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2024 ESC Guidelines for the management of elevated blood pressure and hypertension Supplementary data

Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and *endorsed by the European Society of Endocrinology (ESE), and the European Stroke Organisation (ESO)*

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Abbreviations and acronyms

ABI	Ankle–brachial index
ABPM	Ambulatory blood pressure monitoring
ACCORD-BP	Action to Control Cardiovascular Risk in Diabetes–Blood Pressure
ACE	Angiotensin-converting enzyme
ACR	Albumin-to-creatinine ratio
ADHERE	Acute Decompensated Heart Failure National Registry
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
BMI	Body mass index
BP	Blood pressure
BPLTTC	Blood Pressure Lowering Treatment Trialists' Collaboration
BSA	Body surface area
CAC	Coronary artery calcium
CCB	Calcium channel blocker
CHAP	Cardiovascular Health Awareness Program
CI	Confidence interval
CIMT	Carotid intima-media thickness
CK-MD	Creatinine kinase–muscle/brain
CKD	Chronic kidney disease
CO	Carbon monoxide
COVID-19	Coronavirus disease 19
CT	Computed tomography
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension

ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
ENaC	Epithelial sodium channel
EPIC	European Prospective Investigation into Cancer and Nutrition
ESC	European Society of Cardiology
ET_A	Endothelin A
ET_B	Endothelin B
GLP-1	Glucagon-like peptide 1
HBPM	Home blood pressure monitoring
HFpEF	HF Heart failure with preserved ejection fraction
HFrEF	HF Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HMOD	Hypertension-mediated organ damage
HOPE	Heart Outcomes Prevention Evaluation
HR	Hazard ratio
Hs-cTn	High-sensitivity cardiac troponin
HYVET	Hypertension in the Very Elderly Trial
IDHOCO	International Database of HOme Blood Pressure in Relation to Cardiovascular Outcomes
INFINITY	Intensive Versus Standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in Older People
LA	Left atrium
LDH	Lactate dehydrogenase
LV	Left ventricular
LVH	Left ventricular hypertrophy
MEN	Multiple endocrine neoplasia
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
NO	Nitric oxide
NO_2	Nitrogen dioxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
OSAS	Obstructive sleep apnoea syndrome
PAST-BP	Prevention after Stroke—Blood Pressure
PODCAST	Prevention of Decline in Cognition after Stroke Trial
PPGL	Phaeochromocytoma/paraganglioma
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PROGRESS	Perindopril Protection against Recurrent Stroke Study
PURE	Prospective Urban Rural Epidemiology
PWV	Pulse wave velocity
RAAS	Renin–angiotensin–aldosterone system
RADIANCE-HTN	A Study of the Recor Medical Paradise System in Clinical Hypertension
RCT	Randomized controlled trial
RESPECT	Recurrent Stroke Prevention Clinical Outcome
RWT	Relative wall thickness
SCOPE	Study on Cognition and Prognosis in the Elderly
SCORE2	Systematic Coronary Risk Evaluation 2
SCORE2-OP	Systematic Coronary Risk Evaluation 2–Older Persons
SHEP	Systolic Hypertension in the Elderly Program
SNP	Single nucleotide polymorphism
SO_2	Sulfur dioxide
SPS3	Secondary Prevention of Small Subcortical Strokes
SPRINT	Systolic Blood Pressure Intervention trial
SGLT2	Sodium-glucose cotransporter-2
STEP	Strategy of Blood Pressure Intervention in Elderly Hypertensive Patients
STEP-1	Semaglutide Treatment Effect in People with Obesity
Syst-Eur	Systolic Hypertension in Europe
TIA	Transient ischaemic attack

1. Pathophysiology of elevated blood pressure

Persistently high blood pressure (BP) in systemic arteries is the hallmark of hypertension. Hypertension is the most important modifiable risk factor for all-cause morbidity and mortality globally. Historically it was believed that most patients (90%–95%) with high BP have essential or primary hypertension, where the exact cause remains unknown, while 5%–10% have secondary hypertension, with a known cause. However, more recent data indicate that secondary hypertension is more common than previously reported. The pathophysiology of hypertension involves complex interactions between environmental and behavioural factors, genes, hormonal networks, and multiple organ systems.

There are two major physiological components of BP: a static component, mainly determined by peripheral resistance, and a pulsatile component, which depends on aortic elastic properties. Both components are regulated by a number of physiological pathways, including renal (sodium: volume homeostasis), neural (sympathetic nervous system), hormonal [renin–angiotensin–aldosterone system (RAAS)], and others) and vascular mechanisms.[1] Dysregulation of these processes can lead to BP elevation, which over time results in hypertension-mediated organ damage (HMOD) and adverse cardiovascular outcome. Blood pressure trajectories over the life course differ by sex, with lower values in youth and steeper BP increase in women from the third decade of life.[2]

1.1. Renal mechanisms

The kidneys are a key regulator of BP, and impaired renal function leads to hypertension. The most important renal mechanisms for BP control are the pressure–natriuresis relationship and the RAAS. The pressure–natriuresis relationship reflects the ability of kidneys to balance urinary sodium excretion with dietary sodium intake to maintain a normal BP.[3] In healthy subjects, the RAAS is activated by low sodium intake, stimulating renal sodium reabsorption and preserving intravascular volume and BP. High sodium intake leads to suppression of the RAAS to facilitate natriuresis.[4] Chronic activation of the RAAS shifts the pressure–natriuresis curve to the right, with higher BP values required to excrete an equivalent sodium load. In contrast, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) shift the curve to the left, reducing BP values necessary for effective natriuresis. Paracrine regulation of tubular ion transport (i.e. sodium, potassium, and chloride) and crosstalk in the different nephron segments also play a key role in regulating BP. Impaired tubular ion transport leads to the development of salt-sensitive hypertension and excessive sodium and volume retention.[5–7] Renal vasoconstriction can lead to renal ischaemia, which stimulates inflammation and local generation of reactive oxygen species; these factors contribute to microvascular remodelling, arteriolar damage, impaired sodium excretion, and ultimately, hypertension.[8] Salt-sensitive hypertension is more common in patients

with obesity or diabetes, in women, and in patients of African ethnicity.[9,10] Many renal- and RAAS-related BP regulatory mechanisms differ between men and women.[11]

1.2. Vascular mechanisms

Structural and functional changes in small and large arteries are involved in the pathophysiology of hypertension. Peripheral vascular resistance is mainly controlled at the level of small arteries and arterioles (diameter < 250 μm) by the sympathetic nervous system, humoral factors, and local autoregulation. Endothelial dysfunction and vascular remodelling are early hallmarks of hypertension and target-organ damage.[12] These vascular alterations both initiate and maintain hypertension and, therefore, are both a cause and consequence of high BP. Endothelial dysfunction may precede structural changes and can also contribute to atherosclerotic plaque development in large vessels and long-term complications such as established cardiovascular disease (CVD). The endothelium produces several factors that regulate vascular tone, cellular adhesion, inflammation, thrombosis, and vascular smooth-muscle cell growth.[13,14] Endothelial dysfunction is characterized by reduced nitric oxide (NO) availability due to an altered balance between production and degradation.[15] At the molecular level, many of these processes are associated with oxidative stress (increased bioavailability of reactive oxygen species) and activation of redox-sensitive signalling pathways.[16] In post-menopausal women, oestrogen deficiency reduces the biological availability of NO.[17] In response to hypertensive stimuli, such as angiotensin II and high salt intake, T cells become pro-inflammatory and mediate endothelial dysfunction, infiltrating the brain, blood vessels, heart, and kidneys. This immune activation is suspected to have a role in developing and maintaining hypertension.[18] The role of adaptive immunity seems to be greater in men than in women.[19] The age-associated large-arterial remodelling with increased collagen deposition and rupture of elastin fibres also precedes and accelerates the onset of hypertension.[20] Importantly, since synthesis of elastin takes place *in utero* and during the first years of life and stops thereafter, elastin damage is mostly irreversible.[21]

Increased vascular stiffening of large arteries leads to a reduction of their buffering function on pulsatile flow generated by cardiac contractions, with a decline in central diastolic BP and increase in central systolic BP. The resulting increased haemodynamic pulsatile load on target organs is implied in the pathophysiology of HMOD and increased incidence of CVD events.[22,23] Sex differences in arterial ageing assessed by small-artery remodelling and arterial stiffness are well documented, with a steeper increase over time occurring in women than in men, and starting from the third decade of life.[24–26]

1.3. Neural mechanisms

The sympathetic nervous system is more activated in patients with hypertension compared with those who have normal BP.[27] Sympathetic activation increases BP by several mechanisms, including peripheral vasoconstriction, potentiation of cardiac contraction, reduction of venous capacitance, and modulation of the renal sodium and water excretion.[28,29] Sympathetic activation is present already in early stages of hypertension, and increases with age and hypertension severity; being especially involved in pathophysiology of obesity-related hypertension, hypertension secondary to chronic kidney disease (CKD) and obstructive sleep apnoea syndrome (OSAS).[30] Cardiovascular autonomic regulation differs between women and men. Women demonstrate larger increases in sympathetic nervous activity with age and obesity than men, and have a lower baroreceptor reflex sensitivity and lower heart rate variability.[31,32] Stress may also activate a stronger response from the central autonomic system in women than in men, involving brain–heart crosstalk through neurohumoral circuits that stimulate the immune system, heart, and adrenal glands, thereby promoting BP increase and a pro-inflammatory state.[33]

1.4. Hormonal mechanisms

Besides the RAAS, numerous circulating factors acting in an endocrine/paracrine manner, such as endothelin-1 and natriuretic peptides, and sex hormones, influence BP regulation. Natriuretic peptides play a key role in BP regulation through their natriuretic, diuretic, and vasorelaxant effects.[34] Endothelin-1 is a potent endogenous vasoconstrictive peptide, synthesized in almost any cell type including vascular endothelial and smooth-muscle cells; it acts in an autocrine/paracrine way through its receptors endothelin A (ET_A) and endothelin B (ET_B).[35] The importance of natriuretic peptides and endothelin on hypertension pathophysiology make them ideal targets for novel BP-lowering antihypertensive drugs.[34,35] The X chromosome contains autosomal-like regions that affect the cardiovascular system, immune system, and the brain, separate from reproduction and sex hormonal influences.[36] Oestrogens modulate BP directly through non-genomic effects on vascular, renal, and cardiac cells, by reducing calcium pathways and, indirectly through genomic actions, controlling expression of potent vasoconstrictors, such as angiotensin II, endothelin-1, and catecholamines, and the RAAS and endothelin-1 pathway.[37,38] Whereas the fall in endogenous oestrogen with menopause has been associated with hypertension, exogenous oestrogen-progesterone oral contraceptive drugs are a well-known cause of hypertension.[39,40] Progesterone is a potent mineralocorticoid receptor antagonist (MRA), which acts on the mineralocorticoid receptor to prevent sodium retention, and counteracts the sodium-retaining effect of oestrogen. Testosterone both increases and decreases BP depending on age, and may contribute to the increase in CVD risk observed with ageing in males and after menopause in females,[41] as well as the BP elevation seen in some transgender individuals.[42]

1.5. Environmental factors

Environmental factors, such as air and noise pollution, can facilitate chronic non-communicable diseases and are associated with an increased burden of CVD.[43] More specifically, chronic exposure to road traffic, railway, or aircraft noise is modestly associated with elevated BP and hypertension.[44,45] Exposure to air pollution, especially combustion-related particulate matter [especially particles <2.5 μm in diameter ($PM_{2.5}$)] and associated co-pollutants (such as nitrogen dioxide (NO_2), carbon monoxide (CO), and sulfur dioxide (SO_2)), also contributes to high BP and overall cardiovascular mortality.[46] The $PM_{2.5}$ fraction, which includes black carbon, passes the blood–air barrier in the alveoli and is systemwide recirculated, thus inducing systemic effects. Mechanisms implicated include perturbation of the autonomic nervous system, and endothelial dysfunction caused by oxidative stress and release of pro-inflammatory mediators.[45,47]

Among environmental factors, the role of infectious diseases in CVD has been increasingly acknowledged. For example, human immunodeficiency virus (HIV) infection has been consistently associated with hypertension, both through direct mechanisms, including: chronic inflammation and microbial gut translocation; immunosenescence and impact on vascular function; RAAS and sympathetic nervous system; and indirect mechanisms, such as the effect of antiretroviral therapy.[48] A number of population studies revealed an increase in BP during the coronavirus disease 2019 (COVID-19) pandemic, which were more marked in women than in men;[49] hypertension diagnosis was increased

after COVID-19 regardless of COVID-19 severity.[50] Both direct effects, related to vascular dysfunction induction, and indirect effects, related to disruption of healthcare system, are implied.[51]

1.6. Socio-economic and psychosocial factors

Social factors and deprivation are important determinants of hypertension. Low socio-economic status is associated with increased hypertension prevalence. Several mechanisms have been identified, such as disparities in material circumstances, socio-economic deprivation, health behaviours, and psychological stressors.[52,53] Psychosocial stress promotes increased BP through direct biological effects (activation of the sympathetic nervous system and pro-inflammatory pathways), but also through socio-economic, environmental, and behavioural risk factors (e.g. unhealthy lifestyle, poor adherence).

Gender and ethnicity are also important factors contributing to hypertension. Gender includes gender identity, as well as gender norms, roles, and societal relations, and has strong intersections with social determinants of health, such as socio-economic and sociocultural conditions, psychosocial stress, discrimination, and ethnicity.[54] Increased stress relating to discrimination is associated with higher hypertension risk in African-Americans, an effect only partially explained by classical hypertension risk factors.[55] Women having experienced sexual assault and harassment had a greater risk of hypertension after adjusting for relevant covariates.[56] Increasing evidence indicates that the refugee and migrant experience is an independent risk factor for CVD and hypertension.[57] Hypertension is common in this population and the prevalence is higher in women than in men.[58] Factors contributing to hypertension in refugees and migrants include challenges with drug adherence and medication beliefs, psychosocial stress, malnutrition, and barriers to healthcare.[59,60] Guidelines for health assessment among refugees and migrants have been established in some countries, and screening for hypertension has been highlighted as a recommendation.[61]

1.7. Behavioural factors

Though the pathophysiology of hypertension is complex and multifaceted, consistent evidence highlights the importance of behavioural factors, such as physical inactivity, smoking, excess alcohol consumption, and unhealthy dietary habits (i.e. diets favouring high sodium, low potassium, and limited fruit and vegetable intake), in developing and maintaining hypertension.[62]

1.7.1. Dietary habits

Excess salt intake is a major contributor to hypertension and CVD.[63] Reducing dietary salt is mostly effective in patients with elevated BP who are salt sensitive, though true salt sensitivity can be identified only with complex tests that are non-applicable in clinical practice. Progesterone deficiency after menopausal transition leads to higher sodium reabsorption and sodium-sensitive hypertension in women.[38]

Multiple factors have been implicated in salt-sensitive hypertension, including impaired pressure natriuresis, vascular dysfunction, gut microbiome, and activation of immune and inflammatory processes.[64–66] Low potassium intake is associated with increased BP; the proportion of hypertension attributable to low potassium excretion is 6.2%.[67] BP-elevating mechanisms of low-potassium diet involve up-regulation of the sodium chloride co-transporter leading to increased renal sodium retention.[68] Increased salt sensitivity in black hypertensive individuals may be influenced by low potassium intake.[64] The association between potassium intake, systolic BP, and CVD events is sex specific; women with a high sodium intake in particular benefit most from a higher potassium intake with regard to systolic BP.[69]

Dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Mediterranean diet, both high in fruit, vegetables, whole grains, nuts, and unsaturated oils, and minimizing the consumption of red and processed meat, are beneficial for reducing BP vs. a standard Western diet.[70,71]

1.7.2. Obesity and physical inactivity

Obesity, defined as increased body mass index (BMI), or abdominal obesity, defined as increased waist circumference, are directly associated, regardless of dietary habits, with an increased risk of hypertension.[72] Reducing body weight to normal in overweight or obese individuals reduces the relative risk of incident hypertension by 24%–40% and 40%–54%, respectively.[73] Many mechanisms are involved in obesity-induced hypertension, including increased sympathetic nervous system and RAAS activity, altered production and secretion of adipokines (e.g. high leptin, reduced adiponectin), OSAS, and renal mechanisms (e.g. compression of the kidneys by visceral fat and increased renal sodium reabsorption with volume expansion).[74] Notably, even non-obese patients should be explored for OSAS in cases of resistant hypertension.[75]

Visceral adipose tissue also becomes resistant to insulin and leptin and is the site of altered secretion of molecules and hormones such as adiponectin, leptin, resistin, tumour necrosis factor, and interleukin 6, which exacerbate obesity-associated CVD.[76]

Observational studies have consistently demonstrated the inverse, dose–response effect of physical inactivity with risk of hypertension. In 2017, a meta-analysis of 29 studies including more than 330 000 people reported that each reduction of leisure-time physical activity by 10 metabolic-equivalent h/week increased the risk of hypertension by 6%.[77] Mechanisms underlying the BP-lowering effects of physical activity include weight and fat loss, reduced sympathetic nervous system and RAAS activity, and improved vascular function and structure.[78] Interestingly, occupational physical activity may not be beneficial in terms of cardiovascular health and may be associated with vascular HMOD.[79]

1.7.3. Alcohol and smoking

Acute alcohol ingestion is associated with a decrease in BP in the first hours and a sustained increase in BP after 12 h of intake. By contrast, chronic consumption of alcoholic beverages is associated with increased incidence of hypertension in men and women, with this association being linear and dose-responsive in nature, meaning there is no nadir level of chronic alcohol consumption associated with lower risk of developing hypertension.[80,81] Results from observational studies, which are subject to confounding by other behavioural and sociodemographic factors, have been supported by Mendelian randomization studies, providing evidence on the causal nature of this association, and also did not support the putative cardioprotective effect of low-to-moderate consumption of alcoholic beverages.[82] Mechanisms involved in the harmful effects of alcohol consumption are probably related to sympathetic activation and oxidative stress.[83]

Though the deleterious effect of smoking on cardiovascular health is well established, the relationship with BP is less clear.[84,85] However, smoking causes vascular injury and is a vascular risk factor, and accordingly, smoking cessation is recommended to maintain vascular health and prevent CVD, including erectile dysfunction, among adults with elevated BP and hypertension.[86–88]

Concerns about cardiovascular impact of electronic cigarette (e-cigarette) use have been raised.[89] A recent meta-analysis showed a modest but significant BP raise associated with e-cigarette use,[90] whereas in a recent population sample representative of US population smoking, but not e-cigarette use, increased the risk of self-reported hypertension.[91]

1.7.4. Sleep

Increasing evidence supports a causal relationship between sleep disorders and elevated BP.[92] Both short sleep duration and poor sleep quality have been associated with high BP.[93,94] Sleep loss and fragmentation can induce dysregulation of neuroendocrine, adrenergic, and pro-inflammatory pathways. In OSAS, repetitive hypoxia cycles additionally contribute to sympathetic activation.[92] Although OSAS is more prevalent in men, and an independent risk factor for hypertension in both sexes, the risk for hypertension starts at a lower sleep apnoea severity in women than in men.[95]

1.8. Genetic factors

Several rare, monogenic forms of secondary hypertension exist, such as familial hyperaldosteronism I to IV, Liddle syndrome, and Gordon syndrome (see *Section 3 of the supplement*). Also, there are certain forms of congenital adrenal hyperplasia, due to genetic defects in steroidogenic genes, which manifest with hypertension. However, most essential or primary hypertension is a complex polygenic disease, and interaction with environmental factors plays a major role in the development and severity of primary hypertension. Nonetheless, heritability of BP is high (approximately 30%–50%) and several BP-associated loci have been identified by analysing single nucleotide polymorphisms (SNPs) from targeted and genome-wide arrays; SNPs associated with hypertension were then combined to create polygenic risk scores.[96,97] However, the SNPs identified to date in genome-wide association studies as being associated with the BP phenotype explain <30% of the estimated heritability of BP, and the effect of each SNP is small.[98] Recent studies have suggested that missing heritability in hypertension may be due, at least in part, to foetal programming, possibly mediated by epigenetic mechanisms.[99] Chromosome effects have also been implicated. A number of autosomal regions on the X chromosome affect phenotypic sex differences in many organs, including in the cardiovascular system.[36] Also, mosaic loss of the Y chromosome in blood cells has been associated with increased risk of CVD.[100]

2. Clinical consequences of elevated blood pressure

2.1. Hypertension-mediated organ damage

HMOD is characterized by structural or functional alterations in the arterial vasculature, and/or the end organs these arteries supply, caused by increased BP.[101] It is acknowledged that HMOD could be considered a misnomer, since other exposures can at times also cause these structural or functional changes (e.g. diabetes and hyperlipidaemia). However, since HMOD is an established term, familiar to clinicians, and since the HMOD types outlined in this document are all consequences of hypertension and are also all known to be risk modifiers among persons with BP abnormalities, we have chosen to continue using the term HMOD. End organs include the heart, brain, kidneys, and eyes (*Figure 2* in the main text). Women more often present with HMOD in the heart [left ventricular hypertrophy (LVH) and left atrial (LA) dilatation].[102] Evidence of HMOD usually indicates long-standing elevated BP and/or hypertension, and confers incremental prognostic information regarding CVD risk in all BP categories.[101,103,104] Unless treated, HMOD typically gradually progresses from asymptomatic to symptomatic, ultimately resulting in overt CVD events.[101]

2.1.1. The heart

Chronically elevated BP leads to increased left ventricular (LV) wall stress and afterload. As a consequence, LV remodelling and hypertrophy occur, both of which influence LV diastolic and systolic function. These pathological changes constitute hypertensive heart disease. LVH is more common in women than in men at similar age.[105,106] LVH may also be less modifiable by BP-lowering treatment in women than in men.[107] In treated, uncomplicated hypertension, absolute risk for CVD is higher in men than in women, but when LVH is present, women and men often have similar absolute risk for CVD.[105] However, the presence of LVH is affected by the method used for indexing LV mass (e.g. body surface area), which should be considered when interpreting available studies, to avoid over- or under-estimating LVH. Nonetheless, the presence of LVH might, at least partially, offset the sex difference in CVD risk. LVH is a powerful prognostic marker in hypertension and is associated with increased risk of myocardial infarction, heart failure, atrial fibrillation (AF), stroke, and cardiovascular death, independent of BP and cardiac biomarkers.[108–112]

Increased LV pressure influences LA performance and promotes LA dilatation and dysfunction and AF, commonly seen in adults with hypertensive heart disease. If LA pressure remains high, pulmonary hypertension and subsequent right ventricular dysfunction may develop. The prevalence of LA dilatation appears higher in women than in men with hypertension, even when obesity or LVH is co-present.[113] BP-lowering treatment may not significantly modify LA dilatation,[113] but prevents AF.[114] Of course, elevated BP is also an important contributor to coronary artery disease.

2.1.2. The brain

The brain is an early target of HMOD, which may manifest as stroke, transient ischaemic attack (TIA), and cognitive decline. In hypertension, silent brain infarcts, white-matter lesions, and cerebral microbleeds predict future stroke and cognitive decline independently of other vascular risk factors.[115] Hypertension alters the structure of cerebral blood vessels and disrupts dynamic autoregulation of brain perfusion. High BP is a major risk factor for the development and rupture of cerebral aneurysms. Small-vessel disease is associated with increased cerebral arterial pulsatility in large cerebral vessels and reduced cerebrovascular reactivity. Hypertension-induced small-vessel disease consequently leads to lacunar infarction, leucoaraiosis, white-matter changes, and atrophy, as well as increased risk for intracerebral haemorrhage.[116] In addition, isolated nocturnal hypertension is associated with white-matter hyperintensity.[117] In a study of older persons with high systolic BP and/or pulse pressure, women (mean age 65 years) demonstrated less white-matter hyperintensity than men.[118]

Prolonged increase in BP is associated with accelerated cognitive decline, possibly due to cerebral vessel remodelling, impaired autoregulation, and hypoperfusion that causes diffuse ischaemic changes in the periventricular and deep white matter. Neuroimaging and biomarker studies have shown that higher systolic BP is associated with smaller regional and total brain volumes and reduced brain volume over time. Furthermore, greater levels of β-amyloid plaques, atrophy, and neurofibrillary tangles are present in the brains of patients with hypertension.[119]

2.1.3. The kidneys

CKD is defined as abnormalities of kidney structure or function present for at least 3 months with implications for health (Kidney Disease Improving Global Outcomes BP in CKD guideline).[120,121] Renal function is evaluated initially using serum creatinine and estimated glomerular filtration rate (eGFR) equations. Additional tests, such as cystatin C or clearance measurements, might be useful in specific circumstances when eGFR based on serum creatinine is less accurate. Kidney damage can further be assessed by the presence of albuminuria, preferably in an early morning urine sample, using the urine albumin:creatinine ratio (ACR). CKD is often graded by both eGFR and albuminuria.[120] The pathogeneses of hypertension and CKD are interrelated, with hypertension being both a complication and driver of kidney disease progression.[122]

2.1.4. The vascular system

Endothelial dysfunction, arterial remodelling, and increased vascular stiffness contribute to the development of hypertension but are also sequelae of hypertension.[22,123,124] Three vascular beds are commonly assessed to detect arterial HMOD: carotid arteries, aorta, and peripheral arteries.[125] Carotid–femoral pulse wave velocity (PWV) is the most commonly used test for measuring large artery stiffness.[126,127] A PWV of >10 m/s is considered abnormal and reflects aortic dysfunction and stiffening. Arterial stiffness increases with age and has short-term and long-term prognostic importance.[22,128]

Atherosclerotic plaques can be assessed at the carotid artery or femoral artery site using ultrasound. While carotid intima-media thickness (CIMT) assessment does provide prognostic information (particularly at the internal carotid location), the improvement in risk prediction over more traditional risk scores is small.[129,130] In addition, CIMT also suffers from inter-reader reliability problems and a lack of widely acceptable reference values (which are age dependent).[131]

The ankle–brachial index (ABI) is the ratio of the systolic BP measured at the ankle to that measured at the brachial artery and is a non-invasive measurement of atherosclerotic burden in medium-to-large arteries.[132] An ABI of <0.9 typically indicates lower-extremity artery disease and advanced atherosclerosis, and is a predictor of future CVD.[133]

2.1.5. The eyes

Hypertension causes retinopathy characterized by retinal microvascular changes comprising generalized and focal retinal arteriolar narrowing, arteriovenous nicking, retinal haemorrhage, microaneurysms and, in severe cases, optic disc and macular oedema. Hypertension is further associated with retinal pathologies such as retinal vascular occlusion (artery and/or vein occlusion), retinal arteriolar emboli, macro-aneurysms, ischaemic optic neuropathy, glaucoma, and age-related macular degeneration. It is also a major determinant of the progression of diabetic retinopathy.[134]

Signs of hypertensive retinopathy may be evident in patients >40 years old, and an estimated 10% of hypertensive adults without diabetes have mild hypertensive retinopathy, and up to 70% of patients with severely uncontrolled hypertension.[135] Malignant hypertension is associated with concurrent analogous multi-organ damage in the brain, heart, and eyes, possibly through common mechanisms involving capillary leakage.[136]

Traditionally diagnosed via a clinical fundoscopic examination, hypertensive retinopathy often co-exists with other markers of HMOD, reflects long-term control of hypertension, and can predict future CVD events. New technologies, including non-invasive optical coherence tomography angiography, analysis of retinal vessel diameters and dilation capacity, artificial intelligence, and mobile ocular imaging instruments have emerged that might facilitate more accurate diagnosis of hypertension-associated eye disease in the future.

2.2. Association of high blood pressure with cardiovascular and non-cardiovascular outcomes

2.2.1. Epidemiology

Hypertension is a leading global risk factor for cardiovascular mortality and disability in adult women and men.[137] In the Global Burden of Diseases 2019 study, hypertension was ranked as the top risk factor contributing to CVD in 1990–2019.[138] Though the worldwide age-standardized prevalence of hypertension has remained constant over the past three decades—approximately 32% of women and 34% of men—the actual number of patients with hypertension has doubled over this period due, in large part, to ageing of the population.[139] This high prevalence of hypertension is consistent worldwide, irrespective of the country's income status. Hypertension becomes progressively more common with advancing age, with a prevalence of >60% in people aged >60 years. As populations age, adopt more sedentary lifestyles, and increase body weight, the prevalence and burden of hypertension is expected to continue to rise. It is estimated that the number of people with hypertension will increase by 15%–20% by 2025, reaching close to 1.5 billion.[139]

2.2.2. Stroke and cognitive impairment

Hypertension is the most prevalent risk factor for stroke and has been reported in 64% of patients with stroke.[140] In patients with intracerebral haemorrhage, BP is often elevated and hypertension is linked to greater haematoma expansion, neurological deterioration, and worse prognosis.[141]

Epidemiological and clinical studies have shown that hypertension in mid-life predicts cognitive decline and dementia (both Alzheimer's disease and vascular dementia) in the elderly,[115] even after a short duration of exposure to hypertension.[142,143]

2.2.3. Renal consequences

High BP can result in both acute and chronic kidney damage. Indeed, hypertension and kidney disease are tightly intertwined, with hypertension being both a cause and complication of kidney disease, as well as a driver of kidney disease progression.[144–147] Hypertension is the second commonest cause of end-stage kidney disease after diabetes mellitus.[148] Reduced eGFR is associated with an increased prevalence of multiple traditional CVD risk factors, including hypertension and insulin resistance, indicating that kidney damage from high BP is modified by the presence of other conditions, such as diabetes.[149] An inverse-graded relationship exists between CVD and cerebrovascular events and mortality with eGFR, which is independent of age, sex, and other traditional CVD risk factors. Decreased eGFR is also associated with the increased prevalence of non-traditional CVD risk factors, including vascular calcification, inflammation, and myocardial alterations, such as the development of CKD-associated cardiomyopathy.[150–152] Increasing albuminuria is a strong risk factor for CVD and cerebrovascular outcomes independent of eGFR.[153–155]

2.2.4. Heart failure

Hypertension can cause heart failure, and most patients with heart failure will have an antecedent history of hypertension.[156] Adjusting

for age and other cardiovascular risk factors, the hazard for developing heart failure in hypertensive patients in the Framingham Heart Study was about two-fold in men and three-fold in women.[157] Hypertension remains one of the main causes of development and progression of heart failure with preserved ejection fraction (HFpEF).[158,159] The same is true for heart failure with reduced ejection fraction (HFrEF). For example, data from the Acute Decompensated Heart Failure National Registry (ADHERE) database, which included 50.4% patients with HFpEF and 49.6% patients with HFrEF, showed that 69% of patients with HFrEF and 77% of those with HFpEF had a history of hypertension.[160] Of nearly 400 cases of new heart failure in the Framingham Heart Study, 91% were preceded by the development of hypertension.[161] Furthermore, in a cohort of patients with acute heart failure and an identified triggering factor, hypertension was the precipitating factor in 8.2%.[162]

2.2.5. Atrial fibrillation

Sex differences in the association of elevated BP with AF are well described.[163] High BP is a stronger risk factor for AF in women than in men,[164,165] and may be potentiated by the co-presence of obesity or psychological distress.[166,167] Accordingly, high BP is the most common risk factor contributing to AF in women, while alcohol consumption and coronary artery disease may be more important contributing risk factors in men.[163,165] AF, which is more strongly associated with elevated systolic than elevated diastolic BP,[168] can be considered a manifestation of hypertensive heart disease.[169,170] Even mildly increased BP is associated with an increased risk for incident AF.[168,171]

2.2.6. Valvular disease

Data suggest that elevated BP contributes to valvular heart disease.[172] Initial evidence to support this hypothesis came from cross-sectional studies showing a positive association between elevated systolic BP and risk of aortic stenosis and aortic regurgitation.[173,174]

2.2.7. Diabetes

High BP is a common feature of type 1 and, particularly, type 2 diabetes. Masked hypertension and a blunted nocturnal fall in BP are more commonly seen in people with diabetes.[175] Substantial evidence supports the benefits of reducing BP in people with diabetes to reduce major macrovascular and microvascular complications of diabetes, as well as reducing mortality. Proven benefits of BP-lowering treatment in diabetes also include a significant reduction in the rate of end-stage renal disease, retinopathy, and albuminuria.[176] Hypertensive patients usually have insulin resistance and have an increased risk of developing diabetes vs. those with non-elevated BP.[177]

Furthermore, elevated BP is strongly associated with incident diagnosis of type 2 diabetes.[178] This relationship has recently been confirmed to be causal and modifiable.[179]

2.3. Contribution of different measures of blood pressure to cardiovascular disease risk (systolic, diastolic, pulse pressure, blood pressure variability)

2.3.1. Systolic and diastolic blood pressure

Observational and Mendelian randomization analyses have demonstrated a log-linear association of physiological systolic BP and diastolic BP with CVD events among men and women free from CVD.[156,180,181] Systolic BP appears to be a stronger determinant of CVD risk than diastolic BP.[182] This continuum of CVD risk begins below thresholds used to define hypertension and has been observed across different age ranges.[180]

BP trajectories differ among men and women throughout their life course. Men have higher systolic BP in early and mid-life, while women experience a steeper increase in systolic BP beginning in their third decade of life, often yielding higher systolic BP on average than men in older age categories.[2] Men have higher diastolic BP than women throughout their life course, but women experience a more rapid increase in their diastolic BP during early adulthood before diastolic BP begins to decrease in both men and women in their fifth decade.[2]

Observational studies examining sex differences in the relative risk of CVD across BP levels have yielded mixed results.[183,184] Among 27 542 participants from four community-based cohort studies without established CVD, across categories of BP, the relative risk of CVD (including myocardial infarction, heart failure, or stroke) was higher for women than for men.[2] In a Norwegian observational study of 12 239 participants, after adjusting for smoking status, BMI, cholesterol, diabetes, and physical activity, a systolic BP of 130–139 mmHg or a diastolic BP of 80–89 mmHg was associated with a higher relative risk of acute coronary syndrome in women.[185] Similarly, among 471 998 participants in the UK Biobank, women with stage 1 hypertension had a 45% higher relative risk of myocardial infarction compared with men with stage 1 hypertension.[186] However, other studies found no sex difference in the relative risk of CVD. In a meta-analysis of 124 prospective observational studies including 1.2 million participants (44% women), there was no sex difference in the relative risk of stroke or ischaemic heart disease associated with systolic BP.[187] Similarly, no sex differences were observed in the relative risk of CVD across systolic BP down to 115 mmHg in a meta-analysis of Asian Pacific cohort studies including over 400 000 participants.[188] Notably, a consistent finding across observational studies is that the crude incidence or absolute risk of CVD events is higher for men than for women across BP categories.[2,185,189] Further epidemiology studies including Mendelian randomization analyses are needed to clarify the effect of sex on CVD risk associated with BP, particularly at lower BP.

2.3.2. Pulse pressure

Pulse pressure refers to the difference between systolic and diastolic BP. Due to differences in systolic and diastolic BP trajectories, pulse pressure begins to increase in the fifth decade as diastolic BP starts to decrease while systolic BP continues to increase.[2] The rise in pulse pressure in later life appears more pronounced for women.[55] These differences in systolic and diastolic BP trajectories in later life are thought to be related to alterations in arterial wall stiffness due to increased collagen deposition and vascular calcification.[190–192] Increased pulse pressure is most commonly seen in isolated systolic hypertension.

Observational studies of community-based populations have reported that incremental pulse pressure is associated with an increased risk of CVD events, including coronary heart disease and heart failure.[193–195] However, after adjusting for other BP parameters such as systolic BP, diastolic BP, or mean arterial pressure, pulse pressure is a weaker predictor of CVD events than these other BP parameters.[196] Accordingly, at this time, the use of pulse pressure to guide risk assessment or BP-lowering treatment appears limited.[197]

2.3.3. Blood pressure variability

BP variability refers to the variation in BP with time. It may be classified as very short-term (beat-to-beat), short-term (within 24 h, including nighttime dipping), medium-term (day-to-day), or long-term (yearly) variation. Several factors contribute to BP variability. Short-term variability is

mediated through baroreceptor reflexes influenced by emotions, behaviour, heart rhythm, sleep, and postural changes.[198] While normal dipping on ambulatory blood pressure monitoring (ABPM) is considered a decrease in mean systolic BP by 10%–20% from day to night, non-dipping status is considered an independent cardiovascular risk factor,[199,200] and has been associated with an increased risk of all-cause mortality in older hypertensive adults.[201] Notably, short-term BP variability also helps explain the phenomena of white-coat hypertension and masked hypertension, highlighting the importance of confirming BP with home or ambulatory BP testing to guide treatment allocation. In contrast, long-term variability may be predominantly influenced by medication adherence and changes in arterial stiffness.[202] Observational studies have found that BP variability is associated with higher risk of CVD events.[203,204] Related to this association between BP variability and risk, among patients on BP-lowering medication, time in target range seems to be the best measurement to predict the risk of major adverse CVD events.[205] Nevertheless, the clinical role of BP variability in guiding treatment decisions appears limited, in particular because it has not been established that (i) the link between BP variability and CVD events is causal, and (ii) interventions specifically designed to reduce BP variability result in fewer CVD events, particularly over and above the effect of BP-lowering medication on mean BP value.[206,207]

3. Diagnosing hypertension and investigating underlying causes

Table S1 Criteria for defining hypertension-mediated organ damage

Test	Criteria for HMOD definition
Cardiac HMOD	
ECG	Sokolow–Lyon: SV1 + RV5 > 35 mm RaVL ≥ 11 mm Cornell voltage: SV3 + RaVL > 28 mm (men); >20 mm (women)
Echocardiography	LVH: LV mass/height$^{2.7}$ (g/m$^{2.7}$) > 50 (men); >47 (women) LV mass/BSA (g/m^2) > 115 (men); >95 (women) LV concentric geometry: RWT ≥ 0.43 Diastolic dysfunction: Left atrial volume/height^2 (mL/m^2) > 18.5 (men); >16.5 (women) Left atrial volume index (mL/m^2): 34 Increased LV filling pressure: e′ < 7 cm; E/e′ > 14
Cardiac biomarkers	Hs-cTnT or TnI >99th percentile upper reference limit NT-proBNP > 125 pg/mL if aged <75 years, or >450 pg/mL if aged ≥75 years
Vascular HMOD	
Carotid ultrasound	Plaque (focal wall thickening > 1.5 mm)
Arterial stiffness	Carotid–femoral PWV > 10 m/s Brachial–ankle PWV > 14 m/s
Cardiac CT	Coronary artery calcium score > 100 Agatston units
Renal HMOD	
eGFR and urinary albumin-to-creatinine ratio (ACR)	eGFR < 60 mL/min/1.73 m^2 irrespective of albuminuria ACR > 30 mg/g irrespective of eGFR[120,208,209]

Continued

BSA, body surface area; CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hs-cTn, high-sensitivity cardiac troponin; HMOD, hypertension-mediated organ damage; LV, left ventricular; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PWV, pulse wave velocity; RWT, relative wall thickness.

Table S2 Key information to be collected in medical history

Risk factors
Family and personal history of hypertension, CVD, or renal disease.
Family and personal history of associated CVD risk factors.
Smoking history (including vaping).
Dietary history (including but not exclusive to salt intake).
Alcohol consumption.
Physical activity/sedentary lifestyle.
History of erectile dysfunction.
Migraine with aura.
Autoimmune inflammatory diseases.
Human immunodeficiency virus.
Sleep history, snoring, sleep apnoea.
Psychosocial factors (chronic stress, depression, social deprivation, low socio-economic status, discrimination, gender-based violence).
Previous hypertension in pregnancy/pre-eclampsia and other pregnancy-related complications (gestational diabetes, miscarriage/stillbirth, pre-term labour).
Early menopause, polycystic ovary disease.
History and symptoms suggesting HMOD, established CVD, and renal disease
Brain and eyes: syncope, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization, cognitive impairment, dementia.
Heart: chest pain, shortness of breath, oedema, myocardial infarction, coronary revascularization, history of palpitations, arrhythmias (especially AF), heart failure.
Kidneys: polyuria, nocturia, haematuria, urinary tract infections, patient or family history of CKD (e.g. polycystic kidney disease).
Peripheral arteries: cold extremities, intermittent claudication, leg ulcers, peripheral revascularization.
History and symptoms suggesting secondary hypertension
All causes:
BP > 160/100 mmHg in young adults (<40 years), BP > 180/110 mmHg irrespective of age.
Sudden development of hypertension or rapidly worsening BP.
Resistant hypertension.
Hypertensive emergency.
Primary aldosteronism:
History of spontaneous or diuretic-provoked hypokalaemia.
Episodes of muscle weakness and tetany.

Continued

Adrenal incidentaloma on abdominal imaging.
History of AF not due to identifiable causes.
HMOD or CVD and renal disease disproportionate for the observed BP values and CVD risk.
Family history of early-onset hypertension and/or cerebrovascular accident at a young age (<40 years) and/or first-degree relatives with primary aldosteronism.
Obstructive sleep apnoea syndrome:
Witnessed apnoea.
Heavy snoring.
Disturbed sleep.
Recurrent awakenings from sleep with choking, gasping, and sweating.
Daytime sleepiness, fatigue, and impaired concentration.
Non-dipping or reverse-dipping pattern at 24 h BP monitoring.
Renovascular hypertension:
Hypertension in women aged <40 years (fibromuscular dysplasia).
Migraine, pulsatile tinnitus (fibromuscular dysplasia).
History of arterial dissections and/or aneurysms (fibromuscular dysplasia).
Multiple CVD risk factors (atherosclerosis).
Multisite/generalized atherosclerosis (atherosclerosis).
Reduced eGFR and/or presence of albuminuria and/or markedly elevated renin concentration (both).
Acute worsening renal function (decreased eGFR) after administration of ACE inhibitors or ARBs (both).
Unexplained small kidney or size discrepancy between kidneys of >1.5 cm (both).
Sudden, unexplained pulmonary oedema.
Renoparenchymal hypertension:
Patient or family history of CKD (e.g. polycystic kidney disease).
History of renal/urinary tract disease.
Reduced eGFR and/or presence of albuminuria or microalbuminuria.
Phaeochromocytoma/paraganglioma (PPGL):
Symptoms of catecholamine excess (repetitive episodes of sweating, pallor, headache, anxiety, or palpitations).
Symptoms/signs suggesting syndromic PPGL, like neurofibromata, features of MEN 2, or Von Hippel–Lindau features.
Carriers of a germline mutation in one of the PPGL susceptibility genes.
Previous history or family history of a PPGL.
Others:
Previous diagnosis or symptoms suggestive of Cushing's disease, thyroid disease, or hyperparathyroidism.

Continued

Medication history
Current/past BP-lowering medication including effectiveness and intolerance and adverse events with previous medications.
Adherence to and persistence with prior and current treatments.
Use of drugs or substances that may increase BP.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HMOD, hypertension-mediated organ damage; MEN, multiple endocrine neoplasia; PPGL, phaeochromocytoma/paraganglioma; TIA, transient ischaemic attack. Adapted from the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[210]

Table S3 Key steps in physical examination

Anthropometric measures
Weight and height for BMI calculation.
Waist circumference.
Signs of HMOD or established CVD
Neurological examination and cognitive status (based on clinical suspicion).[211]
Palpation and auscultation of heart and carotid arteries.
Auscultation of abdominal aorta, iliac, and femoral arteries.
Palpation of peripheral arteries.
Comparison of BP in both arms (at least once).
Signs of secondary hypertension
Skin inspection: cafe-au-lait patches of neurofibromatosis (phaeochromocytoma/paraganglioma).
Kidney palpation for signs of renal enlargement (polycystic kidney disease).
Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension.
Comparison of radial with femoral pulse, inter-arm BP difference in young individuals with aortic coarctation (aortic murmur may also be heard).
Signs of Cushing's disease or acromegaly.
Signs of thyroid or parathyroid disease.
Neck circumference of >40 cm in men, >35 cm in women (OSAS).

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HMOD, hypertension-mediated organ damage; OSAS, obstructive sleep apnoea syndrome. Adapted from the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[210]

Table S4 Drugs or substances that may increase blood pressure

Contraceptive drugs	Oral contraceptive pills cause hypertension in 5% of women, especially compounds containing at least 50 μg of oestrogen and 1–4 mg of progestin;[212,213] this hypertension is usually mild, but severe hypertension occurs rarely (up to 20% of contraceptive-induced hypertension cases in older studies).[214] The combined hormonal contraceptive vaginal ring has a minor effect.[215] Post-menopausal hormonal replacement therapy has no pressor effect.[216]
Sympathomimetics	Weight loss drugs, e.g. phenylpropanolamine and sibutramine. Nasal decongestants, e.g. phenylephrine hydrochloride and naphazoline hydrochloride. Drugs used for attention deficiency and hyperactivity disorder, e.g. methylphenidate. Stimulant drugs, e.g. amphetamine, cocaine, and ecstasy; these substances usually cause acute hypertension. Herbal remedies, e.g. ephedra/ma huang.
Non-steroidal anti-inflammatory drugs	Chronic use raises BP by around 5 mmHg, especially indomethacin, naproxen, piroxicam and ibuprofen.[217] They also diminish the effectiveness of some BP-lowering drug classes, especially RAS blockers. Selective cyclooxygenase-2 inhibitors also increase BP.[217,218]
Paracetamol (acetaminophen)	Chronic use at high doses (4 g/day) raises BP by around 5 mmHg.[219,220]
Corticosteroids	Increase BP in a dose-dependent manner.
Immunosuppressive medications	Cyclosporin A induces hypertension in >50% of treated patients. Tacrolimus has a smaller effect on BP; rapamycin and mycophenolate have no effect on BP.
Anti-angiogenic cancer therapies	Vascular endothelial growth factor inhibitors (e.g. bevacizumab, sorafenib, sunitinib, pazopanib) increase BP in most patients and induce hypertension in 20%–90% of patients. Tyrosine kinase inhibitors (e.g. ibrutinib, acalabrutinib) increase BP in up to 72% of patients. About 1% of all patients develop a hypertensive emergency.
Other anticancer drugs	Fluoropyrimidines, cisplatin, abiraterone, bicalutamide, enzalutamide, cyclosporine, tacrolimus.[221]
Triptans	Induce vasoconstriction; conflicting data on BP elevation and risk of CVD events.
Antidepressant drugs	Antidepressant drugs (i.e. venlafaxine and monoamine oxidase inhibitors) increase BP in a dose-dependent manner, probably via noradrenergic stimulation.
Other psychiatric drugs	Clozapine, carbamazepine, lithium.
Liquorice	Increases BP via its mineralocorticoid-like activity (inhibition of the enzyme 11β-hydroxysteroid dehydrogenase 2). Regular use of 50–200 g/day liquorice induces a dose-dependent increase in systolic BP (3–14 mmHg).[222]
Others	Anabolic steroids (testosterone, growth hormone), erythropoietin—often used as doping drugs. Highly active anti-retroviral therapy, through weight gain. Commercially available caffeinated drinks acutely increase systolic BP by around 4 mmHg.[223]
Sodium-containing medications	Effervescent, dispersible, and soluble drugs. Regular use of effervescent paracetamol 3 g/day is associated with a 4 mmHg increase in systolic BP[224] and CVD,[225] compared with non-effervescent paracetamol.

BP, blood pressure; CVD, cardiovascular disease; RAS, renin–angiotensin system. Various drugs may increase BP and should be considered when investigating secondary hypertension. This is especially pertinent when a patient with previously well-controlled hypertension presents with an acute elevation of BP.[212]

Table S5 Considerations for optional tests for hypertension-mediated organ damage assessment

When do optional tests for HMOD assessment change patient management?	For which optional tests is there established evidence for this application?
Risk reclassification of individuals with elevated BP from low-to-moderate CVD risk to sufficiently high risk to warrant consideration of BP-lowering treatment.	CAC,[226,227] carotid–femoral PWV,[22,23,101] brachial–ankle PWV,[228] carotid plaque.[226]
Identify individuals that will benefit most from achieving lower BP treatment targets, thus overcoming patient and physician inertia or to decide treatment intensity in cases in uncertain cases (i.e. BP or risk close to thresholds, masked or white-coat hypertension, presence of non-traditional CVD risk factors).	Carotid plaque,[229–231] CAC,[226,227] carotid–femoral PWV,[22,23,101] brachial–ankle PWV,[228] echocardiography.[232–234]
Risk reclassification in individuals with elevated BP and hypertension younger than 40 years old.	Carotid–femoral PWV,[22,23] echocardiography.[235]

CAC, coronary artery calcium; CVD, cardiovascular disease; PWV, pulse wave velocity.

Table S6 Identified monogenic forms of hypertension

Identified monogenic forms of hypertension	Mutations
Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism)	Chimeric *CYP11B1–CYP11B2* gene
Familial hyperaldosteronism type II	*CICN2* mutations
Familial hyperaldosteronism type III	*KCNJ5* mutations
Familial hyperaldosteronism type IV	*CACNA1H* mutations
Geller syndrome	*NR3C2* activating mutation (coding for the mineralocorticoid receptor)
Liddle syndrome	*SCNN1A*, *SCNN1B*, and *SCNN1G* mutations
Gordon syndrome (pseudo-hypoaldosteronism type II or familial hyperkalaemic hypertension)	*WNK1*, *WNK4*, *CUL3*, and *KLHL3* mutations
Phaeochromocytoma/paraganglioma (syndromic and sporadic PPGL) due to germline mutations	*NF1*, *RET*, *VHL*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHA*, *SDHAF2*, *FH*, *MDH2*, *EGLN1*, *EGLN2*, *KIF1B*, *MET*, *IDH3B*, *GOT2*, *SLC25A11*, *MAX*, *TMEM127*, *DNMT3A*, *DLST*

PPGL, phaeochromocytoma/paraganglioma.

4. Preventing and treating elevated blood pressure and hypertension

4.1. Prevention strategies in early life

Prior documents refer to normative tables of expected BP by sex, age, and height, with childhood hypertension up to age 16 years being defined as a ≥95th percentile BP reported in these normative tables.[236,237] For children aged ≥16 years, hypertension was defined in the 2022 European Society of Cardiology (ESC) Consensus Document as ≥130/85 mmHg.[236] Similar to BP measurements in adults, two visits are needed to confirm diagnosis in children, and it was recommended to use home blood pressure monitoring (HBPM) to manage BP-lowering therapy in children. Because of the slight differences in how hypertension is defined between the 2022 ESC Consensus Document and the current 2024 ESC Guidelines, we acknowledge it is possible for a teenager, for example aged 17 years and with a BP of 135/85 mmHg, to be classified as having hypertension but then not be classified as having hypertension on reaching adulthood at the age of 18 years.

The estimated prevalence of global childhood hypertension is less than 4% (defined as ≥95th percentile on three or more separate occasions) and below 10% for pre-hypertension (defined as 90th–95th percentile or ≥120/80 mmHg).[238] Epidemiological surveys demonstrate a temporal increase in the population-based prevalence of elevated or high BP in children and adolescents, likely related to the concomitant increase of obesity and associated sedentary lifestyle among children.[239,240] Prematurity and very low birth weight are also risk factors for the development of hypertension in childhood.[241,242]

Elevated childhood BP predicts arterial stiffness and other markers of subclinical CVD risk in adulthood.[243,244] Systolic BP in late adolescence also independently predicts clinical coronary heart disease and stroke in mid-adulthood.[245,246] To predict development of adult hypertension and associated CVD risk, repeated BP measurements during childhood should be considered, as two or more observations of high BP during childhood and adolescence, compared with a single measurement, improves prediction of adult hypertension.[247] There are sex differences in the development of BP across the life course, with maximum differences in young adulthood; these may need to be considered when evaluating BP development in childhood and adolescence.[248]

Measuring BP during childhood with a device validated in children enables timely implementation of non-pharmacological and pharmacological prevention strategies to reduce CVD risk trajectories in children with elevated or high BP. However, more evidence is needed on the long-term efficacy and relative cost-effectiveness of systematic BP screening of children on a population level. Moreover, there is a need to develop specific European normative tables, including multi-ethnic, sex-, age-, and height-specific data, for office and home BP measurements, as well as 24 h ABPM in normal-weight children and adolescents.[236] Furthermore, while primordial prevention of hypertension and lifestyle treatment of hypertension in children and teens is recommended, and while BP-lowering medications do reduce BP in children and teens, there is a strong need for clinical outcome (and even intermediate outcome) trials evaluating BP-lowering medications in children and teens.

4.2. Non-pharmacological interventions

4.2.1. Dietary sodium and potassium intake

4.2.1.1. Potassium

In the Prospective Urban Rural Epidemiology (PURE) study, higher potassium intake, estimated by urinary excretion of ≥1.5 g/day, was associated with a lower risk of death and CVD events.[249,250] In the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort study, higher potassium intake was also associated with a lower risk of CVD events.[69] In this study, the association between potassium intake, systolic BP, and CVD events appeared to be sex specific. In women, but not men, with the highest sodium intake, the association of high potassium intake with lower systolic BP was stronger than it was for women with the lowest sodium intake. The CVD outcomes benefits of high dietary potassium intake also appeared stronger in women than in men. In another dose–response meta-analysis of randomized trials, higher potassium intake was associated with BP-lowering effects, which were more pronounced in patients with hypertension than in patients with non-elevated BP.[251] Relatedly, the BP-lowering effect sizes of increased potassium intake in this meta-analysis were stronger among the subgroup of participants with higher baseline dietary sodium intake. Of note, this meta-analysis also reported that the BP-lowering effect of dietary potassium was no longer evident (and indeed BP appeared to be increased) above relative increases in daily potassium intake of >3 g/day, suggesting that excessive potassium supplementation should be avoided.[251]

A lower urinary sodium-to-potassium ratio has been associated with a greater reduction in systolic and diastolic BP than with a higher ratio.[252] This observation is consistent with causal data from the 2022 Salt Substitute and Stroke Study (SSaSS) randomized trial.[253] However, some research has suggested that there is no association of baseline dietary potassium with the dose–response relationship between sodium reduction and change in BP, i.e. the benefit of sodium reduction may not be modified by baseline potassium intake.[254]

Estimates for the BP-lowering effects of potassium should still be given with caution, as the availability of longer-term outcomes-driven randomized controlled trials (RCTs) remains limited and the relationship

to sodium intake needs to be considered. In the Chinese SSaSS trial, participants had an average baseline sodium intake of 4.8 g/day and a sodium reduction of only 8% was achieved. By contrast, the relative increase in potassium intake reached 57%, equivalent to an increase of 0.8 g/day in absolute terms, coming from a baseline as low as 1.4 g/day. This reduced the Na^+/K^+ ratio from 3.1 at baseline to 1.8 after the salt substitute intervention.[253,255] A comparable decrease in the Na^+/K^+ ratio was estimated to reduce CVD risk by about 30%.[256] In patients with persistently high sodium intake (>5 g/day), and particularly in women, an increase in potassium intake by 0.5–1.0 g/day may be considered to achieve a favourable Na^+/K^+ ratio of 1.5–2.0 and to reduce CVD risk. This may be achieved by substituting sodium using potassium enriched salts (75% sodium chloride and 25% potassium chloride) or increasing dietary potassium intake (for example, a 125 g banana contains about 450 mg of potassium).

4.2.2. Physical activity and exercise

In a previous 2022 ESC Consensus Document, which was based on a systematic review and meta-analyses, aerobic (endurance) exercise was suggested as the first-line exercise therapy for reducing BP in patients with elevated BP and hypertension, compared with alternative forms of exercise like dynamic or isometric resistance training.[257] In patients with hypertension, regular aerobic exercise substantially lowers systolic BP by 7–8 mmHg and diastolic BP by 4–5 mmHg.[257] For non-white patients with hypertension, dynamic resistance training elicits BP reductions comparable to, if not greater than, for aerobic exercise.[258] Isometric resistance training has also been shown to achieve clinically relevant BP reductions in patients with hypertension, but more data from more high-quality intervention trials are required.[257,259] With respect to mode and intensity of aerobic exercise, high-intensity interval training elicits comparable BP reductions to moderate continuous exercise, with high-intensity interval training achieving greater improvement in physical fitness.[260] Of note, sufficient supply with fluids is important during and after exercise, especially in the case of prolonged, intensified exercise. In patients with resistant hypertension, low-certainty evidence suggests that adding exercise to usual care has additional BP-lowering effects.[261]

Based on existing data and more recent evidence, the recommendations from previous ESC Guidelines of at least 150 min/week moderate aerobic exercise (≥30 min, 5–7 days/week) can be maintained.[210,262] Alternatively, 75 min of vigorous exercise per week over 3 days may be performed, with additional benefits derived by achieving 300 min of moderate-intensity or 150 min of vigorous-intensity aerobic physical activity per week.[262,263] As acute aerobic exercise induces intensity-dependent, short-term reductions in ambulatory BP, patients with elevated BP and hypertension may benefit from daily exercise to improve their 24 h BP profile and avoid BP peaks on sedentary days.[264] Aerobic exercise should be complemented by low- or moderate-intensity resistance training (2–3 times per week), starting at 1–2 sets of 10–15 repetitions at 40%–50% of one-repetition maximum.[265] In case of uncontrolled hypertension at rest, high-intensity exercise should be applied with caution, with resting systolic BP of >200 mmHg and diastolic BP of >110 mmHg indicating relative contraindications.[266] Age, sex, ethnicity, and comorbidities, as well as individual preferences, should be considered for individual exercise prescription. Detailed information on exercise prescription in terms of frequency, intensity, time (duration) and type, and progression can be found in the 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.[262] The same guidelines include recommendations for pre-participation screening and cardiopulmonary exercise testing.[262]

4.2.3. Weight reduction and diet

Obesity is associated with incident hypertension.[267,268] An average weight loss of 5 kg has been associated with an average systolic and diastolic BP reduction of 4.4 and 3.6 mmHg, respectively.[269] Maintaining weight loss can improve not only BP, but also glucose and lipid metabolism, and potentially reduce premature all-cause mortality.[270–272]

Compared with a low-fat diet, the Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced major CVD events in primary prevention in adults with high CVD risk over a period of 5 years.[273] Similar benefits on CVD outcomes were noted in a mixed trial cohort of secondary prevention patients with and without hypertension.[274] Accordingly, evidence-based diets such as the Mediterranean diet and the DASH diet are established interventions in patients with hypertension to reduce their BP and CVD risk. For more information on healthy dietary patterns, we refer readers to the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.[209]

Two previous meta-analyses found significant but relatively small BP-lowering effects of the Mediterranean diet, with a BP reduction of approximately 1.5 mmHg.[275,276] Higher baseline BP (≥130 mmHg) and longer trial duration (≥16 weeks) were associated with greater BP reductions,[275] and in observational studies, the odds of developing hypertension were 13% lower with higher adherence to the Mediterranean diet.[276] The DASH diet, on the other hand, may have stronger BP-lowering effects, with a net reduction of 7.2 mmHg in systolic BP and 4.2 mmHg in diastolic BP.[277] In combination with weight loss and exercise interventions,[278] and low sodium intake,[279] the DASH diet can result in even greater BP reductions. For comparison, pharmacological treatment of obesity with orlistat achieved a slight BP reduction of 2.6 mmHg in systolic BP and 2.0 mmHg in diastolic BP after 6–12 months of treatment in patients with elevated BP.[280] The greatest BP-lowering effects of weight-loss medications may be achieved with the glucagon-like peptide 1 (GLP-1) receptor agonists. For example, in the Semaglutide Treatment Effect in People with Obesity (STEP-1) trial, the GLP-1 analogue semaglutide resulted in a mean weight reduction of 12.4% and a 5.1 mmHg reduction in systolic BP.[281]

4.2.4. Smoking

Growing evidence suggests that electronic cigarettes, also known as e-cigarettes, increase BP. A systemic review including 13 e-cigarette trials (12 cross-over designs) and one observational study evaluated systolic and diastolic BP. BP increased in most nicotine e-cigarette arms, in some non-nicotine e-cigarette arms, and in none of the placebo arms. The observational study followed e-cigarette users and non-smokers for 3.5 years with inconsistent findings.[282] A study of 275 762 individuals (120 766 men and 154 996 women) investigating BP effects of conventional cigarettes and e-cigarettes, alone or in combination, reported that those who smoked both e-cigarettes and conventional cigarettes were the most likely to have the highest prevalence of hypertension.[283]

Brief advice to stop smoking has a small but significant effect on quitting rates compared with unassisted quit rates,[284] but intensive smoking-cessation interventions are much more effective than shorter interventions.[285] As recommended by previous ESC Guidelines, smoking cessation is recommended to reduce CVD risk and improve non-CVD health.[209,210]

Smoking cessation reduces overall cardiovascular risk but not BP.

Table S7 Doses of first-line blood pressure-lowering drugs

Drug class	Drug name	Low dose (mg/day)	Standard dose (mg/day)	High dose (mg/day)	Recommended dosing regimen
ACE inhibitors					
	Captopril	12.5	50	100	b.i.d.
	Enalapril	5	10	40	o.d.
	Lisinopril	5	10–20	40	o.d.
	Perindopril	2.5	5	10	o.d.
	Ramipril	2.5	5–10	10	o.d.
ARBs					
	Candesartan	4	8–16	32	o.d.
	Irbesartan	75	150	300	o.d.
	Losartan	25	50–100	100	o.d.
	Olmesartan	10	20	40	o.d.
	Telmisartan	40	40–80	80	o.d.
	Valsartan	80	16	320	o.d.
	Azilsartan	40	40–80	80	o.d.
Calcium channel blockers					
Dihydropyridines	Amlodipine	5	5–10	10	o.d.
	Felodipine	5	5–10	10	o.d.
	Lercanidipine	10	10–20	20	o.d.
	Nifedipine	30	30–60	90	o.d.
	Manidipine	10	10–20	40	o.d.
Diuretics					
Thiazide and thiazide-like diuretics	Chlorthalidone	12.5	12.5–25	25	o.d.
	Hydrochlorothiazide	12.5	25	50	o.d.
	Indapamide	1.25	2.5	2.5	o.d.
Potassium-sparing diuretics	Amiloride	5	10	20	o.d.
	Eplerenone	25	50	200	o.d. (b.i.d. may be needed)
	Spironolactone	12.5	25	100	o.d.
Beta-blockers[a]					
	Atenolol	25	50	100	o.d.
	Bisoprolol	2.5	5	10–20	o.d.
	Carvedilol[b]	6.25	25	50	b.i.d.
	Labetalol[b]	100	200	400	b.i.d.
	Metoprolol succinate	25	50	100	o.d.
	Metoprolol tartrate	25	50	100–200	b.i.d.
	Nebivolol[b]	2.5	5	10	o.d.
	Propranolol	40	80	160	b.i.d.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; b.i.d., twice daily; o.d., once daily.
[a]If special indication, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.
[b]Vasodilating beta-blockers.

Table S8 Doses of other drugs with blood pressure-lowering effects

Drug class	Drug name	Low dose (mg/day)	Usual dose (mg/day)	High dose (mg/day)	Typical dosing regimen
Alpha-blockers[a]					
	Doxazosin	1	4	8	o.d.
	Prazosin	1	2	5	b.i.d.
	Terazosin	1	1	2	o.d.

Continued

Diuretics					
Loop diuretics[b]	Bumetanide	0.5	1	2	o.d.
	Furosemide	20	40	100	o.d.
	Torsemide	2.5	5	10–20	o.d.
Calcium channel blockers					
Non-dihydropyridines[c]	Diltiazem	120	240	360	o.d.[e]
	Verapamil	120	240	480	o.d.
Vasodilators[d]					
	Hydralazine	10	25	100	t.i.d.
	Minoxidil	2.5	5	10	o.d.
Central-acting (CNS) hypertensives[d]					
	Clonidine	0.10	0.15	0.30	t.i.d.
	Methyldopa	250	500	750	t.i.d.
	Moxonidine	0.2	0.4	0.6	o.d.

b.i.d., twice a day; CNS, central nervous system; o.d., once a day; t.i.d., three times daily.
[a]Benign prostate hypertrophy.
[b]Chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) and heart failure.
[c]Tachycardia and angina with no obstructive coronary artery disease.
[d]During pregnancy and in emergencies.
[e]Modified-release preparations.

Table S9 Contraindications for approved blood pressure-lowering drug classes

Drug class	Absolute contraindication	Special precautions
ACE inhibitors	Pregnancy Previous angioneurotic oedema Hyperkalaemia (K^+ > 5.5 mmol/L) Bilateral severe renal artery stenosis Severe renal artery stenosis in a single functioning kidney	Women of childbearing potential without reliable contraception
ARBs	Pregnancy Hyperkalaemia (K^+ > 5.5 mmol/L) Bilateral severe renal artery stenosis Severe renal artery stenosis in a single functioning kidney	Women of childbearing potential without reliable contraception
CCBs		
Dihydropyridines		Tachyarrhythmia Heart failure (HFrEF, class III or IV) Pre-existing severe leg oedema
Non-dihydropyridines	Any high-grade sinoatrial or atrioventricular block Severe LV dysfunction (LVEF < 40%) Bradycardia (heart rate < 50 b.p.m.)	Severe constipation
Diuretics		
Thiazide and thiazide-like diuretics	Active gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcaemia Hypokalaemia Gout history Urinary incontinence
Beta-blockers	Acute asthma exacerbation Any high-grade sinoatrial or atrioventricular block Bradycardia (heart rate <50 b.p.m.)	Asthma[a] Metabolic syndrome Glucose intolerance Athletes and physically active patients

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.
[a]Cardioselective beta-blockers may be trialled if asthma is not severe/brittle. Adapted from the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[210]

Table S10 Choice of starting blood pressure-lowering treatment, depending on comorbidity

Comorbidity	Initial drug class
Diabetes mellitus Metabolic syndrome	ACE inhibitor ARB CCB
Chronic kidney disease Proteinuria/albuminuria	ACE inhibitor ARB Diuretic CCB SGLT2 inhibitors
Post-myocardial infarction	Beta-blocker ACE inhibitor ARB MRA
AF	Beta-blocker ACE inhibitor ARB
Heart failure	ACE inhibitor ARB MRA Beta-blocker SGLT2 inhibitor Diuretic

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor blocker; SGLT2, sodium–glucose co-transporter 2.

4.3. Intensity of blood pressure-lowering therapy and ideal treatment targets

4.3.1. The ideal target of blood pressure-lowering treatment

It is important to stress that the BP threshold to initiate BP-lowering therapy is not, necessarily, the same as the recommended BP target once therapy is commenced (in other words, treatment threshold and treatment target may not be the same for a given patient). Specifically, for all hypertensive patients in whom BP-lowering treatment is recommended above a baseline BP of ≥140/90 mmHg (office), the recommended target of BP-lowering therapy is 120–129/70–79 mmHg, as assessed ideally by out-of-office measurement, provided treatment is well tolerated. Among patients with elevated BP and high CVD risk in whom treatment initiation is recommended above a baseline BP of ≥130/80 mmHg, the recommended target of BP-lowering therapy is 120–129/70–79 mmHg. As such, while the treatment target in these guidelines is always 120–129/70–79 mmHg (if tolerated), the treatment threshold may differ on the basis of CVD risk. Furthermore, there is a group of adults with systolic BP of 130–139 mmHg and/or diastolic BP of 80–89 mmHg (both by office) who are not at high CVD risk in whom BP-lowering drug treatment is not recommended. These patients should be offered lifestyle counselling and other non-pharmacological interventions to reduce their BP, and their BP target with these non-pharmacological treatments is also 120–129/70–79 mmHg.

Therefore, irrespective of the threshold BP above which BP-lowering treatment (whether that be lifestyle or pharmacological or other treatment) is recommended, the on-treatment BP target is 120–129/70–79 mmHg for all adults, provided this treatment is well tolerated. This BP target was chosen to reflect the most current evidence from contemporaneous RCTs[286–291] and from meta-analyses of RCTs.[292] Of note, the BP-lowering treatment target of 120–129/70–79 mmHg recommended here is also known to reduce CVD events in older adults,[291,293] with evidence for efficacy of more intensive BP-lowering treatment targets established up to the age of 85 years.[292]

It should be highlighted that trial data confirming efficacy for a BP-lowering treatment target of 120–129/70–79 mmHg do not apply to very frail adults (such as adults residing in nursing homes), who were generally excluded from trials. Also, data supporting this BP target in adults aged ≥85 years are inconclusive.[292] Frailty can occur at different ages and is, together with tolerability of BP-lowering treatment, an important parameter when considering the BP target for a given patient. Clinicians should consequently individualize BP-lowering treatment in older people (age ≥85 years) and those with significant frailty.

4.3.2. Duration and monitoring of drug therapy

Blood pressure-lowering treatment is often lifelong. This raises the question of long-term efficiency, long-term side effects, and long-term adherence. While BP-lowering therapies typically provide an overall durable effect, some attenuation of effect may be seen over time, a finding that may relate to ageing of the vasculature and other mechanisms.[294] A legacy effect for BP-lowering medication, as seen with lipid-lowering therapy, has not been proven.[295] Therefore, prolonged use of BP-lowering medication is needed to keep BP controlled and to maintain lower CVD risk. First-line BP-lowering medication classes appear to be safe for long-term use.[296–298]

Once BP is controlled, at least a yearly follow-up is advised. Because of the known temporal variability in BP[299,300] and medication efficacy in the long term,[294] medication changes may be necessary over time.

4.4. Device-based blood pressure lowering

Several device-based therapies designed to lower BP have been investigated.[301,302] To date, the best evidence exists for catheter-based renal denervation.

4.4.1. Catheter-based renal denervation

Sympathetic nervous system overactivity contributes to the development and progression of hypertension.[303] Renal denervation aims to interrupt afferent and efferent sympathetic nerves located in the adventitia and perivascular tissue of the renal arteries. Efferent renal sympathetic nerve activation increases renin release, renal tubular sodium reabsorption, and decreases renal blood flow.[304] Mechanosensitive and chemosensitive afferent sympathetic nerves provide feedback to the central nervous system.[304] The previous 2018 ESC/ESH Guidelines on the management of arterial hypertension did not recommend the use of device-based therapies for routine treatment of hypertension, unless in the context of clinical studies and RCTs.[210] This lack of endorsement was based on the results of three sham-controlled trials,[305–307] which did not demonstrate BP-lowering efficacy of a mono-electrode radiofrequency catheter system compared with a sham procedure in patients with severe resistant hypertension. The largest of these trials, the Symplicity HTN-3 trial, had several methodological limitations that may have influenced the results, including frequent medication changes, limited experience of the proceduralists, and likely incomplete circumferential ablation in most patients.[305,308] In the wake of these sobering results from sham-controlled studies of the first generation of catheters, a second generation of renal denervation catheters was designed and studied, informed by new insights on renal nerve distribution.[309]

Since then, four sham-controlled trials investigating second-generation radiofrequency and ultrasound catheters have been published, which demonstrated a BP-lowering efficacy in a broad range of patients, with and without concomitant BP-lowering medications, including those with resistant hypertension.[310–315]

Long-term, non-randomized, follow-up data from the Global Symplicity Registry,[316] Symplicity HTN-3 trial,[317] Spyral HTN-ON MED pilot trial,[318] and A Study of the Recor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN) SOLO trial[319] suggest a sustained BP-lowering effect for up to 3 years. A single-centre, open-label study suggested sustained BP reductions up to 10 years.[320] These data also highlight a potentially important advantage of renal denervation, namely that the BP-lowering effect of this intervention might be 'always on'. Therefore, should future research indicate that the durability of the BP-lowering effects persists beyond 5 years, this 'always on' advantage of the procedure could be an important consideration, especially for patients with suboptimal medication adherence (a major problem in controlling BP).[321] The task force also recognizes that some patients may prefer a one-off procedure rather than taking daily medications, and that some patients may request this procedure. These preferences and perspectives were important considerations in formulating the recommendations.

Importantly, there were also no procedure-related serious safety signals in the first- and second-generation trials beyond the usual risk of femoral arterial access procedures (the task force could find no published meta-analysis data on major bleeding and major femoral artery vascular access complications after renal denervation procedures). However, the rate of major bleeding and major femoral artery vascular access complications for coronary angiography using a femoral approach is typically reported as 1%–4%[322,323] but has been reported as 5%–10% in some studies.[324] If renal denervation was scaled up outside of the trial setting to the large numbers of adults with hypertension potentially eligible for the procedure, this potential major bleeding and vascular access complication rate would be concerning. However, trials investigating radial access for renal denervation are currently ongoing (NCT05234788). After renal denervation, there is also an approximately 0.25%–0.5% rate of renal artery stenosis/dissection requiring stenting.[325] Long-term follow-up data up to 3 years have not suggested worsening of renal function beyond the expected rates in patients with hypertension with mild-to-moderately reduced renal function.[316,326] Of note, however, the patients included in sham-controlled trials had normal or mild-to-moderately reduced kidney function at baseline.[310,312–314]

4.4.2. Other devices

Creating a central iliac arteriovenous anastomosis using a stent-like device between the external iliac artery and vein lowered BP immediately, including in isolated systolic hypertension.[327] A sham-controlled trial investigating the approach was terminated early after longer-term follow-up data indicated an increase in heart failure in the stent group.[302]

4.5. Unintended and potentially harmful consequences of therapeutic blood pressure lowering and implications for treatment targets

4.5.1. Adverse effects of blood pressure-lowering therapy

4.5.1.1. General adverse effects

Evidence from RCTs on individual adverse effects of BP-lowering drugs is somewhat limited, with previous studies powered for CVD efficacy and not for assessing adverse effects, in addition to focusing on the overall cumulative rate of adverse effects rather than individual drug-specific side effects.[328,329] In addition, variation in definitions and reporting of adverse effects in different trials makes comparison challenging across studies. Nonetheless, in randomized trials of adults aged >60 years, the overall rate of BP-lowering drug withdrawal was higher than the rate of placebo withdrawal (approximately 15% vs. 5%,[330] with a relative risk increase for withdrawal with BP-lowering drugs of 2–3).[328]

One of the most common adverse effects of BP-lowering drugs is ankle oedema due to calcium channel blockers (CCBs), especially dihydropyridine CCBs.[331] The incidence rate of CCB-induced oedema is about 22% and often leads to discontinuation of treatment.[332] Adverse effects of these drugs have been associated with genetic variants in *NUMA1*, *CYP3A5*, and *RYR3*.[333] Another frequently reported adverse effect of a common BP-lowering drug is cough caused by angiotensin-converting enzyme (ACE) inhibitors.[334] The frequency of ACE inhibitor-induced cough in the literature is variable. However, evidence from real-world studies indicate that the incidence of cough caused by ACE inhibitors is lower than that reported in clinical trials.[334] Patients who experience a dry persistent cough may be subjected to a challenge/re-challenge of ACE inhibitors to determine whether the drug is the underlying cause of the cough. Often, patients are switched to an angiotensin receptor blocker (ARB) or other class of BP-lowering drugs.

Angioedema due to ACE inhibitors is a serious adverse effect and potentially life-threatening complication of this drug class. The incidence of ACE inhibitor-induced angioedema is 0.1%–0.7%.[335] Although the exact pathophysiology of this condition is unclear, accumulation of bradykinin is important. Treatment requires prompt evaluation and emergency stabilization and airway management.

A systematic review, which included 280 638 participants in 58 RCTs and focused on risks of individual adverse events, reported no evidence for an increased relative risk of falls in those taking BP-lowering drugs.[336] There was, however, an increased relative risk of mild hyperkalaemia (risk ratio 1.9), acute kidney injury (risk ratio 1.2), hypotension (risk ratio 2.0), and syncope (risk ratio 1.3). Furthermore, very frail adults were excluded from BP-lowering trials, which is relevant because such patients are far more prone to adverse effects and polypharmacy.[337]

In general, women have a greater risk of an adverse drug effect compared with men,[338] and this holds true for BP-lowering drugs.[339] This may relate to differences in pharmacokinetics between sexes, making women generally more susceptible to dose-dependent adverse effects of drugs.

Some BP-lowering drugs, such as ACE inhibitors and beta-blockers, are reported to have more adverse effects in women than in men.[340] In a cross-sectional analysis of reports from a pharmacovigilance database in Sweden, women reported a higher prevalence of adverse events for ACE inhibitors, ACE inhibitor combinations, ARB combinations, diuretics, and CCBs, with a potential link to dose exposure.[341] For MRAs, there was a higher prevalence of adverse events for men than women, but without any sex difference in dose exposure. Loop diuretics are associated with more frequent emergency hospitalizations for adverse drug effects in women than men.[342]

4.5.1.2. Renal effects

A systematic review found an increased risk of acute kidney injury and hyperkalaemia associated with BP-lowering treatment.[336] Analyses of outcomes by specific drug class showed that drugs affecting the RAAS were more likely to be associated with acute kidney injury and hyperkalaemia.[336]

Patients with significant CKD tend to be excluded from RCTs.[343] The Systolic Blood Pressure Intervention trial (SPRINT) excluded patients with an eGFR of <20 mL/min/1.73 m^2 or urinary protein excretion of >1 g/day.[290] Furthermore, the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD-BP) trial excluded patients with a serum creatinine of >132.6 μmol/L.[344] It is important to remember these exclusion criteria, and the fact that patients with CKD are more likely to suffer from resistant hypertension, when extrapolating the results of more intensive BP lowering to patients with moderate-to-severe CKD.[345]

4.5.1.3. Erectile dysfunction

Older classes of BP-lowering drugs [diuretics (including MRAs), non-cardioselective beta-blockers, and centrally acting drugs] are associated with negative effects on erectile function;[346] however, newer classes of drugs (calcium antagonists and ACE inhibitors) appear to have more neutral effects,[347] and there is even some evidence for beneficial effects with angiotensin receptor antagonists.[348] The Heart Outcomes Prevention Evaluation-3 (HOPE-3) RCT suggested that use of diuretics and angiotensin receptor antagonists either alone or in combination did not adversely affect erectile function.[348] Intense BP management (systolic BP < 120 mmHg) in SPRINT did not have an unfavourable clinical impact on erectile function in the overall trial population.[349]

4.5.2. Pill burden and non-adherence

More intensive treatment of elevated BP and hypertension may be associated with an increased risk of polypharmacy and pill burden, which are themselves associated with non-adherence.[350,351] Single-pill combinations can help to reduce pill burden and should be considered to improve adherence (Refer to *Section 8.3.4.* in the main text).

Increased intensity of BP lowering (while ultimately cost-effective in terms of cardiovascular event reduction)[352] can also result in higher upfront direct and indirect healthcare costs, with more people requiring medication, and higher demand for technology-based adherence strategies, which can be challenging for implementation in resource-poor settings.[351]

4.5.3. Potentially harmful consequences of blood pressure lowering for frail older people

Unintended consequences of BP lowering (orthostatic hypotension, syncope, potential falls) can be hazardous for frail older people in particular.[353] Retrospective studies have shown that adults aged >75 years from the general population, who would have met the criteria for inclusion in SPRINT, had a rate of injurious falls and syncope that was nearly five times that of the standard care group in the trial. This suggests that a significant healthy participant bias may have contributed to the findings of SPRINT and other similar BP-lowering trials, and that the results may not fully generalize to older adults in more routine clinical care.[354]

Patients' functional ability should be considered rather than age alone to help negate any unintended consequences of BP lowering in a frailer cohort. Despite their chronological age, older patients with hypertension who are robust and can independently carry out activities of daily living will benefit from guideline-directed treatment similar to younger cohorts. However, tailoring treatment targets and treatment plans for more frail older patients is necessary to avoid unintended consequences. This should include assessing frailty, including cognitive status, risk of falls, propensity for orthostatic hypotension, polypharmacy, and other comorbid conditions.[355,356] Of note, and as further detailed in *Section 8* in the main text, some data indicate a benefit of more intensive BP-lowering on cognitive functions.[357–359] For those with loss of function but preserved activities of daily living, a more detailed geriatric assessment is required to explore the risks and benefits of treatment, as well as considerations for tailoring therapeutic strategies where appropriate. For patients who are both functionally impaired and unable to carry out activities of daily living, the therapeutic goals of hypertension treatment should be reviewed and medications discontinued where appropriate.[337]

4.5.4. Clinician inertia and patient involvement

The fear of serious adverse events is often cited as a reason for clinician inertia, although the evidence to date from meta-analyses of RCTs suggests these concerns might be exaggerated. However, RCTs often select populations with less frailty and multimorbidity who are more likely to tolerate treatment.[360] Consequently, fewer adverse effects might be reported than would be expected in the general population. The promises of precision medicine have yet to be realized. Until then, it remains up to individual clinicians to initiate shared decision-making in conjunction with each patient, especially patients in vulnerable groups and those who have experienced previous adverse events, weighing up potential benefits against risks of treatment.[361,362]

5. Managing specific patient groups or circumstances

5.1. Young adulthood (18–40 years)

5.1.1. Definition and epidemiology

A recent meta-analysis of 17 observational cohorts (4.5 million individuals aged 18–45 years) demonstrated a graded, progressive association between BP categories and increased CVD risk. Increased risk is evident even for BP of 130–139/80–89 mmHg.[363] In the Framingham Heart Study, early-onset hypertension (<45 years old) was associated with a higher rate of CVD events than late-onset hypertension.[364] In particular, systolic and diastolic hypertension and isolated diastolic hypertension are associated with increased CVD risk compared with isolated systolic hypertension in the young.[365]

5.1.2. Secondary hypertension in young adulthood

Screening for secondary hypertension is recommended in young adults with hypertension. The American College of Obstetricians and Gynaecologists, in its 2019 practice statement, suggests that in women with hypertension, combined oestrogen-progesterone contraceptives should not be used unless there is no other method available or acceptable to the patient.[366] Conversely progestin-only contraceptives are generally considered safe in women with hypertension.[367]

5.1.3. Investigating hypertension in pregnancy

All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease and, in the second half, to screen for pre-eclampsia. A dipstick test of ≥1+ should prompt further investigations, including ACR, which can be quickly determined in a single spot-urine sample (interestingly, pregnant women can visually read a dipstick for urinary protein with similar accuracy to healthcare professionals).[368]

In one study, 10% of pregnant women with chronic hypertension had secondary hypertension (estimated to affect 0.24% of all pregnancies).[369] Secondary hypertension during pregnancy is associated with an increased risk of adverse foetal and, especially, maternal outcomes, including maternal death.[369] The most common cause of secondary

hypertension during pregnancy is CKD. Secondary hypertension should be considered in women with severe or difficult-to-treat hypertension or suggestive laboratory results (e.g. elevated creatinine, hypokalaemia). Phaeochromocytoma in pregnant women is rare (0.002% of all pregnancies) but extremely dangerous.[370] If undiagnosed, maternal and foetal mortality may be as high as 50%.[371]

5.1.4. Preventing hypertension and pre-eclampsia

Low-to-moderate-intensity exercise, especially if supervised and initiated during the first trimester of pregnancy, decreases the incidence of developing gestational hypertension.[372] As such, after consultation with their obstetrician, all pregnant women should participate in physical activity, unless contraindicated.[373]

About 15%–25% of women with gestational hypertension will develop pre-eclampsia.[374]

Clinical factors indicating a high risk of pre-eclampsia include the following:

(1) Hypertension, chronically or during a previous pregnancy
(2) CKD
(3) Auto-immune diseases such as systemic lupus erythematosus or antiphospholipid syndrome
(4) Type 1 or type 2 diabetes

Moderate risk of pre-eclampsia includes one or more of the following risk factors:

(1) First pregnancy
(2) Age ≥40 years
(3) Pregnancy interval of >10 years
(4) BMI ≥ 35 kg/m^2 at first visit
(5) Family history of pre-eclampsia
(6) Multiple gestation pregnancy

Of note, assessing relevant maternal risk factors at 11–13 weeks predicted only about 40% of pre-term and 30%–35% of term pre-eclampsia, at a 10.3% false-positive rate.[375,376] Combining maternal risk factors, BP, uterine artery Doppler, and measurement of placental growth factor can increase the predictive accuracy to 80%.[375,376]

Women at high or moderate risk of pre-eclampsia should be advised to take 100–150 mg of aspirin daily at bedtime from Weeks 12–36.[377–379]

Oral calcium supplementation of 1.5–2 g daily is recommended for preventing pre-eclampsia in women with low dietary intake of calcium (<600 mg daily).[380]

5.1.5. Treatment initiation and blood pressure targets

Severe maternal hypertension is a risk factor for adverse maternal and perinatal outcomes,[381] including ante- and post-partum stroke.[382] In the Cardiovascular Health Awareness Program (CHAP) trial, treating pregnant women with chronic hypertension and BP of ≥140/90 mmHg reduced the occurrence of pre-eclampsia with severe features and also reduced medically indicated pre-term birth at <35 weeks; compared with only treating severe hypertension (BP ≥ 160/105 mmHg).[383] There was no evidence of an increased risk of severe neonatal complications in the intensive treatment group, including small-for-gestational-age birth weight.[383] Of note, the mean BP between randomization and delivery in this trial was 129/79 mmHg in the intensive-treatment arm and 133/82 mmHg in the conservative arm.[383] In another trial, tight BP control (target diastolic BP < 85 mmHg) compared with less-tight BP control (target diastolic BP < 100 mmHg) improved the incidence of subsequent severe maternal hypertension (BP ≥ 160/110 mmHg), but not foetal or other maternal outcomes in women with mild hypertension at baseline (diastolic BP of 85–105 mmHg).[384]

Nonetheless, based on the CHAP trial[383] and a meta-analysis,[385] treatment with BP-lowering drugs in all pregnant women with confirmed BP of ≥140/90 mmHg is recommended to reduce the progression to severe hypertension and the related risks for adverse pregnancy outcomes. Therefore, in women with pre-existing and gestational hypertension with and without pre-eclampsia, we recommend lowering BP to below 140 mmHg for systolic and between 80 and 90 mmHg for diastolic BP.[384]

5.1.6. Managing mild hypertension in pregnancy (office blood pressure of 140–159/90–109 mmHg)

Women with pre-existing hypertension on BP-lowering drugs may continue their BP-lowering medication, but RAS inhibitors and most thiazide diuretics are contraindicated during pregnancy and not recommended due to adverse foetal and neonatal outcomes.

The BP-lowering drugs of choice are: beta-blockers (most data available for labetalol, a non-selective beta-blocker that also acts as an alpha-blocker in higher doses; metoprolol and bisoprolol are also considered safe), CCBs (most data available for nifedipine, also felodipine, nitrendipine, amlodipine, and isradipine can be used), and methyldopa.[386,387] A meta-analysis suggests that beta-blockers and CCBs are more effective than methyldopa in preventing severe hypertension.[385] Of note, however, atenolol should be avoided, as it is associated with foetal growth restriction.[388,389] It should also be highlighted that methyldopa has been associated with increased risk of post-partum depression and caution is therefore advised, both intra-partum and post-partum.[390] A large trial is currently evaluating labetalol vs. nifedipine in hypertension of pregnancy (ISRCTN87208603).

5.1.7. Managing severe hypertension in pregnancy (≥160/110 mmHg)

Acute onset of severe hypertension (systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 110 mmHg) persisting for ≥15 min is considered a hypertensive emergency in pregnancy. Women with severe hypertension are at increased risk of life-threatening complications.[391] Data on BP-lowering treatment are limited.[390] In an RCT of women with severe hypertension, BP control within 6 h was achieved in more than three-quarters of women treated with oral nifedipine, labetalol, or methyldopa. Treatment with nifedipine resulted more often in BP control within 6 h than methyldopa, while there was no difference between the methyldopa and the labetalol, or the labetalol and the nifedipine groups.[392]

5.1.8. Managing blood pressure post-partum

For women with hypertension during pregnancy, BP should be measured within 6 h of delivery and, if possible, daily for at least a week after discharge from the hospital.[390] Post-partum hypertension is common in the first week and associated with prolonged hospitalization.[393]

Women with hypertension in pregnancy are at increased risk of chronic hypertension,[394] CKD,[395] and CVD.[396–399] The relative risk of chronic hypertension is highest in the first 6 months following delivery, motivating regular screening in these women.[400] Women with gestational hypertension, especially those with pre-eclampsia, are also at higher risk of masked hypertension.[401] BP measurements, ideally including out-of-office measurements, urine analyses, and CVD risk assessment, should at least be performed 6–12 weeks, 6 months, and

12 months post-partum and, after that, annually. As in all patients with hypertension aged <40 years, women with post-partum hypertension should be screened for secondary causes of hypertension.

Any drug recommended for post-partum hypertension can be used according to the hypertension treatment algorithm. All BP-lowering drugs are excreted into breast milk.[390] Except for propranolol, atenolol, acebutolol, and nifedipine, most drugs are excreted in very low concentrations in breast milk.[390] *Table S11* provides a list of BP-lowering drugs usually compatible with breastfeeding.

Table S11 Blood pressure-lowering medications that are considered safe with breastfeeding[367,390]

Drug class	Drug
ACE inhibitors	Benazepril
	Captopril
	Enalapril
	Quinapril
Calcium channel blockers	Diltiazem
	Nifedipine
	Verapamil
Beta-blockers	Labetalol
	Metoprolol
	Nadolol
	Oxprenolol
	Propranolol
	Timolol
Diuretics	Furosemide
	Hydrochlorothiazide
	Spironolactone
Other	Clonidine
	Hydralazine
	Methyldopa
	Minoxidil

ACE, angiotensin-converting enzyme.

5.1.9. Risk of recurrence of hypertensive disorders in a subsequent pregnancy

About 20%–30% of women with hypertensive disorders in a previous pregnancy will experience recurrence in a subsequent pregnancy.[402,403] The earlier the onset of hypertension in the first pregnancy, the higher the risk of recurrence in a subsequent pregnancy.[403]

Further details on managing hypertension[390] and other cardiovascular disorders[367] in pregnancy are available elsewhere.

5.2. Very old age (≥85 years), frailty, multimorbidity, and polypharmacy

5.2.1. Definition of frailty

The most common definition of frailty is an age-associated, biological syndrome characterized by decreased biological reserves, due to dysregulation of several physiological systems. This puts an individual at risk when facing physiological stressors, and is associated with poor outcomes, such as disability, death, and hospitalization.[404] The estimated prevalence of frailty in people aged >65 years is 7%–16% and is greater in women than in men.[405,406] Although the main determinant of frailty is age, chronological age must be differentiated from biological age.[407] A very old patient can be very fit or a multimorbid patient can be young. Using multiple drugs may have more unpredictable effects on BP in older patients, because of increased competition for underlying mechanisms responsible for their degradation and elimination, and because the ability of the baro-[408] and chemo-reflex[409] systems in maintaining a steady BP declines with ageing.

With respect to BP considerations, two issues compound interpretation of the frailty literature. First, frailty is on its own a strong predictor of mortality and cardiovascular complications[410] and is accompanied by a decrease in systolic BP.[411] This raises the issue of the so-called BP J-curve (see *Section 9.8* in the main text) and reverse causality, with frailty rather than excessive BP lowering being the root cause of adverse health outcomes. Only properly randomized and controlled clinical trials can differentiate between the effects of frailty vs. overly intensive BP-lowering treatment, but unfortunately, few BP-lowering trials have included a substantial proportion of frail patients. Second, there is no consensus on how to grade frailty in day-to-day clinical practice.[353] Complex frailty scales exist for application in research,[293,412] but unless they are electronically generated,[413] they are typically not practical in routine clinical care. Nonetheless, the clinical frailty scale (*Figure 21* main manuscript) is intuitive and easy to administer and has been validated against 5-year risk of death.[414]

5.2.2. Randomized controlled trials of blood pressure lowering in frail older patients

In the SPRINT trial, 2636 ambulatory adults aged ≥75 years were randomized to a systolic BP target of <120 mmHg compared with a systolic BP target of <140 mmHg.[293] The prevalence of pre-frailty (55.2%) and frailty (30.9%), assessed by a 37-item index, was similar in both groups. Intensive treatment resulted in significantly lower rates of fatal and non-fatal major CVD events and death from any cause, with similar overall rates of serious adverse events reported in both groups (48.4% and 48.3% in the intensive and the usual treatment group, respectively). The Chinese Strategy of Blood Pressure Intervention in Elderly Hypertensive Patients (STEP) replicated the SPRINT findings in adults aged 60–80 years, but did not report on frailty as a modifier of the treatment effect.[291] The Hypertension in the Very Elderly Trial (HYVET) had a double-blind, placebo-controlled design and randomized 3845 patients aged ≥80 years to be treated to a BP of 150/80 mmHg.[415] The trial showed significant reductions with active treatment: 21% for mortality, 34% for a composite cardiovascular endpoint, 64% for heart failure, and 32% for stroke.[415] Active treatment was also associated with a 42% reduction in incident fractures. In multivariable analyses, orthostatic hypotension at baseline did not modify the mortality benefit seen with treatment.[416] However, few adults ≥85 years have been included in trial and data from the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) indicate that the benefits of intensive BP-lowering treatment demonstrated in adults aged <85 years are not as clear among persons aged ≥85 years due to a lack of power in this very old subgroup.[292]

In addition, generalizing data from RCTs to very frail patients may not be possible. Specifically, RCTs typically excluded very frail adults such as those in residential care. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, a frailty index was retrospectively constructed.[417] Frailty slightly attenuated the treatment effect of more intensive BP and glycaemic control on major microvascular complications, but not on total and cardiovascular mortality or major CVD events. In a large,

prospective, observational study of 415 980 people aged >75 years, which used a 36-item electronic frailty index to include severely frail patients,[413] the lowest mortality risk over ≤10 years of follow-up was observed at systolic BP of 140–160 mmHg and diastolic BP of 80–90 mmHg. A systolic BP of <130 mmHg or diastolic BP of <80 mmHg was associated with excess mortality.[418] Similarly, in 173 treated octogenarians enrolled in the International Database of HOme Blood Pressure in Relation to Cardiovascular Outcomes (IDHOCO), the multivariable-adjusted association of the 5-year risk of a major CVD event with the home systolic BP was curvilinear with nadir near 150 mmHg,[419] while the risk increased linearly and inversely with the home diastolic BP.[419] However, as noted above and in *Section 9.8* in the main text, these observational J-curve findings are unreliable when dictating clinical care, as unidentified biases potentially confound the results. For instance, in addition to reverse causality, stiffness of the large arteries is associated with both low diastolic BP and increased mortality.[420] Furthermore, it is worth noting that the currently available evidence from RCTs has not demonstrated weakening of the benefits of BP-lowering treatment (i.e., no effect modification) among frailer patients enrolled in these trials.

The relative risk of CVD events associated with hypertension declines with older age, whereas absolute risk increases, indicating that considerably fewer older than younger patients with hypertension need to be treated to prevent one adverse health outcome.[421] Therefore, given the totality of evidence from clinical trials,[293,415–417] very old and very frail patients with hypertension should not be denied the benefits of BP-lowering treatment. Together with management of BP, a major consideration should be whether reversible causes of frailty can be addressed,[356] e.g. by treating underlying comorbidities or undergoing supervised muscle-strengthening physiotherapy or supervised exercise and co-ordination and balance training.[422]

5.3. Isolated systolic and diastolic hypertension

5.3.1. Definition of isolated systolic hypertension

Isolated systolic hypertension is typically defined as systolic BP of ≥140 mmHg with a diastolic BP of <90 mmHg, based on conventional office brachial BP measurements (noting that equivalent thresholds can be applied for out-of-office BP). While isolated systolic hypertension is quite uncommon in younger patients, affecting <3% in a general population setting (with the highest prevalence in people of African descent),[423] it is the most common type of hypertension in older ages; >80% of untreated patients with hypertension aged >60 have isolated systolic hypertension.[424]

5.3.2. Isolated systolic hypertension, risk factors, and ageing

Systolic BP changes in ageing relate to increased aortic stiffening with age,[425,426] which in large part is determined by the mechanical pulsatile wear-and-tear of elastin fibres in the extracellular matrix of the tunica media of the proximal aorta. As people age, the elastic fibres fragment and the mechanical load is transferred to collagen fibres, which are up to 1000 times stiffer than elastin. Arterial wall calcium deposits also contribute to age-related stiffness and to the isolated systolic hypertension phenotype.

A meta-analysis of eight trials including 15 693 patients with isolated systolic hypertension showed that the relative hazard ratios (HR) associated with a per 10 mmHg higher initial systolic BP were 1.26 [95% confidence interval (CI) 1.13–1.40] for total mortality, 1.22 (95% CI 1.04–1.40) for stroke, 1.15 (95% CI 1.04–1.28) for CVD events, but non-significant for coronary events.[427] The same meta-analysis demonstrated the beneficial effects of BP-lowering treatment in patients with isolated systolic hypertension: the pooled estimates of the reductions in relative risk were 13% ($P = .02$) and 16% ($P = 0.04$) for total and cardiovascular mortality, respectively. Even stronger benefits were seen when combining fatal and non-fatal CVD events.[427] Early isolated systolic hypertension studies used systolic BP targets of 160 or 150 mmHg. However, results from the SPRINT and the STEP trials (mean BP at study entry of 140/78 and 146/82 mmHg, respectively, indicating that many of the patients had isolated systolic hypertension) confirm that lower systolic BP targets are effective in reducing CVD events in patients with isolated systolic hypertension.[288,291]

Since relative risk reduction by BP-lowering treatment is homogeneous in any age group, whereas absolute risk reduction is larger with advancing age,[292] therapeutic inertia in older patients with isolated systolic hypertension should be avoided. Based on the aforementioned placebo-controlled trials, thiazide diuretics and long-acting dihydropyridine CCBs are the drug classes of choice to initiate BP-lowering treatment in patients with isolated systolic hypertension, irrespective of race, with RAS blockers as a third choice. However, in older patients (e.g. ≥85 years) with isolated systolic hypertension, factors such as comorbidities and frailty must be assessed in the clinical decision process of classical vs. intensive BP-lowering treatment goals, as well as in drug choice.

5.3.3. J-shaped curve of blood pressure and risk of cardiovascular disease in patients with diabetes

Numerous trials and meta-analyses have shown that pharmacological BP reduction is effective in preventing both micro- and macrovascular events in patients with diabetes. However, until recently, evidence on the BP threshold and target for treatment in patients with diabetes had been subject to debate. Reports of a J-shaped association between BP and risk of CVD in diabetes,[428] and the lack of a clear benefit of treatment on cardiac outcomes at lower BP in some meta-analyses,[176,429,430] had led to cautious recommendations for intensive treatment in this patient population.

A large-scale observational study showed that the previously observed J-shaped relationship between systolic BP and risk of CVD in patients with diabetes is likely due to uncontrolled confounding factors and that methodological approaches to reduce confounding suggest a continuous relationship between BP and risk of CVD.[431] Moreover, an individual patient data meta-analysis by the BPLTTC has now clarified some of the previous uncertainties about treatment thresholds in patients with diabetes.[432] This detailed stratified analysis of treatment effects in 103 325 patients with diabetes provided evidence against effect modification by categories of baseline BP down to a systolic BP of 120 mmHg. Although this study also showed that relative risk reductions for major CVD appear weaker in patients with diabetes than in those without, heterogeneity of relative treatment effects had no implications on absolute risk reductions; given that patients with diabetes are, on average, at higher risk of CVD, a fixed level of BP reduction led to a similar absolute risk reduction (and number needed to treat) in patients with and without diabetes. Furthermore, BP reduction in patients with diabetes is expected to reduce the risk of diabetes-associated complications including retinopathy, vasculopathy, and nephropathy (albuminuria and end-stage renal disease), which adds weight to the importance of reducing BP in these patients.[429,430,433]

5.3.4. Managing blood pressure in diabetes

Although a tabular meta-analysis of RCTs had suggested that RAS blockers are more effective in patients with diabetes than without diabetes,[430] a more recent individual patient data meta-analysis found no such difference in effect on major CVD outcomes.[432] Overall, all major BP-lowering medication classes were effective in preventing CVD in people with or without diabetes. Of note, however, albuminuria is more common in diabetes and, for this reason, ACE inhibitors and ARBs have potential advantages that may warrant consideration for BP-lowering in patients with diabetes.[434]

Since both pre-diabetes and obesity are risk factors for CVD, it would be important to monitor BP and CVD risk in patients with such conditions and consider treatment if they fulfil the criteria for treatment in the general population. It is also noteworthy that recent evidence suggests that elevated BP itself may increase the risk of diabetes.[179] This finding emphasizes the potential role of BP lowering in preventing diabetes, in addition to preventing CVD. Among the major classes of BP-lowering drugs, ACE inhibitors and ARBs were particularly effective in preventing new-onset diabetes and should be considered in patients at risk of diabetes and who are indicated for BP-lowering therapy.[179] Of note, while in the minority, some patients with type 2 diabetes aged <60 years may have 10-year CVD risk estimates of <10% by the SCORE2-Diabetes risk equation,[435] and in these cases, initiation of BP medication may be deferred to a BP of 140/90 mmHg in the absence of other high risk CVD conditions.

Increasing evidence indicates that Sodium-glucose cotransporter-2 (SGLT2) inhibitors and GLP-1 agonists are cardiovascular protective in patients with diabetes.[436] These drugs also have modest but significant BP-lowering effects.[437] In patients with diabetes, these drugs may have added benefit in BP-lowering, especially in those with hypertension.

5.3.5. Blood pressure targets in chronic kidney disease

Systematic reviews have examined the benefit of intensive BP control in patients with CKD. The first included nine major hypertension trials, including SPRINT, with 8127 patients. Over 3.3 years of follow-up, there was no benefit of intensive BP control on renal outcomes, though there was also no evidence for worsening of renal outcomes.[438] The second meta-analysis included 18 trials, including SPRINT and ACCORD, with 15 924 patients with CKD. Achieving a BP of 132 mmHg was associated with lower mortality compared with achieving a BP of 140 mmHg (HR 0.86; 95% CI 0.63–0.99).[439] The third meta-analysis included four major hypertension and CKD trials, including SPRINT and ACCORD, with 4983 patients.[440] There were no differences in all-cause mortality or cardiovascular outcomes between a target BP of <130 and <140 mmHg. Only after exclusion of patients with an eGFR of >60 mL/min/1.73 m^2 and intensive glycaemic control was there a possible difference in all-cause mortality favouring more intensive treatment (HR 0.79; 95% CI 0.63–1.00).

5.4. Chronic cerebrovascular disease and cognitive impairment

5.4.1. Role of hypertension in chronic cerebrovascular disease

Hypertension is a risk factor for chronic cerebrovascular disease through its direct effects on brain structure and microvasculature. This manifests as TIA and stroke in the acute setting, but chronic hypertension can lead to covert stroke and white-matter ischaemic change over time, resulting in cognitive decline and progressive vascular dementia.[441–445] Hypertension is also associated with increased risk of Alzheimer's disease,[446] and is a risk factor for developing AF, heart failure, and CKD, all of which are associated with increased risk of developing cognitive impairment and dementia.[143,447–449]

5.4.2. Treatment in patients with history of stroke or transient ischaemic attack

The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, which included patients with recent ischaemic stroke, did not show a statistically significant reduction in risk of recurrent stroke with telmisartan vs. placebo (HR 0.95; 95% CI 0.86–1.04) but the magnitude of BP reduction was small in the active treatment group compared with control (3.8/2.0 mmHg).[450] In the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial, a combination of perindopril and indapamide resulted in a larger reduction in BP (12/5 mmHg) and a lower risk of any recurrent stroke over 4 years of follow-up (HR 0.73; 95% CI 0.64–0.84) compared with placebo.[451]

Most prior guidelines recommend an intensive BP target in patients with a prior history of stroke, typically using combination treatment (typically with an ACE inhibitor/ARB plus either a calcium channel antagonist or a thiazide/thiazide-like diuretic), with therapy commencing immediately after TIA and within a few days of ischaemic stroke[452–456] (see *Section 10.3* in the main text for acute BP management during hospitalization for stroke).

Of note, a recent network meta-analysis and large-scale observational study designed to look at comparative effectiveness of BP-lowering agents suggested that regimens containing ACE inhibitors and thiazide/thiazide-like diuretics may be superior in terms of stroke risk reduction.[457,458] Intense BP control after stroke, typically targeting a systolic BP of <130 mmHg, was evaluated in the Prevention of Decline in Cognition after Stroke Trial (PODCAST),[459] Secondary Prevention of Small Subcortical Strokes (SPS3),[287] Recurrent Stroke Prevention Clinical Outcome (RESPECT),[460] and Prevention After Stroke—Blood Pressure (PAST-BP)[461] trials. While the individual trials were somewhat inconclusive, a meta-analysis showed a reduced risk of recurrent stroke of 22% in the intensive-treatment group randomized to a target systolic BP as low as 120 mmHg.[460] Caveats to this recommendation would be for frail cohorts, who were not represented in these trials and have a much higher rate of stroke and recurrent stroke than the general population, and are more sensitive to adverse effects of BP-lowering agents[337,353,354,462] (see *Section 9.3* in the main text).

5.4.3. Treatment in patients with cerebrovascular disease and cognitive impairment

Evidence for lowering BP to reduce risk of dementia has been limited due to heterogeneity in populations studied, cognitive testing methods used, and the varied use of dementia or cognitive impairment or both as a primary outcome.[463,464] The HYVET, Systolic Hypertension in the Elderly Program (SHEP), HOPE-3, and The Study on Cognition and Prognosis in the Elderly (SCOPE) trials, which excluded people with prior stroke or dementia, did not report a significant difference in cognitive outcomes between the active-treatment and placebo groups.[464–467]

Although a follow-up study of the Systolic Hypertension in Europe (Syst-Eur) trial showed a relative risk reduction for dementia of 54%

with long-term BP-lowering treatment,[211] this was not replicated in the SPRINT MIND trial, which reported that intensive BP-lowering treatment reduced risk of incident mild cognitive impairment (HR 0.81; 95% CI 0.69–0.95) and combined mild cognitive impairment and dementia (HR 0.85; 95% CI 0.74–0.97), but not the primary endpoint of dementia alone (HR 0.83; 95% CI 0.67–1.04).[357] The effect of BP-lowering treatment on white-matter intensities was evaluated in the SPRINT MIND[357] and the Effects of Intensive Versus Standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in Older People (INFINITY) trials,[468] which concluded that those in the intensive control arm had less white-matter intensity accumulation than in the standard-treatment arm. PROGRESS, which included people with stroke and TIA, also reported a reduced risk of dementia and cognitive decline for the active-treatment group associated with recurrent stroke but not a clear signal for dementia alone.[469]

While individual trials have had mixed results, meta-analysis of these RCTs, including SPRINT MIND, reported a reduced risk of incident dementia or cognitive impairment with BP lowering of 7%–13%.[358,359] There is no evidence on which BP-lowering agent, if any, is preferable for preventing dementia and cognitive impairment.[470,471]

The role of competing risk mechanisms including orthostatic hypotension[472] and BP variability[473] may be important factors in treatment decisions for people with frailty, multimorbidity, and/or chronic cerebrovascular disease.

5.5. Nocturnal hypertension

5.5.1. Definition

Nocturnal hypertension is defined as night-time BP of >120 mmHg systolic and/or >70 mmHg diastolic by 24 h ABPM. Nocturnal hypertension can occur as day–night sustained hypertension or isolated nocturnal hypertension (daytime BP of <135/85 mmHg on 24 h ABPM).

Physiologically, BP is expected to normally decrease during sleep by 10%–20% relative to daytime BP.[474] Night-time dipping patterns are classified into four groups.[475,476]

Inverse dipping (riser): nocturnal increase in BP (night-to-day ratio of >1.0).

Non-dipper: reduced night-time BP dip of <10% (or night-to-day ratio of >0.9 and ≤1.0).

Normal dipping: fall in night-time BP of >10% and <20% (or night-to-day ratio of 0.8 to 0.9).

Extreme dipping: marked fall in night-time BP of >20% (or night-to-day ratio of <0.8).

Patients with nocturnal hypertension may be dippers or non-dippers. Of note, the long-term reproducibility of dipping patterns appears to be low.[477,478]

5.5.2. Epidemiology

Nocturnal hypertension has been observed in up to half of patients with hypertension,[479–482] and is associated with increased HMOD, such as LVH, increased arterial stiffness,[479] impaired renal function, and diabetes mellitus.[175] Nocturnal hypertension is more prevalent in black[483–485] and Asian[486,487] populations. Masked uncontrolled hypertension, which occurs in 30% of patients treated for hypertension, has been reported to be more often due to poorly controlled nocturnal BP than daytime BP on ABPM.[488]

Environmental factors, including sleep duration and higher humidity,[489] nocturia,[490] OSAS,[491] obesity, high salt intake in salt-sensitive patients,[492] orthostatic hypotension, autonomic dysfunction, CKD,[493–495] diabetic neuropathy/diabetes,[496] and old age,[497] are associated with non-dipping. Moreover, nocturnal hypertension and absent night-time dipping pattern are more common in secondary hypertension.[498,499]

6. Acute and short-term lowering of blood pressure

Table S12 Diagnostic work-up for patients with a suspected hypertensive emergency

Common tests for all potential causes
Fundoscopy is a critical part of the diagnostic work-up
12-Lead ECG
Haemoglobin, platelet count, fibrinogen
Creatinine, eGFR, electrolytes, LDH, haptoglobin
Urinary albumin:creatinine ratio, urine microscopy for red cells, leucocytes, casts
Pregnancy test in women of child-bearing age
Specific tests by indication
Troponin, CK-MB (in suspected cardiac involvement, e.g. acute chest pain or acute heart failure), and NT-proBNP
Chest X-ray (fluid overload)
Echocardiography (aortic dissection, heart failure, or ischaemia)
CT angiography of thorax and/or abdomen in suspected acute aortic disease (e.g. aortic dissection)
CT or MRI brain (nervous system involvement)
Renal ultrasound (renal impairment or suspected renal artery stenosis)
Urine drug screen (suspected methamphetamine or cocaine use)

CK-MB, creatinine kinase–muscle/brain; CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B natriuretic peptide. Adapted from the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[210]

Table S13 Most common drugs used for the treatment of hypertensive emergencies

Drug	Onset of action	Duration of action	Dose	Contraindications	Adverse effects
Esmolol	1–2 min	10–30 min	0.5–1 mg/kg as i.v. bolus; 50–300 µg/kg/min as i.v. infusion	Second or third-degree AV block, systolic heart failure, asthma, bradycardia	Bradycardia
Metoprolol	1–2 min	5–8 h	2.5–5 mg i.v. bolus over 2 min – may be repeated every 5 min to a maximum dose of 15 mg	Second or third-degree AV block, systolic heart failure, asthma, bradycardia	Bradycardia
Labetalol	5–10 min	3–6 h	0.25–0.5 mg/kg i.v. bolus; 2–4 mg/min infusion until goal BP is reached, thereafter 5–20 mg/h	Second or third-degree AV block, systolic heart failure, asthma, bradycardia	Bronchoconstriction, foetal bradycardia
Fenoldopam	5–15 min	30–60 min	0.1 µg/kg/min i.v. infusion, increase every 5 min with 0.05–0.1 µg/kg/min increments until goal BP is reached	Caution in glaucoma	
Clevidipine	2–3 min	5–15 min	2 mg/h i.v. infusion, increase every 2 min with 2 mg/h until goal BP		Headache, reflex tachycardia
Nicardipine	5–15 min	30–40 min	5–15 mg/h i.v. infusion, starting dose 5 mg/h, increase every 15–30 min with 2.5 mg until goal BP, thereafter decrease to 3 mg/h	Liver failure	Headache, reflex tachycardia
Nitroglycerin	1–5 min	3–5 min	5–200 µg/min i.v. infusion, 5 µg/min increase every 5 min		Headache, reflex tachycardia
Nitroprusside	Immediate	1–2 min	0.3–10 µg/kg/min i.v. infusion, increase by 0.5 µg/kg/min every 5 min until goal BP	Liver/kidney failure (relative)	Cyanide intoxication
Enalaprilat	5–15 min	4–6 h	0.625–1.25 mg i.v. bolus	History of angioedema	
Urapidil	3–5 min	4–6 h	12.5–25 mg as bolus injection; 5–40 mg/h as continuous infusion		
Clonidine	30 min	4–6 h	150–300 µg i.v. bolus over 5–10 min		Sedation, rebound hypertension
Phentolamine	Immediate	Less than 5 min	5 mg i.v. bolus; additional bolus doses every 10 minutes as needed	Hypersensitivity, myocardial infarction	Injection site pain, nasal congestion, burning or pain in eye

AV, atrioventricular; BP, blood pressure; i.v., intravenous. Adapted from the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[210]

7. Patient-centred care in hypertension

7.1. Communicating consequences of treatment

Standard approaches to communicating the consequences of treatment can involve communicating estimated absolute 10-year risk of a CVD event with Systematic COronary Risk Evaluation 2 (SCORE2) or Systematic COronary Risk Evaluation 2–Older Persons (SCORE2-OP). Alternatively, individual risk and risk reduction can be communicated in terms of 'risk age' or 'heart age' as described in *Section 7.3* in the main text. It is important to identify what matters most to patients when communicating the consequences of treatment, as this might not align with a provider's typical emphasis on pharmacotherapy and hypertension-related morbidity and mortality.

7.2. Facilitating medication adherence and persistence in treatment

A significant proportion of apparent treatment-resistant hypertension can be accounted for by non-adherence to medications.[500] Various methods are available to assess adherence, namely patient self-report, prescription fill data from pharmacy databases, pill count, biochemical detection of hypertension medication levels, electronic drug monitoring, smart technology, and direct observation.[501] A key recommendation in using any of these methods is that adherence should always be assessed with a no-blame approach.

Table S14 Methods of assessing drug adherence in hypertension clinical practice

Method	Advantages	Disadvantages
Self-report by patient or proxy, e.g. an ongoing social contact or family member	Most feasible method for most contexts that can capture initiation, implementation, and persistence data	Subject to reporting and recall biases that may overestimate adherence
Prescription fill data	Usually easy to access through pharmacy databases and can confirm initiation and persistence over time	Requires linked pharmacy databases across all healthcare settings. Does not confirm that medications have been ingested, i.e. implementation
Pill count	Can confirm if dispensed drugs are being taken as per prescription, i.e. implementation	This can be time consuming and may not be feasible to carry out in the community context
Biochemical detection of hypertension medications	Objective and sensitive measure that is not affected by reporting biases	This captures a snapshot of adherence in a small window of time and may be affected by 'white-coat adherence', where the awareness of the assessment prompts adherence
Direct observation	Relatively easy to carry out in a clinical setting and useful to assess apparent treatment-resistant hypertension when used in conjunction with BP measurement over subsequent hours via HBPM or ABPM	This is not a feasible method for implementation and persistence over the longer term in the community

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HBPM, home blood pressure monitoring.

Table S15 Common barriers to patient adherence and persistence, and proposed strategies to overcome them

Barrier	Proposed strategies	Digital/technological solutions that may help
Complexity of therapy and related cognitive load of using multiple medications as prescribed	• Consider single-pill combinations in fixed doses when appropriate. • Use simplified regimens and once-daily dosing. • Monitor adherence and emphasize importance of persistence over time. • Review concomitant prescriptions. • Aim to reduce complexity of overall therapy, e.g. deprescribing where indicated.	• Reminder apps (cue-dosing). • Telemonitoring. • Smart dispensers, or caps. • Educational websites and apps. • Interactive apps to increase patient engagement.
Patient beliefs/attitudes about hypertension and medication	• Acknowledge and address patient beliefs/fears about stress, symptoms. • Provide an accurate description of the benefits and adverse effects of treatment. • Use patient-centred approaches, particularly those that are nurse or pharmacist led. • Provide accessible information for school children and adults on preventive strategies (e.g. diet, exercise from a young age) and to improve hypertension-related health literacy. See *Section 7.3* of the guidelines. • Suggest easy-to-adopt lifestyle modification.	• Devices that monitor BP with apps that provide feedback on risk levels, or provide results electronically to physicians. • Educational websites and apps. • Interactive apps to increase patient engagement. • Interactive exercise and dietary modification apps.
Socio-demographic considerations	• Consider approaches that address age, and socio-economic-specific needs and concerns. • Younger: tailor education to personal risk, beliefs, and attitudes. • Older: review cognitive abilities and digital literacy of patients, their family and caregivers, regular reminder systems, and easy-to-manage pill containers. • Lower socio-economic status: financial barriers to obtaining medications where people have lower incomes and there are medication payments	• Technology is a matter of patient preference and accessibility. • Do not assume that age is a reason not to suggest websites or apps. • Where patients need to make payments (or co-payments) for medications, consider lower-cost medications, e.g. generic hypertension medications or reducing the number of agents overall.

Continued

Physician–patient relationship	• Cultivate a strong physician–patient relationship, customized to patient's needs and lifestyle. • Listen to patients and gain trust. • Use a collaborative communication style rather than an inquisition style. • Discuss patients' socio-demographic circumstances and their hypertension medications. • Engage patients in decisions and agree on tasks and goals.	• Telemonitoring. • HBPM to monitor BP linked to apps that provide feedback on risk levels, or provide results electronically to physicians. • Interactive apps to increase patient–physician interactions and patient engagement.

BP, blood pressure; HBPM, home blood pressure monitoring. *Table S15* adapted from Parati *et al.*[502]

8. Implementation of guidelines

8.1. A pilot study to gain insights into implementation of hypertension guidelines in Europe

Advancements in science, growing numbers of RCTs, and the huge and growing volume of data, all pose challenges for clinicians to make the most appropriate clinical decisions for their patients. To address this, clinical practice guidelines scrutinize, summarize, and attempt to simplify information, making it easier for the clinician to make evidence-based decisions. Despite the growing number of excellent national and international clinical guidelines for the management of hypertension, it seems that implementation of these guidelines is suboptimal, due to multiple factors. These factors include guidelines being too academic, lack of harmonization across guidelines, lack of access to guidelines, as well as attitudes and practice behaviours that drive clinician and patient therapeutic inertia.[503–505] This negatively impacts quality of care and patient outcomes.

Since little is known about implementation of hypertension guidelines in Europe, the task force of the 2024 ESC Hypertension Guidelines undertook a new initiative as a pilot project to gather information through a survey from national hypertension societies linked to the ESC. A number of salient findings emerged. First, many European cardiologists and physicians surveyed had access to registry or electronic health record data that could inform their practice of hypertensive patients and that could facilitate audit and quality improvement initiatives. Second, most European cardiologists and physicians surveyed reported access to out-of-office BP measurements, which are core in the present guidelines. However, many European cardiologists and physicians surveyed appeared to have concerns about the estimation of global CVD risk as part of their management of patients with elevated BP and hypertension. Reasons for this need to be better explored through implementation science, and strategies to improve implementation of CVD risk assessment need to be developed. Along with other implementation approaches, such as those outlined in a recent American Heart Association scientific statement,[506] we hope the findings of our survey will inform implementation priorities in future clinical guidelines.

9. References

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