CHD	< 140/90
2013 ASH/ISH[59a]	Adults 55–80 years	< 140/90
	Young adults	< 130/80
	Elderly > 80 years	< 150/90
2014 Hypertension guideline[89] (formerly known as JNC 8)	Adults < 60 years	< 140/90
	Adults ≥ 60 years	< 150/90
	Adults with diabetes	< 140/90
	Adults with CKD	< 140/90
CHEP 2016[92]	Adults < 80 years	< 140/90
	Adults ≥ 80 years	< 150
	High-risk adults ≥ 50 years	≤ 120
2016 Australian guidelines[93]	Adults at high CV risk without diabetes, including CKD patients and those >75 years	< 120 mmHg
	Adults with diabetes in whom	< 120 mmHg

	prevention of stroke is priority	
ADA[94]	Adults with diabetes	< 140/90
	Adults with diabetes and high risk for CVD	< 130/80
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA[9] [3a]	Adults with known CVD or 10-year ACVD event risk ≥ 10%	< 130/80
	Adults without additional markers of increased CVD risk	< 130/80
	Older adults ≥ 65 years of age, noninstitutionalized, ambulatory	< 130/80
	Older adults ≥ 65 years of age, with comorbidities and limited life expectancy	Individualized goal based on clinical judgement and patient preference

BP, blood pressure; ESH, European Society of Hypertension; ESC, European Society of Cardiology; CKD; chronic kidney disease; CHD, coronary heart disease; CHEP, Canadian Hypertension Education Program; ADA, American Diabetes Association; CVD, cardiovascular disease. ACC, American College Cardiology; AHA, American Heart Association; AAPA, American Academy of Physician Assistants; ABC, ; ACPM, American College of Preventive Medicine; AGE; AGS, American Geriatric Society; APhA, American Public Health Association; ASH, American Society of Hypertension; ASPC, American Society of Preventive Cardiology; NMA, National Medical Association; PCNA, Preventive Cardiovascular Nurses Association.

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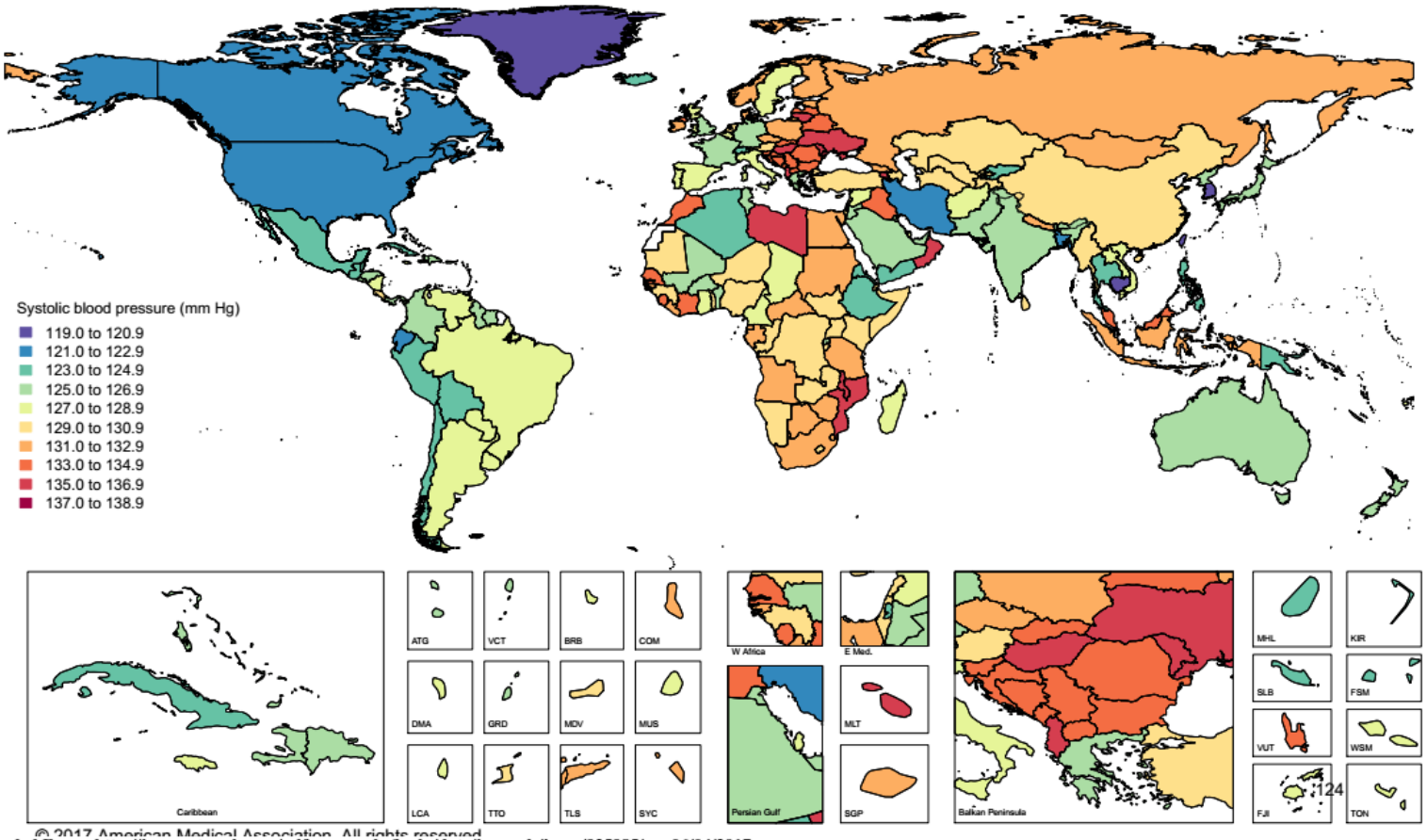
Figure 1

eFigure 2. Global map of age−standardized mean systolic blood pressure (in mm Hg) for both sexes combined in 2015. ATG = Antigua and Barbuda. VCT = Saint Vincent and the Grenadines. BRB = Barbados. COM = Comoros. DMA = Dominica. GRD = Grenada. MDV = Maldives. MUS = Mauritius. LCA = Saint Lucia. TTO = Trinidad and Tobago. SYC = Seychelles. MLT = Malta. SGP = Singapore. MHL = Marshall Islands. KIR = Kiribati. SLB = Solomon Islands. FSM = Federated States of Micronesia. VUT = Vanuatu. WSM = Samoa. FJI = Fiji. TON = Tonga.



from Forouzanfar MH, Liu P, Roth GA, et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. JAMA 2017;317:165-82.

Figure 2A

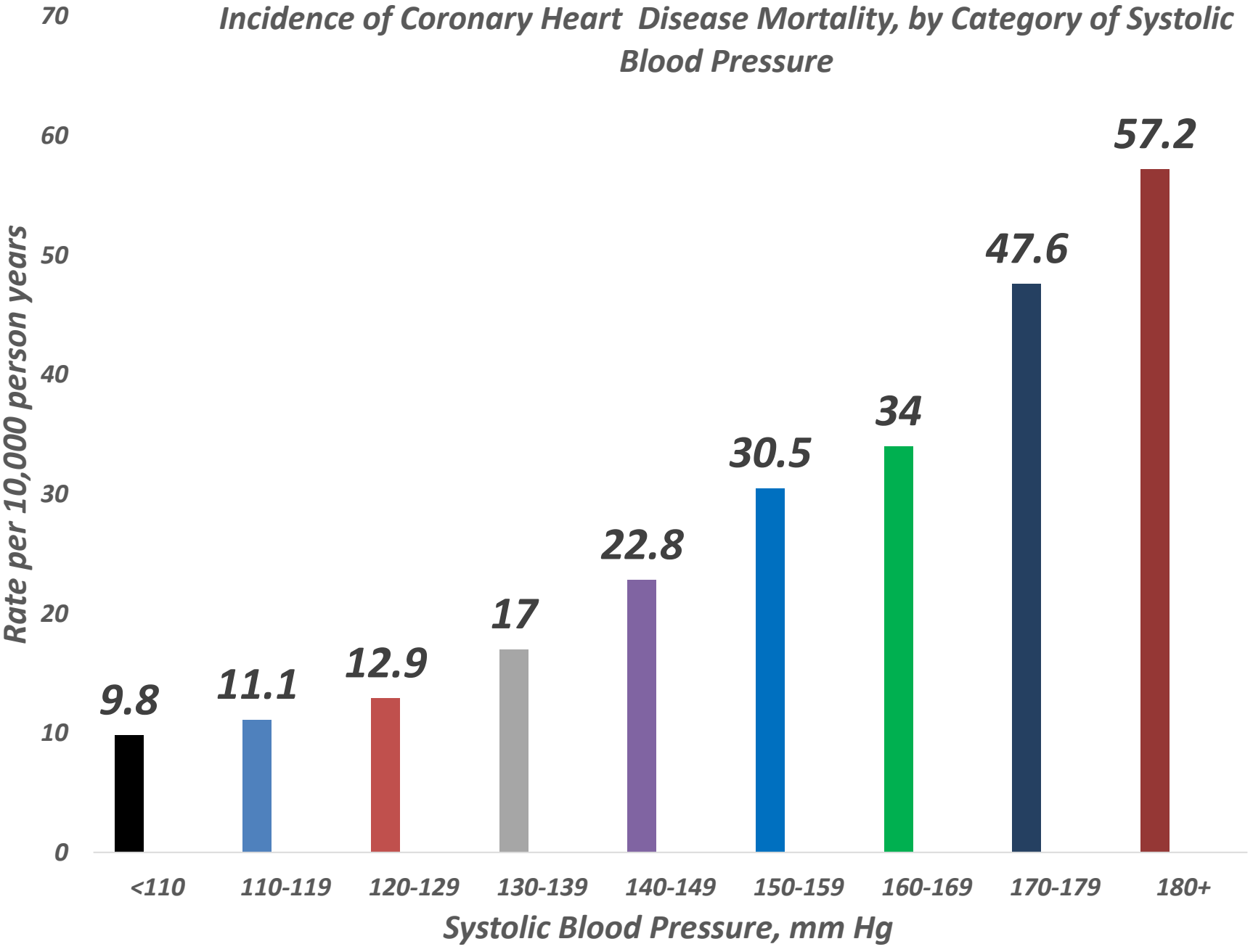

Incidence of Coronary Heart Disease Mortality, by Category of Systolic Blood Pressure
Rate per 10,000 person years
70
60
50
40
30
20
10
0
9.8
11.1
12.9
17
22.8
30.5
34
47.6
57.2
<110
110-119
120-129
130-139
140-149
150-159
160-169
170-179
180+
Systolic Blood Pressure, mm Hg

Figure 2B

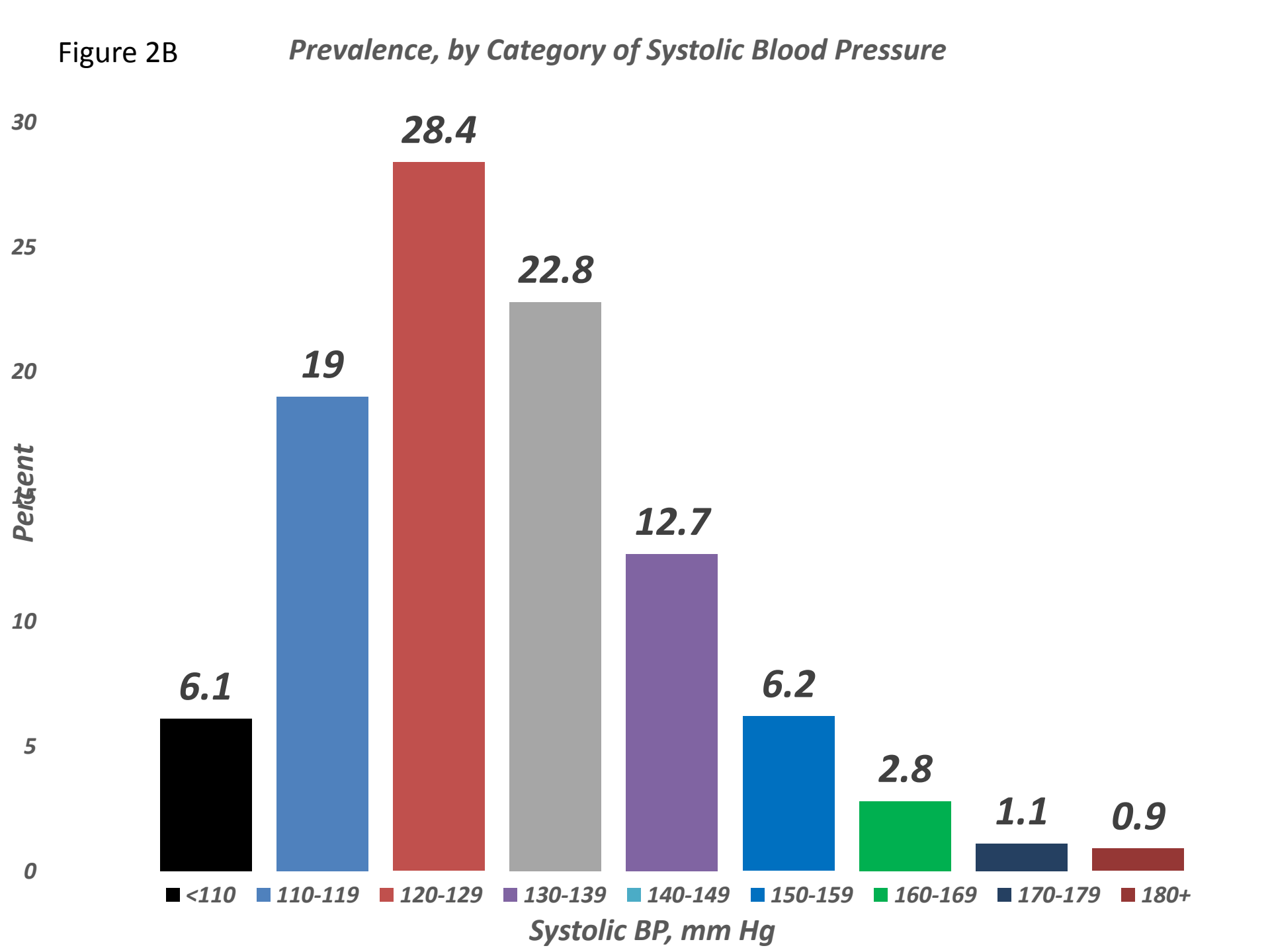

Prevalence, by Category of Systolic Blood Pressure
30
25
20
10
5
0
Percent
28.4
22.8
19
12.7
6.2
2.8
1.1
0.9
<110
110-119
120-129
130-139
140-149
150-159
160-169
170-179
180+
Systolic BP, mm Hg

Figure 2C

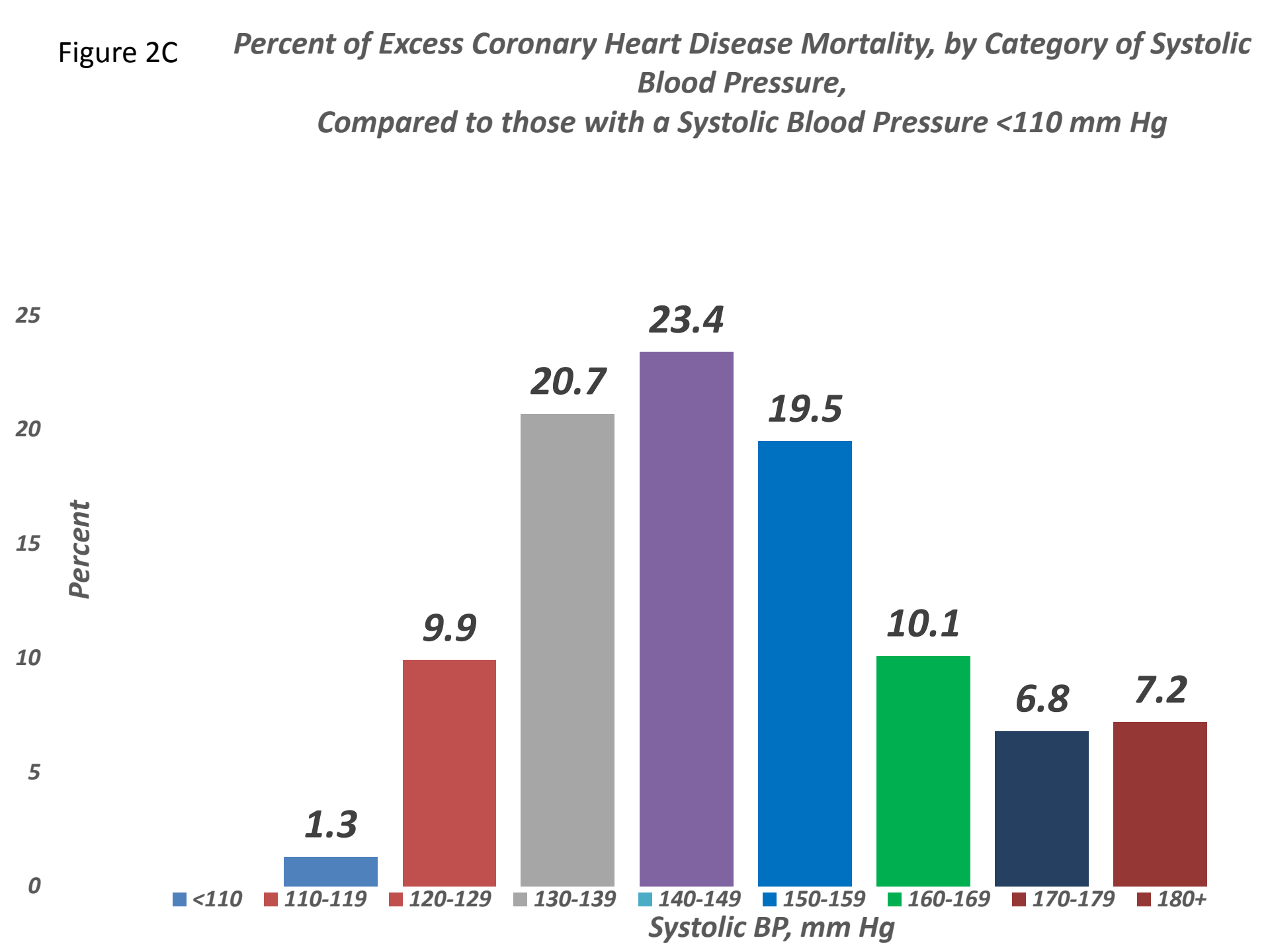

Percent of Excess Coronary Heart Disease Mortality, by Category of Systolic Blood Pressure,
Compared to those with a Systolic Blood Pressure <110 mm Hg
25
20
15
10
5
0
Percent
1.3
9.9
20.7
23.4
19.5
10.1
6.8
7.2
<110
110-119
120-129
130-139
140-149
150-159
160-169
170-179
180+
Systolic BP, mm Hg

Figure 3

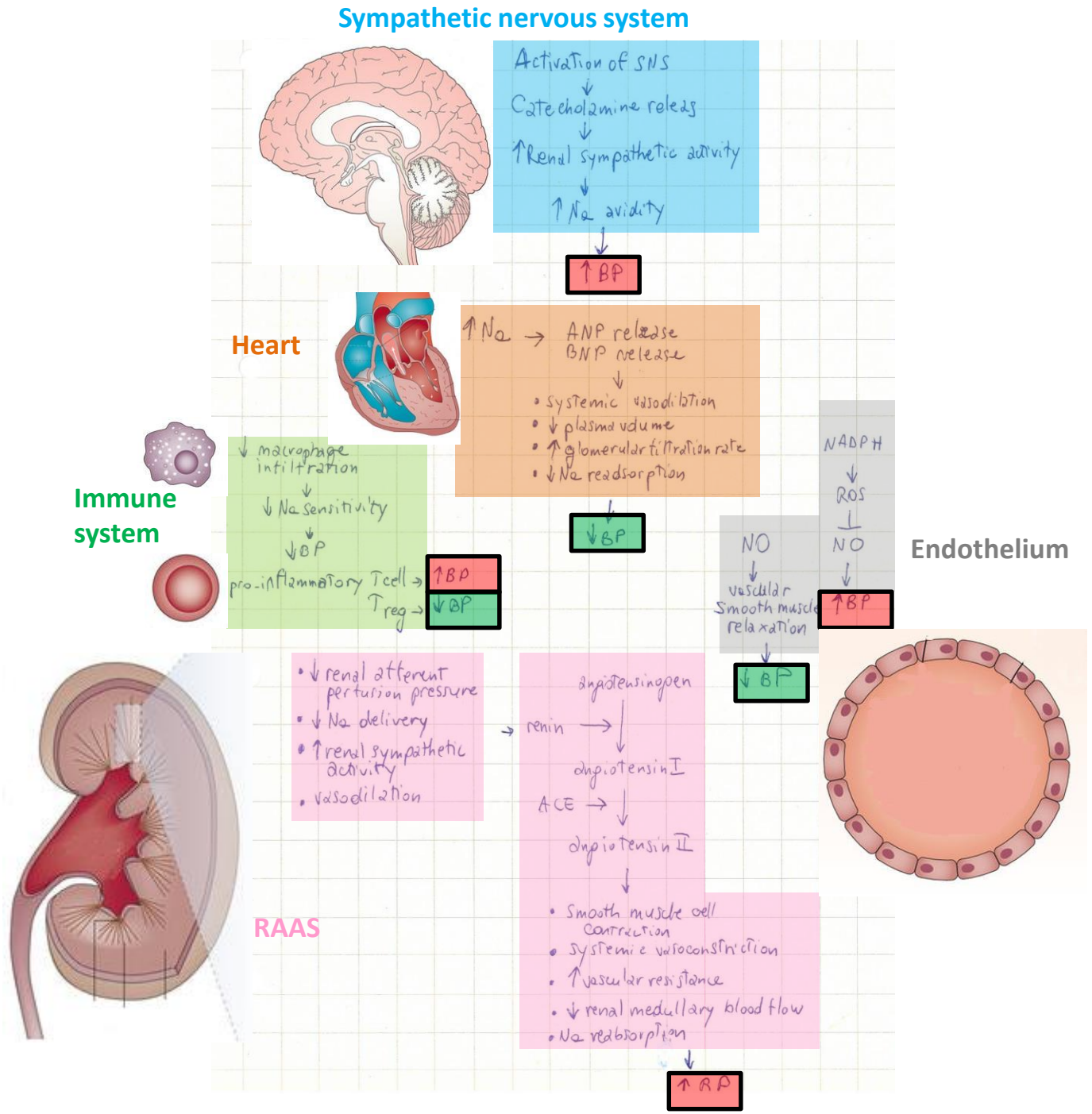

Sympathetic nervous system
Activation of SNS
Catecholamine releas
↑Renal sympathetic activity
↑Na avidity
↑BP
Heart
↑Na → ANP release
BNP release
• Systemic vasodilation
• ↓plasma volume
• ↑glomerular filtration rate
• ↓Na readsorption
↓BP
Immune system
↓macrophage infiltration
↓Na sensitivity
↓BP
pro-inflammatory Tcell → ↑BP
Treg → ↓BP
NADPH
ROS
NO
↑BP
NO
vascular Smooth muscle relaxation
↓BP
Endothelium
• ↓renal afferent pertusion pressure
• ↓Na delivery
• ↑renal sympathetic activity
• vasodilation
angiotensinogen
renin →
angiotensin I
ACE →
angiotensin II
• Smooth muscle cell contraction
• Systemic vasoconstriction
• ↑vascular resistance
• ↓renal medullary blood flow
• Na readsorption
↑BP
RAAS

Figure 4

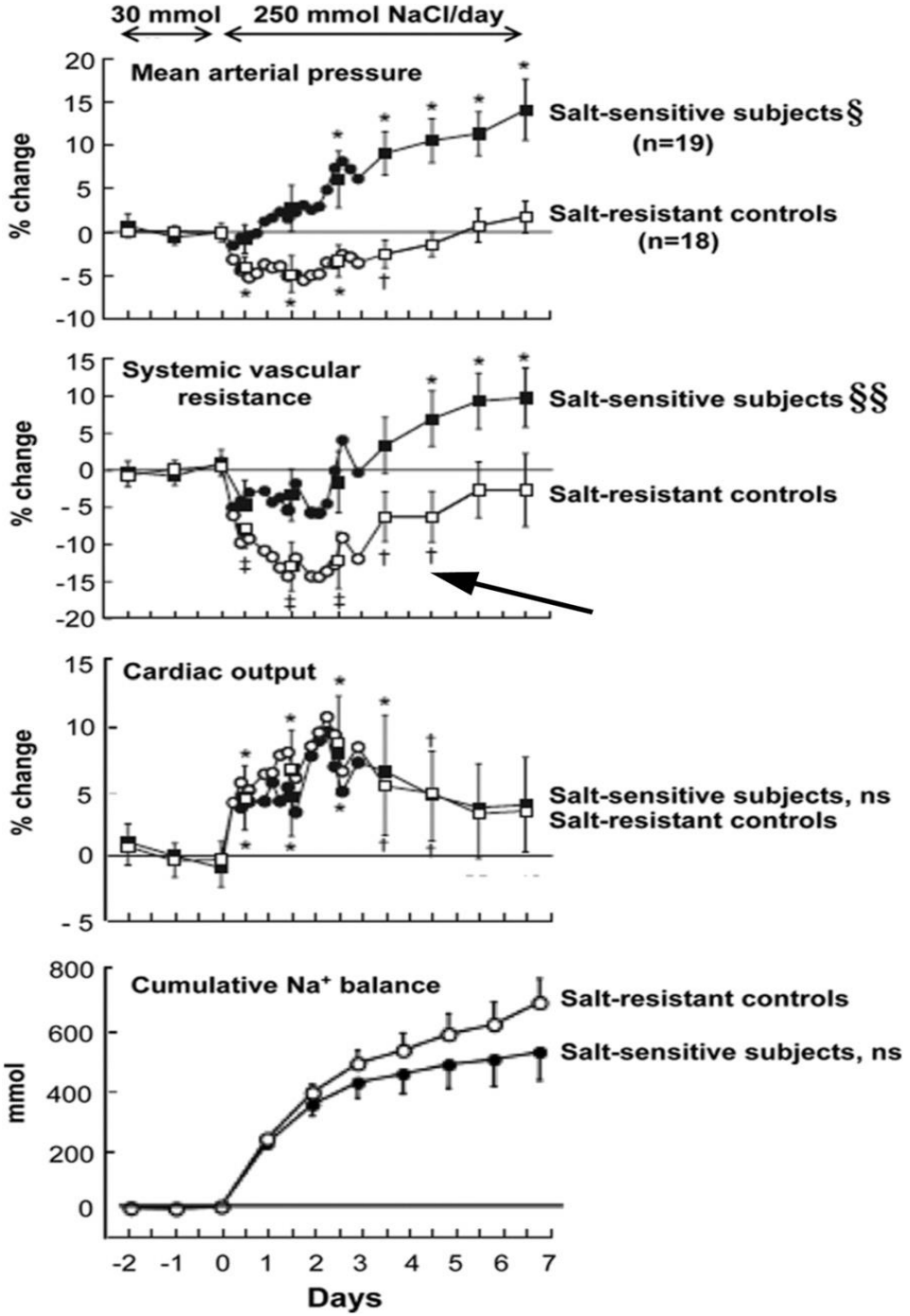
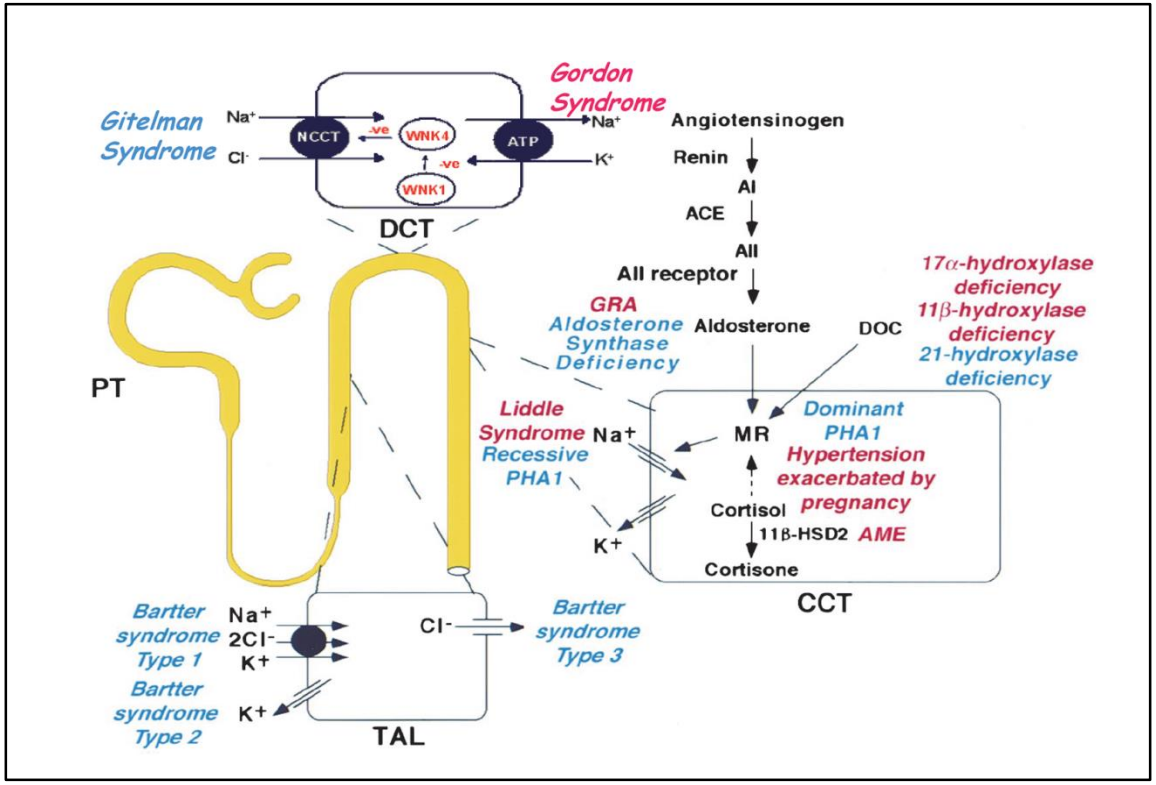

30 mmol
250 mmol NaCl/day
Mean arterial pressure
% change
Salt-sensitive subjects §
(n=19)
Salt-resistant controls
(n=18)
Systemic vascular resistance
% change
Salt-sensitive subjects §§
Salt-resistant controls
Cardiac output
% change
Salt-sensitive subjects, ns
Salt-resistant controls
Cumulative Na⁺ balance
mmol
Salt-resistant controls
Salt-sensitive subjects, ns
Days

Figure 5


Gitelman Syndrome
Na+
Cl-
NCCT
-ve
WNK4
-ve
WNK1
ATP
Na+
K+
Gordon Syndrome
DCT
PT
Angiotensinogen
Renin
AI
ACE
AII
AII receptor
GRA
Aldosterone Synthase Deficiency
Aldosterone
DOC
17α-hydroxylase deficiency
11β-hydroxylase deficiency
21-hydroxylase deficiency
Liddle Syndrome
Recessive PHA1
Na+
MR
Dominant PHA1
Hypertension exacerbated by pregnancy
Cortisol
11β-HSD2
AME
Cortisone
K+
CCT
Bartter syndrome Type 1
Na+
2Cl-
K+
Bartter syndrome Type 2
K+
Cl-
Bartter syndrome Type 3
TAL