# 2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

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Abbrovia	tions and acronyms		5
Abbrevia	tions and acronyms	ESH	European Society of Hypertension
ABI	Ankle-brachial index	FEVER	Felodipine Event Reduction
ABPM	Ambulatory blood pressure monitoring	HAS-BLED	Hypertension, Abnormal renal/liver function
ACCOMPLISH	Avoiding Cardiovascular Events Through		(1 point each), Stroke, Bleeding history or
, 10001 2.01 .	Combination Therapy in Patients Living With		predisposition, Labile INR, Elderly (>65),
	Systolic Hypertension		Drugs/alcohol concomitantly (1 point each)
ACCORD	Action to Control Cardiovascular Risk in	HbA1c	Haemoglobin A1c
ACCORD	Diabetes	HBPM	Home blood pressure monitoring
ACE	Angiotensin-converting enzyme	HDL-C	HDL cholesterol
ACEi	Angiotensin-converting enzyme inhibitor	HELLP	Haemolysis, elevated liver enzymes, and low
ACR	Albumin:creatinine ratio		platelets
		HFpEF	Heart failure with preserved ejection fraction
ADVANCE	Action in Diabetes and Vascular Disease:	HFrEF	Heart failure with reduced ejection fraction
	Preterax and Diamicron – MR Controlled	HMOD	Hypertension-mediated organ damage
٨٦	Evaluation	HOPE	Heart Outcomes Prevention Evaluation
AF	Atrial fibrillation	HYVET	Hypertension in the Very Elderly Trial
ALLHAT	Antihypertensive and Lipid-Lowering	i.v.	Intravenous
A	Treatment to Prevent Heart Attack Trial	IMT	Intima-media thickness
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using	INVEST	International Verapamil-Trandolapril Study
	Cardiovascular and Renal Disease Endpoints	ISH	Isolated systolic hypertension
ARB	Angiotensin receptor blocker	JUPITER	Justification for the Use of Statins in
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial	:	Prevention: an Intervention Trial Evaluating
AV	Atrioventricular	:	Rosuvastatin
BMI	Body mass index	LDH	Lactate dehydrogenase
BP	Blood pressure	LDL-C	LDL cholesterol
bpm	Beats per minute	LEAD	Lower extremity artery disease
BSA	Body surface area	LIFE	Losartan Intervention For Endpoint reduction
CAD	Coronary artery disease		in hypertension
CAPPP	Captopril Prevention Project	LV	Left ventricular
CCB	Calcium channel blocker	LVH	Left ventricular hypertrophy
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age	MAP	Mean arterial pressure
	≥75 years, Diabetes mellitus, Stroke, Vascular	MI	Myocardial infarction
	disease, Age 65–74 years, Sex category	MR	Magnetic resonance
	(female)	MRA	Mineralocorticoid receptor antagonist
CKD	Chronic kidney disease	MRI	Magnetic resonance imaging
CK-MB	Creatinine kinase-muscle/brain	MUCH	Masked uncontrolled hypertension
CMR	Cardiac magnetic resonance	NORDIL	Nordic Diltiazem
COLM	Combination of OLMesartan and a calcium	NS	Non-significant
	channel blocker or diuretic in Japanese elderly	NT-proBNP	N-terminal pro-B natriuretic peptide
	hypertensive patients	o.d.	Omni die (every day)
CONVINCE	Controlled Onset Verapamil Investigation of	ONTARGET	Ongoing Telmisartan Alone and in
	Cardiovascular End Points		combination with Ramipril Global Endpoint
COPD	Chronic obstructive pulmonary disease		Trial
COPE	Combination Therapy of Hypertension to	PAC	Plasma aldosterone concentration
	Prevent Cardiovascular Events	PAD	Peripheral artery disease
CT	Computed tomography	PATHS	Prevention and Treatment of Hypertension
CV	Cardiovascular	•	Study
CVD	Cardiovascular disease	PRA	Plasma renin activity
DBP	Diastolic blood pressure	PRC	Plasma renin concentration
DENERHTN	Renal Denervation for Hypertension	PROGRESS	Perindopril protection against recurrent stroke
DLID	D:1 1 :1:	:	

DHP

ECG

eGFR

ELSA

**ENaC** 

ESC

Dihydropyridine

Electrocardiogram

Epithelial sodium channel

Estimated glomerular filtration rate

European Society of Cardiology

European Lacidipine Study on Atherosclerosis

PWV Pulse wave velocity
RAS Renin—angiotensin system
RCT Randomized controlled trial
RWT Relative wall thickness
SBP Systolic blood pressure

study

SCOPE Study on Cognition and Prognosis in the

Elderly

SCORE Systematic COronary Risk Evaluation
SHEP Systolic Hypertension in the Elderly Program

SPC Single-pill combination

SPRINT Systolic Blood Pressure Intervention Trial

STOP-H Swedish Trial in Old Patients with

Hypertension

SUCH Sustained uncontrolled hypertension
Syst-China Systolic Hypertension in China
Syst-Eur Systolic Hypertension in Europe
TIA Transient ischaemic attack

TTE Transthoracic echocardiography
VALUE Valsartan Antihypertensive Long-term Use

Evaluation

VEGF Vascular endothelial growth factor
WUCH White-coat uncontrolled hypertension

#### 1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) and by the European Society of Hypertension (ESH), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC and ESH to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy and approved by the ESH. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk—benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in Tables 1 and 2.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and ESH

and updated. The Task Force received its entire financial support from the ESC and ESH without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts, and in this case by ESH appointed experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG and ESH for publication in the European Heart Journal and in the Journal of Hypertension as well as Blood Pressure. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC and ESH Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC AND ESH websites and hosted on the EHJ AND JOURNAL OF HYPERTENSION websites. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC and ESH Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC and ESH Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

#### 2 Introduction

Substantial progress has been made in understanding the epidemiology, pathophysiology, and risk associated with hypertension, and a wealth of evidence exists to demonstrate that lowering blood pressure (BP) can substantially reduce premature morbidity and mortality. A number of proven, highly effective, and well-tolerated lifestyle and drug treatment strategies can achieve this reduction in BP. Despite this, BP control rates remain poor worldwide and are far from satisfactory across Europe. Consequently, hypertension remains the major preventable cause of cardiovascular disease (CVD) and all-cause death globally and in our continent. 11–14

Table I ESC Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 ESC Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

These 2018 ESC/ESH Guidelines for the management of arterial hypertension are designed for adults with hypertension, i.e. aged  $\geq$ 18 years. The purpose of the review and update of these Guidelines was to evaluate and incorporate new evidence into the Guideline recommendations. The specific aims of these Guidelines were to produce pragmatic recommendations to improve the detection and treatment of hypertension, and to improve the poor rates of BP control by promoting simple and effective treatment strategies.

These joint 2018 Guidelines follow the same principles upon which a series of hypertension Guidelines were jointly issued by the two societies in 2003, 2007, and 2013. These fundamental principles

are: (i) to base recommendations on properly conducted studies, identified from an extensive review of the literature; (ii) to give the highest priority to data from randomized controlled trials (RCTs); (iii) to also consider well-conducted meta-analyses of RCTs as strong evidence (this contrasts with network meta-analyses, which we do not consider to have the same level of evidence because many of the comparisons are non-randomized); (iv) to recognize that RCTs cannot address many important questions related to the diagnosis, risk stratification, and treatment of hypertension, which can be addressed by observational or registry-based studies of appropriate scientific calibre; (v) to grade the level of scientific evidence and the strength of recommendations according to ESC recommendations (see section 1); (vi) to recognize that opinions may differ on key recommendations, which are resolved by voting; and (vii) to recognize that there are circumstances in which there is inadequate or no evidence, but that the question is important for clinical practice and cannot be ignored. In these circumstances, we resort to pragmatic expert opinion and endeavour to explain its rationale.

Each member of the Task Force was assigned specific writing tasks, which were reviewed by section co-ordinators and then by the two chairs, one appointed by the ESC and the other by the ESH. The text was developed over approximately 24 months, during which the Task Force members met collectively and corresponded intensively with one another between meetings. Before publication, the document was reviewed by European reviewers selected by the ESC and ESH, and by representatives of ESC National Cardiac Societies and ESH National Hypertension Societies.

## 2.1 What is new and what has changed in the 2018 ESC/ESH Arterial Hypertension Guidelines?

Changes in recommendations			
2013	2018		
Diagnosis	Diagnosis		
Office BP is recommended for screening and diagnosis of hypertension.	It is recommended to base the diagnosis of hypertension on:  Repeated office BP measurements; or  Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically feasible.		
Treatment thresholds Highnormal BP (130–139/85–89 mmHg): Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high–normal BP.	Treatment thresholds Highnormal BP (130–139/85–89 mmHg): Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD.		
Treatment thresholds  Treatment of low-risk grade 1 hypertension: Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low-moderate-risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures.	Treatment thresholds Treatment of low-risk grade 1 hypertension: In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.		
Treatment thresholds Older patients Antihypertensive drug treatment may be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated.	Treatment thresholds Older patients BP-lowering drug treatment and lifestyle intervention is recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.		
BP treatment targets	BP treatment targets		
An SBP goal of <140 mmHg is recommended.	<ul> <li>It is recommended that the first objective of treatment should be to lower BP to &lt;140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.</li> <li>In patients &lt;65 years it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.</li> </ul>		

Continued

BP treatment targets in older patients (65–80 years)	BP treatment targets in older patients (65–80 years)			
An SBP target of between 140–150 mmHg is recommended for older patients (65–80 years).	In older patients (≥65 years), it is recommended that SBP should be targeted to a BP range of 130–139 mmHg.			
BP treatment targets in patients aged over 80 years	BP treatment targets in patients aged over 80 years			
An SBP target between 140–150 mmHg should be considered in people older than 80 years, with an initial SBP ≥160 mmHg, prove that they are in good physical and mental condition.	An SBP target range of 130–139 mmHg is recommended for people older than 80 years, if tolerated.			
DBP targets	DBP targets			
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended.	A DBP target of <80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities.			
Initiation of drug treatment	Initiation of drug treatment			
Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk.	• •			
Resistant hypertension	Resistant hypertension			
Mineralocorticoid receptor antagonists, amiloride, and the alphablocker doxazosin should be considered if no contraindication exists.	Recommended treatment of resistant hypertension is the addition of low-dose spironolactone to existing treatment, or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, higher-dose thiazide/thiazide-like diuretic or a loop diuretic, or the addition of bisoprolol or doxazosin.			
Device-based therapy for hypertension	Device-based therapy for hypertension			
In case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered.	Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.			
Recommendation Grading				
Grade IIa	Grade III Grade III			

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; RCT = randomized controlled trial; SBP = systolic blood pressure; SPC = single-pill combination.

#### New sections/recommendations

- When to suspect and how to screen for the causes of secondary hypertension
- Management of hypertension emergencies
- Updated recommendations on the management of BP in acute stroke
- Updated recommendations on the management of hypertension in women and pregnancy
- Hypertension in different ethnic groups
- The effects of altitude on BP
- Hypertension and chronic obstructive pulmonary disease
- Hypertension and AF and other arrhythmias
- Oral anticoagulant use in hypertension
- Hypertension and sexual dysfunction
- Hypertension and cancer therapies
- Perioperative management of hypertension
- Glucose-lowering drugs and BP
- Updated recommendations on CV risk assessment and management: (i) using the SCORE system to assess risk in patients without CVD; (ii) the importance of HMOD in modifying CV risk; and (iii) the use of statins and aspirin for **CVD** prevention

#### **New concepts**

#### **RP** measurement

• Wider use of out-of-office BP measurement with ABPM and/or HBPM, especially HBPM, as an option to confirm the diagnosis of hypertension, detect white-coat and masked hypertension, and monitor BP control.

#### Less conservative treatment of BP in older and very old patients

- Lower BP thresholds and treatment targets for older patients, with emphasis on considerations of biological rather than chronological age (i.e. the importance of frailty, independence, and the tolerability of treatment).
- Recommendation that treatment should never be denied or withdrawn on the basis of age, provided that treatment is tolerated.

#### A SPC treatment strategy to improve BP control

- Preferred use of two-drug combination therapy for the initial treatment of most people with hypertension.
- A single-pill treatment strategy for hypertension with the preferred use of SPC therapy for most patients.
- Simplified drug treatment algorithms with the preferred use of an ACE inhibitor or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic, as the core treatment strategy for most patients, with beta-blockers used for specific indications.

#### New target ranges for BP in treated patients

• Target BP ranges for treated patients to better identify the recommended BP target and lower safety boundaries for treated BP, according to a patient's age and specific comorbidities.

#### Detecting poor adherence to drug therapy

• A strong emphasis on the **importance of evaluating treatment adherence** as a major cause of poor BP control.

#### A key role for nurses and pharmacists in the longer-term management of hypertension

• The important role of nurses and pharmacists in the education, support, and follow-up of treated hypertensive patients is emphasized as part of the overall strategy to improve BP control.

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ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CV = cardiovascular; CVD = cardiovascular disease; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; SCORE = Systematic COronary Risk Evaluation; SPC = single-pill combination.

# 3 Definition, classification, and epidemiological aspects of hypertension

#### 3.1 Definition of hypertension

The relationship between BP and cardiovascular (CV) and renal events is continuous, making the distinction between normotension and hypertension, based on cut-off BP values, somewhat arbitrary. 2,4,8 However, in practice, cut-off BP values are used for pragmatic reasons to simplify the diagnosis and decisions about treatment. Epidemiological associations between BP and CV risk extend from very low levels of BP [i.e. systolic BP (SBP) >115 mmHg]. However, 'hypertension' is defined as the level of BP at which the benefits of treatment (either with lifestyle interventions or drugs) unequivocally outweigh the risks of treatment, as documented by clinical trials. This evidence has been reviewed (see section 7.2 for detailed discussion of hypertension diagnostic thresholds) and provides the basis for the recommendation that the classification of BP and definition of hypertension remain unchanged from previous ESH/ESC Guidelines (Table 3). 15,16,17 The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

Hypertension is defined as office SBP values  $\geq$ 140 mmHg and/or diastolic BP (DBP) values  $\geq$ 90 mmHg. This is based on evidence from multiple RCTs that treatment of patients with these BP values is beneficial (see section 7). The same classification is used in younger, middle-aged, and older people, whereas BP centiles are used in children and teenagers, in whom data from interventional trials are not available. Details on BP classification in boys and girls  $\leq$  16 years of

age can be found in the 2016 ESH Guidelines for children and adolescents.<sup>18</sup>

#### 3.2 Classification of blood pressure

Classification of BP			
Recommendation	Class <sup>a</sup>	Level <sup>b</sup>	
It is recommended that BP be classified as optimal, normal, high–normal, or grades 1–3 hypertension, according to office BP.	-	С	©ESC/ESH 2018
BP = blood pressure.  aClass of recommendation bLevel of evidence.			_

#### 3.3 Prevalence of hypertension

Based on office BP, the global prevalence of hypertension was estimated to be 1.13 billion in 2015,<sup>5</sup> with a prevalence of over 150 million in central and eastern Europe. The overall prevalence of hypertension in adults is around 30-45%,<sup>12</sup> with a global agestandardized prevalence of 24 and 20% in men and women, respectively, in 2015.<sup>5</sup> This high prevalence of hypertension is consistent across the world, irrespective of income status, i.e. in lower, middle, and higher income countries.<sup>12</sup> Hypertension becomes progressively more common with advancing age, with a prevalence of >60% in people aged >60 years.<sup>12</sup> As populations age, adopt more sedentary lifestyles, and increase their body weight, the prevalence of hypertension worldwide will continue to rise. It is estimated that the number

Table 3 Classification of office blood pressure<sup>a</sup> and definitions of hypertension grade<sup>b</sup>

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension <sup>b</sup>	≥140	and	<90

 $BP = blood\ pressure;\ SBP = systolic\ blood\ pressure.$ 

The same classification is used for all ages from 16 years.

<sup>&</sup>lt;sup>a</sup>BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.

<sup>&</sup>lt;sup>b</sup>Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.

#### Table 4 Factors influencing cardiovascular risk in patients with hypertension

#### Demographic characteristics and laboratory parameters

Sex<sup>a</sup> (men >women)

 $Age^{a}$ 

Smoking (current or past history)<sup>a</sup>

Total cholesterol<sup>a</sup> and HDL-C

Uric acid

Diabetes<sup>a</sup>

Overweight or obesity

Family history of premature CVD (men aged <55 years and women aged <65 years)

Family or parental history of early-onset hypertension

Early-onset menopause

Sedentary lifestyle

Psychosocial and socioeconomic factors

Heart rate (resting values >80 beats/min)

#### **Asymptomatic HMOD**

Arterial stiffening:

Pulse pressure (in older people) ≥60 mmHg

Carotid-femoral PWV >10 m/s

ECG LVH (Sokolow-Lyon index >35 mm, or R in aVL  $\geq$ 11 mm; Cornell voltage duration product >2440 mm.ms, or Cornell voltage >28 mm in men or >20 mm in women)

Echocardiographic LVH [LV mass index: men >50  $g/m^{2.7}$ ; women >47  $g/m^{2.7}$  (height in  $m^{2.7}$ ); indexation for BSA may be used in normal-weight patients; LV mass/BSA  $g/m^2$  >115 (men) and >95 (women)]

Microalbuminuria (30–300 mg/24 h), or elevated albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)<sup>b</sup>

Moderate CKD with eGFR >30–59 mL/min/1.73 m<sup>2</sup> (BSA) or severe CKD eGFR <30 mL/min/1.73 m<sup>2 b</sup>

Ankle-brachial index < 0.9

Advanced retinopathy: haemorrhages or exudates, papilloedema

#### Established CV or renal disease

Cerebrovascular disease: ischaemic stroke, cerebral haemorrhage, TIA

CAD: myocardial infarction, angina, myocardial revascularization

Presence of atheromatous plaque on imaging

Heart failure, including HFpEF

Peripheral artery disease

Atrial fibrillation

BSA = body surface area; CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HDL-C = HDL cholesterol; HFpEF = heart failure with preserved ejection fraction; HMOD = hypertension-mediated organ damage; LV = left ventricular; LVH = left ventricular hypertrophy; PWV = pulse wave velocity; SCORE = Systematic COronary Risk Evaluation; TIA = transient ischaemic attack.

aCV risk factors included in the SCORE system.

<sup>b</sup>Proteinuria and reduced eGFR are independent risk factors.

See Table 6 for CV risk modifiers.

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Table 5 Ten year cardiovascular risk categories (Systematic COronary Risk Evaluation system)

Very high risk	People with any of the following:
	Documented CVD, either clinical or unequivocal on imaging.
	Clinical CVD includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD
	<ul> <li>Unequivocal documented CVD on imaging includes significant plaque (i.e. ≥50% stenosis) on angiography or ultrasound: it does not include increase in carotid intima-media thickness</li> </ul>
	<ul> <li>Diabetes mellitus with target organ damage, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia</li> <li>Severe CKD (eGFR &lt;30 mL/min/1.73 m²)</li> </ul>
	A calculated 10 year SCORE of ≥10%
High risk	<ul> <li>People with any of the following:</li> <li>Marked elevation of a single risk factor, particularly cholesterol &gt;8 mmol/L (&gt;310 mg/dL), e.g. familial hyper-cholesterolaemia or grade 3 hypertension (BP ≥180/110 mmHg)</li> <li>Most other people with diabetes mellitus (except some young people with type 1 diabetes mellitus and with out major risk factors, who may be at moderate-risk)</li> </ul>
	Hypertensive LVH
	Moderate CKD eGFR 30-59 mL/min/1.73 m <sup>2</sup> )
	A calculated 10 year SCORE of 5-10%
Moderate risk	People with:  • A calculated 10 year SCORE of ≥1 to <5%  • Grade 2 hypertension  • Many middle-aged people belong to this category
Low risk	People with:  • A calculated 10 year SCORE of <1%

BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; PAD = peripheral artery disease; SCORE = Systematic COronary Risk Evaluation.

of people with hypertension will increase by 15-20% by 2025, reaching close to 1.5 billion. <sup>19</sup>

### 3.4 Blood pressure relationship with risk of cardiovascular and renal events

Elevated BP was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths and over 200 million disability-adjusted life years. Importantly, despite advances in diagnosis and treatment over the past 30 years, the disability-adjusted life years attributable to hypertension have increased by 40% since 1990. SBP  $\geq$ 140 mmHg accounts for most of the mortality and disability burden ( $\sim$ 70%), and the largest number of SBP-related deaths per year are due to ischaemic heart disease (4.9 million), haemorrhagic stroke (2.0 million), and ischaemic stroke (1.5 million).

Both office BP and out-of-office BP have an independent and continuous relationship with the incidence of several CV events [haemorrhagic stroke, ischaemic stroke, myocardial infarction, sudden death, heart failure, and peripheral artery disease (PAD)], as well as end-stage renal disease.<sup>4</sup> Accumulating evidence is closely linking

hypertension with an increased risk of developing atrial fibrillation (AF),<sup>20</sup> and evidence is emerging that links early elevations of BP to increased risk of cognitive decline and dementia.<sup>21,22</sup>

The continuous relationship between BP and risk of events has been shown at all ages<sup>23</sup> and in all ethnic groups,<sup>24,25</sup> and extends from high BP levels to relatively low values. SBP appears to be a better predictor of events than DBP after the age of 50 years.<sup>23,26,27</sup> High DBP is associated with increased CV risk and is more commonly elevated in younger (<50 years) vs. older patients. DBP tends to decline from midlife as a consequence of arterial stiffening; consequently, SBP assumes even greater importance as a risk factor from midlife.<sup>26</sup> In middle-aged and older people, increased pulse pressure (the difference between SBP and DBP values) has additional adverse prognostic significance.<sup>28,29</sup>

### 3.5 Hypertension and total cardiovascular risk assessment

Hypertension rarely occurs in isolation, and often clusters with other CV risk factors such as dyslipidaemia and glucose intolerance.  $^{30,31}$ 

This metabolic risk factor clustering has a multiplicative effect on CV risk.  $^{32}$  Consequently, quantification of total CV risk (i.e. the likelihood of a person developing a CV event over a defined period) is an important part of the risk stratification process for patients with hypertension.

Many CV risk assessment systems are available and most project 10 year risk. Since 2003, the European Guidelines on CVD prevention have recommended use of the Systematic COronary Risk Evaluation (SCORE) system because it is based on large, representative European cohort data sets (available at: http://www.escardio.org/Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SCORE-Risk-Charts). The SCORE system estimates the 10 year risk of a first fatal atherosclerotic event, in relation to age, sex, smoking habits, total cholesterol level, and SBP. The SCORE system also allows calibration for different CV risk levels across numerous European countries and has been externally validated. A previous limitation of the SCORE system was that it applied only to patients aged 40–65 years; however, the SCORE system has recently been adapted for patients over the age of 65 years. Detailed information on CV risk assessment is available. S

Factors influencing CV risk factors in patients with hypertension are shown in *Table 4*. Hypertensive patients with documented CVD, including asymptomatic atheromatous disease on imaging, type 1 or type 2 diabetes, very high levels of individual risk factors (including grade 3 hypertension), or chronic kidney disease (CKD; stages 3 - 5), are automatically considered to be at very high (i.e. ≥10% CVD mortality) or high (i.e. 5 - 10% CVD mortality) 10 year CV risk (*Table 5*). Such patients do not need formal CV risk estimation to determine their need for treatment of their hypertension and other CV risk factors. For all other hypertensive patients, estimation of 10 year CV risk using the SCORE system is recommended. Estimation should be complemented by assessment of hypertension-mediated organ damage (HMOD), which can also increase CV risk to a higher level, even when asymptomatic (see *Table 4* and sections 3.6 and 4).

There is also emerging evidence that an increase in serum uric acid to levels lower than those typically associated with gout is independently associated with increased CV risk in both the general population and in hypertensive patients. Measurement of serum uric acid is recommended as part of the screening of hypertensive patients.<sup>36</sup>

The SCORE system only estimates the risk of fatal CV events. The risk of total CV events (fatal and non-fatal) is approximately three times higher than the rate of fatal CV events in men and four times higher in women. This multiplier is attenuated to less than three times in older people in whom a first event is more likely to be fatal.<sup>37</sup>

There are important general modifiers of CV risk (*Table 6*) as well as specific CV risk modifiers for patients with hypertension. CV risk modifiers are particularly important at the CV risk boundaries, and especially for patients at moderate-risk in whom a risk modifier might convert moderate-risk to high risk and influence treatment decisions with regard to CV risk factor management. Furthermore, CV risk estimates by the SCORE system may be modified in first-generation immigrants to Europe and CV risk scores in such patients may be adjusted by correction factors (*Table 7*). Further details of the impact of CV risk modifiers are available from the ESC 2016 CVD prevention Guidelines.<sup>35</sup>

**Table 6** Risk modifiers increasing cardiovascular risk estimated by the Systemic COronary Risk Evaluation (SCORE) system<sup>35</sup>

Social deprivation, the origin of many causes of CVD
Obesity (measured by BMI) and central obesity (measured by waist circumference)
Physical inactivity
Psychosocial stress, including vital exhaustion
Family history of premature CVD (occurring at age <55 years in men and <60 years in women)
Autoimmune and other inflammatory disorders
Major psychiatric disorders
Treatment for infection with human immunodeficiency virus
Atrial fibrillation
LV hypertrophy
CKD
Obstructive sleep apnoea syndrome

BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease: LV = left ventricular.

**Table 7** Correction factors for the Systemic COronary Risk Evaluation (SCORE) cardiovascular risk estimates in first-generation immigrants to Europe<sup>35</sup>

Region of origin	Multiplication factor
Southern Asia	1.4
Sub-Saharan Africa	1.3
Caribbean	1.3
Western Asia	1.2
Northern Africa	0.9
Eastern Asia	0.7
Southern America	0.7

#### 3.6 Importance of hypertensionmediated organ damage in refining cardiovascular risk assessment in hypertensive patients

A unique and important aspect of CV risk estimation in hypertensive patients is the need to consider the impact of HMOD. This was previously termed 'target organ damage', but HMOD more accurately

describes hypertension-induced structural and/or functional changes in major organs (i.e. the heart, brain, retina, kidney, and vasculature) (Table 4). There are three important considerations: (i) not all features of HMOD are included in the SCORE system (CKD and established vascular disease are included) and several hypertensive HMODs (e.g. cardiac, vascular, and retinal) have well-established adverse prognostic significance (see section 5) and may, especially if HMOD is pronounced, lead to a high CV risk even in the absence of classical CV risk factors; (ii) the presence of HMOD is common and often goes undetected;<sup>38</sup> and (iii) the presence of multiple HMODs in the same patient is also common, and further increases CV  ${\rm risk.}^{39-41}$  Consequently, the inclusion of HMOD assessment is important in patients with hypertension and helps identify high-risk or very high-risk hypertensive patients who may otherwise be misclassified as having a lower level of risk by the SCORE system. 42 This is especially true for the presence of left ventricular hypertrophy (LVH), CKD with albuminuria or proteinuria, or arterial stiffening 43 (see section 5). The impact of progression of the stages of hypertension-associated disease (from uncomplicated through to asymptomatic or established disease), according to different grades of hypertension and the presence of CV risk factors, HMOD, or comorbidities, is illustrated in Figure 1 for middle-aged individuals.

### 3.7 Challenges in cardiovascular risk assessment

CV risk is strongly influenced by age (i.e. older people are invariably at high absolute CV risk). In contrast, the absolute risk of younger people, particularly younger women, is invariably low, even in those

with a markedly abnormal risk factor profile. In the latter, relative risk is elevated even if absolute risk is low. The use of 'CV risk age' has been proposed as a useful way of communicating risk and making treatment decisions, especially for younger people at low absolute risk but with high relative risk. This works by illustrating how a younger patient (e.g. a 40-year-old) with risk factors but low absolute risk has a CV risk equivalent to a much older person (60 years) with optimal risk factors; thus, the CV risk age of the younger patient is 60 years. The CV risk age can be automatically calculated using HeartScore (www.heartscore.org).

A second consideration is that the presence of concomitant disease is often recorded in a binary way in CV risk assessment systems (e.g. diabetes, yes/no). This does not reflect the impact of the severity or duration of concomitant diseases on total CV risk. For example, long-standing diabetes is clearly associated with high risk, whereas the risk is less certain for recent-onset diabetes.<sup>34</sup>

A third conundrum specific to hypertension is what BP value to use in CV risk assessment in a patient who is receiving treatment for hypertension. If treatment was commenced recently, it seems appropriate to use the pre-treatment BP value. If treatment has been long-standing, using the current treated BP value will invariably underestimate risk because it does not reflect prior longer-term exposure to higher BP levels, and antihypertensive treatment does not completely reverse the risk even when BP is well controlled. If treatment has been long-standing, then the 'treated BP value' should be used, with the caveat that the calculated CV risk will be lower than the patient's actual risk. A fourth conundrum is how to impute out-of-office BP values into risk calculators that have been calibrated

U and a market			BP (mmH	g) grading	
Hypertension disease staging	Other risk factors, HMOD, or disease	High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
	No other risk factors	Low risk	Low risk	Moderate risk	High risk
Stage 1 (uncomplicated)	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

**Figure 1** Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities. CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions. BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.

according to office BP readings. These various limitations should be kept in mind when estimating CV risk in clinical practice.

#### Hypertension and CV risk assessment

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>	
CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes, a markedly elevated single risk factor (e.g. cholesterol), or hypertensive LVH. 33,35	ı	В	010C H35/335@

 $\mbox{CVD} = \mbox{cardiovascular}$  disease;  $\mbox{LVH} = \mbox{left}$  ventricular hypertrophy;  $\mbox{SCORE} = \mbox{Systematic}$  COronary Risk Evaluation.

#### 4 Blood pressure measurement

### 4.1 Conventional office blood pressure measurement

Auscultatory or oscillometric semiautomatic or automatic sphygmomanometers are the preferred method for measuring BP in the doctor's office. These devices should be validated according to standardized conditions and protocols. <sup>44</sup> BP should initially be measured in both upper arms, using an appropriate cuff size for the arm circumference. A consistent and significant SBP difference between arms (i.e. >15 mmHg) is associated with an increased CV risk, <sup>45</sup> most likely due to atheromatous vascular disease. Where there is a difference in BP between arms, ideally established by simultaneous measurement, the arm with the higher BP values should be used for all subsequent measurements. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

In older people, people with diabetes, or people with other causes of orthostatic hypotension, BP should also be measured 1 min and 3 min after standing. Orthostatic hypotension is defined as a reduction in SBP of  $\geq$ 20 mmHg or in DBP of  $\geq$ 10 mmHg within 3 min of standing, and is associated with an increased risk of mortality and CV events. Heart rate should also be recorded at the time of BP measurements because resting heart rate is an independent predictor of CV morbid or fatal events, A although heart rate is not included in any CV risk algorithm. Table 8 summarizes the recommended procedure for routine office BP measurement. It is emphasized that office BP is often performed improperly, with inadequate attention to the standardized conditions recommended for a valid measurement of office BP. Improper measurement of office BP can lead to inaccurate classification, overestimation of a patient's true BP, and unnecessary treatment.

### 4.2 Unattended office blood pressure measurement

Automated multiple BP readings in the doctor's office improve the reproducibility of BP measurement, and if the patient is seated alone

#### Table 8 Office blood pressure measurement

Patients should be seated comfortably in a quiet environment for 5 min before beginning BP measurements.

Three BP measurements should be recorded, 1-2 min apart, and additional measurements only if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings.

Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patents with AF, in whom manual auscultatory methods should be used as most automated devices have not been validated for BP measurement in patients with AF.<sup>a</sup>

Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger (arm circumference >32 cm) and thinner arms, respectively.

The cuff should be positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependant increases in BP.

When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.

Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.

Measure BP 1 min and 3 min after standing from a seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, people with diabetes, and people with other conditions in which orthostatic hypotension may frequently occur.

Record heart rate and use pulse palpation to exclude arrhythmia.

AF = atrial fibrillation; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

<sup>a</sup>Most automatic devices are not validated for BP measurement in patients with AF and will record the highest individual systolic pressure wave form rather than an average of several cardiac cycles. This will lead to overestimation of BP.

and unobserved, the 'white-coat effect' (see section 4.7.1) can be substantially reduced<sup>48</sup> or eliminated.<sup>49</sup> Moreover, the BP values are lower than those obtained by conventional office BP measurement and are similar to, or even less than, those provided by daytime ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM).<sup>50</sup> Use of unattended office BP measurement in a recent clinical trial [the Systolic Blood Pressure Intervention Trial (SPRINT)]<sup>51</sup> generated controversy about its quantitative relationship to conventional office BP measurement (which has been the basis for all previous epidemiological and clinical trial

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<sup>&</sup>lt;sup>a</sup>Class of recommendation.

bLevel of evidence.

data); its feasibility in routine clinical practice has also been questioned. Presently, the relationship between BP readings obtained with conventional office BP measurement and unattended office BP measurement remains unclear, but available evidence suggests that conventional office SBP readings may be at least 5–15 mmHg higher than SBP levels obtained by unattended office BP measurements. There is also very limited evidence on the prognostic value of unattended office BP measurements, i.e. whether they guarantee at least the same ability to predict outcomes as conventional office BP measurements. BP measurements.

### 4.3 Out-of-office blood pressure measurement

Out-of-office BP measurement refers to the use of either HBPM or ABPM, the latter usually over 24 h. It provides a larger number of BP measurements than conventional office BP in conditions that are more representative of daily life. Recent position papers and practice guidelines provide comprehensive details for ABPM<sup>54</sup> and HBPM,<sup>55</sup> and are briefly summarized below.<sup>54,56</sup>

#### 4.4 Home blood pressure monitoring

Home BP is the average of all BP readings performed with a semiautomatic, validated BP monitor, for at least 3 days and preferably for 6-7 consecutive days before each clinic visit, with readings in the morning and the evening, taken in a quiet room after 5 min of rest, with the patient seated with their back and arm supported. Two measurements should be taken at each measurement session, performed 1-2 min apart.  $^{57}$ 

Compared with office BP, HBPM values are usually lower, and the diagnostic threshold for hypertension is  $\geq$ 135/85 mmHg (equivalent to office BP  $\geq$ 140/90 mmHg) (*Table 9*) when considering the average of 3–6 days of home BP values. Compared with office BP, HBPM provides more reproducible BP data and is more closely related to HMOD, particularly LVH. <sup>58</sup> Recent meta-analyses of the few

Table 9 Definitions of hypertension according to office, ambulatory, and home blood pressure levels

Category	SBP (mmHg)		DBP (mmHg)	
Office BP <sup>a</sup>	≥140	and/or	≥90	
Ambulatory BP				
Daytime (or awake) mean	≥135	and/or	≥85	
Night-time (or asleep) mean	≥120	and/or	≥70	
24 h mean	≥130	and/or	≥80	01,001
Home BP mean	≥135	and/or	≥85	

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

available prospective studies have further indicated that HBPM better predicts cardiovascular morbidity and mortality than office BP. There is also evidence that patient self-monitoring may have a beneficial effect on medication adherence and BP control, 60,61 especially when combined with education and counselling. Telemonitoring and smartphone applications may offer additional advantages, 63,64 such as an aid to memory to make BP measurements, and as a convenient way to store and review BP data in a digital diary and transmit them. We do not recommend the use of apps as a cuff-independent means of measuring BP.

### 4.5 Ambulatory blood pressure monitoring

ABPM provides the average of BP readings over a defined period, usually 24 h. The device is typically programmed to record BP at 15 - 30 min intervals, and average BP values are usually provided for daytime, night-time, and 24 h. A diary of the patient's activities and sleep time can also be recorded. A minimum of 70% usable BP recordings are required for a valid ABPM measurement session. ABPM values are, on average, lower than office BP values, and the diagnostic threshold for hypertension is  $\geq$ 130/80 mmHg over 24 h,  $\geq$ 135/85 mmHg for the daytime average, and  $\geq$ 120/70 for the night-time average (all equivalent to office BP  $\geq$ 140/90 mmHg), see *Table 9*.

ABPM is a better predictor of HMOD than office BP.<sup>65</sup> Furthermore, 24 h ambulatory BP mean has been consistently shown to have a closer relationship with morbid or fatal events, <sup>66–68</sup> and is a more sensitive risk predictor than office BP of CV outcomes such as coronary morbid or fatal events and stroke.<sup>68–72</sup>

BP normally decreases during sleep. Although the degree of nighttime BP dipping has a normal distribution in a population setting, an arbitrary cut-off has been proposed to define patients as 'dippers' if their nocturnal BP falls by >10% of the daytime average BP value; however, the 'dipping' status is often highly variable from day to day and thus is poorly reproducible.<sup>73</sup> Recognised reasons for an absence of nocturnal BP dipping are sleep disturbance, obstructive sleep apnoea, obesity, high salt intake in salt-sensitive subjects, orthostatic hypotension, autonomic dysfunction, CKD, diabetic neuropathy, and old age.<sup>54</sup> Studies that accounted for daytime and night-time BP in the same statistical model found that night-time BP is a stronger predictor of outcomes than daytime BP. 54 The night-to-day ratio is also a significant predictor of outcome, and patients with a reduced nighttime dip in BP (i.e. <10% of the daytime average BP or a night-to-day ratio >0.9) have an increased cardiovascular risk.<sup>54</sup> Moreover, in those in whom there is no night-time dip in BP or a higher night-time than daytime average BP, there is a substantially increase in risk.<sup>74</sup> Paradoxically, there is also some evidence of increased risk in patients who have extreme dipping of their night-time BP,75 although the limited prevalence and reproducibility of this phenomenon makes interpretation of data difficult.

A number of additional indices derived from ABPM recordings have some prognostic value, including 24 h BP variability, <sup>76</sup> morning BP surge, <sup>77</sup> and the ambulatory arterial stiffness index. <sup>78</sup> However, their incremental predictive value is not yet clear. Thus, these indices should be regarded as research tools, with no current indication for routine clinical use.

<sup>&</sup>lt;sup>a</sup>Refers to conventional office BP rather than unattended office BP.

## 4.6 Advantages and disadvantages of ambulatory blood pressure monitoring and home blood pressure monitoring

A major advantage of both ABPM and HBPM is that they enable the diagnosis of white-coat and masked hypertension (see section 4.7). The relative advantages and disadvantages of HBPM and ABPM are shown in Table 10. A particularly important advantage of HBPM is that it is much cheaper and thus more available than ABPM. Another is that it provides multiple measurements over several days or even longer periods, which is clinically relevant because day-to-day BP variability may have an independent prognostic value.<sup>79</sup> Unlike ABPM, typical HBPM devices do not provide BP measurements during routine daily activities and during sleep, although recent technical advances may allow BP during sleep to be measured by HBPM. A further consideration is the potential impact of impaired cognition on the reliability of HBPM measurements and rare instances of obsessional behaviour, circumstances that may favour the use of ABPM if out-ofoffice BP readings are required. In general, both methods should be regarded as complementary rather than absolute alternatives.

Despite the advances in out-of-office BP measurement over the past 50 years, some fundamental questions remain, the most important of which is whether HBPM- or ABPM-guided therapy results in greater reductions in morbidity and mortality than conventional office BP-guided treatment, which has been the diagnostic strategy for all clinical outcome trials.

### 4.7 White-coat hypertension and masked hypertension

White-coat hypertension refers to the untreated condition in which BP is elevated in the office, but is normal when measured by ABPM, HBPM, or both.<sup>80</sup> Conversely, 'masked hypertension' refers to untreated patients in whom the BP is normal in the office, but is

elevated when measured by HBPM or ABPM.<sup>81</sup> The term 'true normotension' is used when both office and out-of-office BP measurements are normal, and 'sustained hypertension' is used when both are abnormal. In white-coat hypertension, the difference between the higher office and the lower out-of-office BP is referred to as the 'white-coat effect', and is believed to mainly reflect the pressor response to an alerting reaction elicited by office BP measurements by a doctor or a nurse, <sup>82</sup> although other factors are probably also involved. <sup>83</sup>

Although the terms white-coat and masked hypertension were originally defined for people who were not being treated for hypertension, they are now also used to describe discrepancies between office and out-of-office BP in patients treated for hypertension, with the terms masked uncontrolled hypertension (MUCH) (office BP controlled but home or ambulatory BP elevated) and white-coat uncontrolled hypertension (WUCH) (office BP elevated but home or ambulatory BP controlled), compared with sustained uncontrolled hypertension (SUCH)<sup>84</sup> (both office and home or ambulatory BP are uncontrolled).

The white-coat effect is used to describe the difference between an elevated office BP (treated or untreated) and a lower home or ambulatory BP in both untreated and treated patients.

#### 4.7.1 White-coat hypertension

Although the prevalence varies between studies, white-coat hypertension can account for up to 30-40% of people (and >50% in the very old) with an elevated office BP. It is more common with increasing age, in women, and in non-smokers. Its prevalence is lower in patients with HMOD, when office BP is based on repeated measurements, or when a doctor is not involved in the BP measurement. A significant white-coat effect can be seen at all grades of hypertension (including resistant hypertension), but the prevalence of white-coat hypertension is greatest in grade 1 hypertension.

 Table I0
 Comparison of ambulatory blood pressure monitoring and home blood pressure monitoring

АВРМ	НВРМ	
Advantages	Advantages	
Can identify white-coat and masked hypertension	Can identify white-coat and masked hypertension	
Stronger prognostic evidence	Cheap and widely available	
Night-time readings	Measurement in a home setting, which may be more relaxed than	
Measurement in real-life settings	the doctor's office	
Additional prognostic BP phenotypes	Patient engagement in BP measurement	
Abundant information from a single measurement session, including	Easily repeated and used over longer periods to assess day-to-day f	
short-term BP variability	variability	
Disadvantages	Disadvantages	
Expensive and sometimes limited availability	Only static BP is available	
Can be uncomfortable	Potential for measurement error	
	No nocturnal readings <sup>a</sup>	

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring. <sup>a</sup>Techniques are being developed to enable nocturnal BP measurement with home BP devices. ©ESC/ESH

HMOD is less prevalent in white-coat hypertension than in sustained hypertension, and recent studies show that the risk of cardiovascular events associated with white-coat hypertension is also lower than that in sustained hypertension. 68,85,86 Conversely, compared with true normotensives, patients with white-coat hypertension have increased adrenergic activity, <sup>87</sup> a greater prevalence of metabolic risk factors, more frequent asymptomatic cardiac and vascular damage, and a greater long-term risk of new-onset diabetes and progression to sustained hypertension and LVH.82 In addition, although the outof-office BP values are, by definition, normal in white-coat hypertension, they tend to be higher than those of true normotensive people, which may explain the increased long-term risk of CV events reported in white-coat hypertension by recent studies after adjustment for demographic and metabolic risk factors. 85,86,88-90 Whitecoat hypertension has also been shown to have a greater CV risk in isolated systolic hypertension and older patients, 91 and does not appear to be clinically innocent.<sup>68</sup> The diagnosis should be confirmed by repeated office and out-of-office BP measurements, and should include an extensive assessment of risk factors and HMOD. Both ABPM and HBPM are recommended to confirm white-coat hypertension, because the CV risk appears to be lower (and close to sustained normotension) in those in whom both ABPM and HBPM are both normal; 82 for treatment considerations see section 8.4.

#### 4.7.2 Masked hypertension

Masked hypertension can be found in approximately 15% of patients with a normal office BP.<sup>17</sup> The prevalence is greater in younger people, men, smokers, and those with higher levels of physical activity, alcohol consumption, anxiety, and job stress.<sup>54</sup> Obesity, diabetes, CKD, family history of hypertension, and high–normal office BP are also associated with an increased prevalence of masked hypertension.<sup>17</sup> Masked hypertension is associated with dyslipidaemia and dysglycaemia, HMOD,<sup>92</sup> adrenergic activation, and increased risk of developing diabetes and sustained hypertension.<sup>81,93</sup> Meta-analyses and recent studies<sup>68</sup> have shown that the risk of CV events is substantially greater in masked hypertension compared with normotension, and close to or greater than that of sustained hypertension.<sup>68,93–96</sup> Masked hypertension has also been found to increase the risk of CV and renal events in diabetes, especially when the BP elevation occurs during the night.<sup>95,97</sup>

### 4.8 Screening for the detection of hypertension

Hypertension is predominantly an asymptomatic condition that is best detected by structured population screening programmes or opportunistic measurement of BP. When structured population screening programmes have been undertaken, an alarming number of people (>50%) were unaware they had hypertension. <sup>12,98</sup> This high rate of undetected hypertension occurred irrespective of the income status of the countries studied across the world.

All adults should have their BP recorded in their medical record and be aware of their BP, and further screening should be undertaken at regular intervals with the frequency dependent on the BP level. For healthy people with an optimal office BP (<120/80 mmHg), BP should be remeasured at least every 5 years and more frequently when opportunities arise. In patients with a normal BP (120–129/80–84),

BP should be remeasured at least every 3 years. Patients with high–normal BP (130–139/85–89 mmHg) should have their BP recorded annually because of the high rates of progression of high–normal BP to hypertension. This is true also for people in whom masked hypertension is detected.

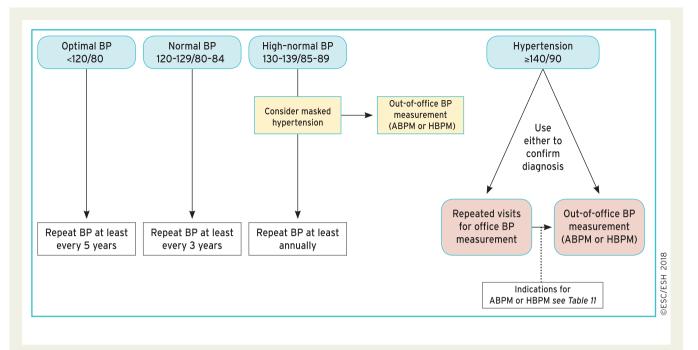
### **4.9 Confirming the diagnosis of hypertension**

BP can be highly variable, thus the diagnosis of hypertension should not be based on a single set of BP readings at a single office visit, unless the BP is substantially increased (e.g. grade 3 hypertension) and there is clear evidence of HMOD (e.g. hypertensive retinopathy with exudates and haemorrhages, or LVH, or vascular or renal damage). For all others (i.e. almost all patients), repeat BP measurements at repeat office visits have been a long-standing strategy to confirm a persistent elevation in BP, as well as for the classification of the hypertension status in clinical practice and RCTs. The number of visits and the time interval between visits varies according to the severity of the hypertension, and is inversely related to the severity of hypertension. Thus, more substantial BP elevation (e.g. grade 2 or more) requires fewer visits and shorter time intervals between visits (i.e. a few days or weeks), depending on the severity of BP elevation and whether there is evidence of CVD or HMOD. Conversely, in patients with BP elevation in the grade 1 range, the period of repeat measurements may extend over a few months, especially when the patient is at low risk and there is no HMOD. During this period of BP assessment, CV risk assessment and routine screening tests are usually performed (see section 3).

These Guidelines also support the use of out-of-office BP measurements (i.e. HBPM and/or ABPM) as an alternative strategy to repeated office BP measurements to confirm the diagnosis of hypertension, when these measurements are logistically and economically feasible (*Figure* 2).<sup>99</sup> This approach can provide important supplementary clinical information, e.g. detecting white-coat hypertension (see section 4.7.1), which should be suspected, especially in people with grade 1 hypertension on office BP measurement and in whom there is no evidence of HMOD or CVD<sup>100</sup> (*Table* 11). A particular challenge is the detection of masked hypertension (see section 4.7.2). Masked hypertension is more likely in people with a BP in the high–normal range in whom out-of-office BP should be considered to exclude masked hypertension (see *Table* 8). Out-of-office BP measurements are also indicated in specific circumstances (see section 4.10 and *Table* 11).

### 4.10 Clinical indications for out-of-office blood pressure measurements

Out-of-office BP measurements are increasingly used, especially HBPM but also ABPM, to confirm the diagnosis of hypertension. Out-of-office BP measurement provides important complementary information, as discussed above. The clinical indications for out-of-office BP measurements are shown in *Table 11*. HBPM is also increasingly used by patients to monitor their BP control, which increases their engagement and may improve their adherence to treatment and BP control. 61,101,102 It is likely that, with increased availability and lower cost of these devices, this will become more commonplace.



**Figure 2** Screening and diagnosis of hypertension. ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring.

<sup>a</sup>After detecting a specific BP category on screening, either confirm BP elevation with repeated office BP measurements on repeat visits or arrange use of out-of-office BP to confirm the diagnosis of hypertension.

#### Table II Clinical indications for home blood pressure monitoring or ambulatory blood pressure monitoring

Conditions in which white-coat hypertension is more common, e.g.:

- $\bullet \;\;$  Grade I hypertension on office BP measurement
- Marked office BP elevation without HMOD

Conditions in which masked hypertension is more common, e.g.:

- High-normal office BP
- Normal office BP in individuals with HMOD or at high total CV risk

Postural and post-prandial hypotension in untreated and treated patients

Evaluation of resistant hypertension

Evaluation of BP control, especially in treated higher-risk patients

Exaggerated BP response to exercise

When there is considerable variability in the office BP

Evaluating symptoms consistent with hypotension during treatment

Specific indications for ABPM rather than HBPM:

• Assessment of nocturnal BP values and dipping status (e.g. suspicion of nocturnal hypertension, such as in sleep apnoea, CKD, diabetes, endocrine hypertension, or autonomic dysfunction)

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage.

### 4.11 Blood pressure during exercise and at high altitude

It is important to recognise that BP increases during dynamic and static exercise, and that the increase is more pronounced for SBP than for DBP, 103 although only SBP can be measured reliably with non-invasive methods. There is currently no consensus on normal BP response during exercise. The increase in SBP during exercise is related to pre-exercise resting BP, age, arterial stiffness, and abdominal obesity, and is somewhat greater in women than in men and in unfit individuals. There is some evidence that an excessive rise in BP during exercise predicts the development of hypertension, independently from BP at rest. 104 Nevertheless, exercise testing is not recommended as part of the routine evaluation of hypertension because of various limitations, including a lack of standardization of methodology and definitions. Importantly, except in the presence of very high BP values (grade 3 hypertension), patients, or athletes, with treated or untreated hypertension should not be discouraged from regular exercise, especially aerobic exercise, which is considered beneficial as part of lifestyle changes to reduce BP (see section 7.4.1).

Evidence is available that BP increases with high altitude exposure, especially above 3000 m and possibly above 2000 m. <sup>105</sup> This is due to a number of factors including sympathetic activation. Patients with grade 2 hypertension and increased CV risk should check their BP values before and during high altitude (>2500 m) exposure. Patients with grade 1 hypertension may reach very high altitude (>4000 m) with adequate medical therapy; uncontrolled severe hypertensive patients (grade 3) should avoid exposure to very high altitude. <sup>105</sup>

#### 4.12 Central aortic pressure

Various techniques allow aortic BP (central BP) to be derived from peripheral BP measurements using dedicated algorithms. <sup>106,107</sup> Some studies and meta-analyses have shown that in hypertensive patients, central BP predicts CV events and that there is a differential effect of antihypertensive drugs on central compared with brachial BP. <sup>108</sup> The incremental prognostic value of central vs. conventional clinic BP measurement remains unclear. <sup>109</sup> An exception may be isolated systolic hypertension in the young, in whom peripheral BP may be disproportionately elevated relative to a normal central BP. This occurs in a small fraction of younger people, mainly men with isolated systolic hypertension, and it remains unclear whether such patients are at lower risk than suggested by their brachial office BP. <sup>110,111</sup>

#### **BP** measurement

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Screening programmes for hypertension are recommended. All adults (18 years or older) should have their office BP measured and recorded in their medical file, and be aware of their BP. 12,98	-	В
Further BP recording is indicated, at least every 5 years if BP remains optimal.	1	С
• Further BP recording is indicated, at least every 3 years if BP remains normal.	- 1	С
<ul> <li>If BP remains high-normal, further BP recording, at least annually, is recommended.</li> </ul>	1	С
<ul> <li>In older patients (&gt;50 years), more frequent screening of office BP should be considered for each BP category because of the steeper rise in SBP with ageing.</li> </ul>	lla	С
It is recommended that office BP should be measured in both arms at least at the first visit because a between-arm SBP difference of >15 mmHg is suggestive of atheromatous disease and is associated with an increased CV risk. <sup>45</sup>	1	A
If a between-arm difference in BP is recorded, then it is recommended that all subsequent BP readings use the arm with the higher BP reading.	1	С
It is recommended that the diagnosis of hypertension should be based on:  Repeated office BP measurements on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). At each visit, three BP measurements should be recorded, 1–2 min apart, and additional measurements should be performed if the first two readings differ by >10 mmHg. The patient's BP is the average of the last two BP readings.	1	С
Or  Out-of-office BP measurement with ABPM and/or HBPM, provided that these measurements are logistically and economically feasible.	1	Continue

Out-of-office BP (i.e. ABPM or HBPM) is specifically recommended for a number of clinical indications, such as identifying white-coat and masked hypertension, quantifying the effects of treatment, and identifying possible causes of side effects 17,54,62,68,72 (e.g. symptomatic hypotension).	-	A	
It is recommended that all hypertensive patients undergo pulse palpation at rest to determine heart rate and search for arrhythmias such as AF. <sup>20,47</sup>	1	C	
Other BP measures and indices (pulse pressure, BP variability, exercise BP, and central BP) may be considered but are not often used for routine clinical use at present.  They may provide useful additional information in some circumstances and are valuable tools for research.	Шь	C	©ESC/ESH 2018

ABPM = ambulatory blood pressure monitoring; AF = atrial fibrillation; BP = blood pressure; CV = cardiovascular; HBPM = home blood pressure monitoring; SBP = systolic blood pressure.

# 5 Clinical evaluation and assessment of hypertension-mediated organ damage in patients with hypertension

#### 5.1 Clinical evaluation

The purpose of the clinical evaluation is to establish the diagnosis and grade of hypertension, screen for potential secondary causes of hypertension, identify factors potentially contributing to the development of hypertension (lifestyle, concomitant medications, or family history), identify concomitant CV risk factors (including lifestyle and family history), identify concomitant diseases, and establish whether there is evidence of HMOD or existing CV, cerebrovascular, or renal disease. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

#### 5.2 Medical history

A thorough medical history (Table 12) should address in particular:

- Time of the first diagnosis of hypertension, including records of any previous medical screening, hospitalization, etc.
- Record any current and past BP values
- Record current and past antihypertensive medications
- Record other medications
- Family history of hypertension, CVD, stroke, or renal disease
- Lifestyle evaluation, including exercise levels, body weight changes, diet history, smoking history, alcohol use, recreational drug use, sleep history, and impact of any treatments on sexual function
- History of any concomitant CV risk factors

### Table 12 Key information to be collected in personal and family medical history

#### **Risk factors**

Family and personal history of hypertension, CVD, stroke, or renal

Family and personal history of associated risk factors (e.g. familial hypercholesterolaemia)

Smoking history

Dietary history and salt intake

Alcohol consumption

Lack of physical exercise/sedentary lifestyle

History of erectile dysfunction

Sleep history, snoring, sleep apnoea (information also from partner)

Previous hypertension in pregnancy/pre-eclampsia

### History and symptoms of HMOD, CVD, stroke, and renal disease

Brain and eyes: headache, vertigo, syncope, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization, cognitive impairment, dementia (in the elderly)

Heart: chest pain, shortness of breath, oedema, myocardial infarction, coronary revascularization, syncope, history of palpitations, arrhythmias (especially AF), heart failure

Kidney: thirst, polyuria, nocturia, haematuria, urinary tract infections

Peripheral arteries: cold extremities, intermittent claudication, pain-free walking distance, pain at rest, peripheral revascularization

Patient or family history of CKD (e.g. polycystic kidney disease)

#### History of possible secondary hypertension

Young onset of grade 2 or 3 hypertension (<40 years), or sudden development of hypertension or rapidly worsening BP in older patients

History of renal/urinary tract disease

Recreational drug/substance abuse/concurrent therapies: corticosteroids, nasal vasoconstrictor, chemotherapy, yohimbine, liquorice

Repetitive episodes of sweating, headache, anxiety, or palpitations, suggestive of Phaeochromocytoma

History of spontaneous or diuretic-provoked hypokalaemia, episodes of muscle weakness, and tetany (hyperaldosteronism)

Symptoms suggestive of thyroid disease or hyperparathyroidism

History of or current pregnancy and oral contraceptive use

History of sleep apnoea

#### **Antihypertensive Drug Treatment**

Current/past antihypertensive medication including effectiveness and intolerance to previous medications

Adherence to therapy

AF = atrial fibrillation; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage; TIA = transient ischaemic attack.

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<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

- Details and symptoms of past and present comorbidities
- Specific history of potential secondary causes of hypertension (see section 8.2)
- History of past pregnancies and oral contraceptive use
- History of menopause and hormone replacement therapy
- Use of liquorice
- Use of drugs that may have a pressor effect.

### **5.3 Physical examination and clinical investigations**

Physical examination provides important indications of potential causes of secondary hypertension, signs of comorbidities, and HMOD. Office BP and heart rate should be measured as summarized in section 4. Measurements of office BP on more than one occasion are usually required to confirm the diagnosis of hypertension unless HBPM or ABPM is used to confirm the diagnosis (see section 4).

Details of the requirements for a comprehensive clinical examination are outlined in *Table 13*, and this should be adapted according to the severity of hypertension and clinical circumstances. Suggested routine clinical investigations are outlined in *Table 14*.

#### Table 13 Key steps in physical examination

#### **Body habitus**

Weight and height measured on a calibrated scale, with calculation of BMI

Waist circumference

#### Signs of HMOD

Neurological examination and cognitive status

Fundoscopic examination for hypertensive retinopathy

Palpation and auscultation of heart and carotid arteries

Palpation of peripheral arteries

Comparison of BP in both arms (at least once)

#### Secondary hypertension

Skin inspection: cafe-au-lait patches of neurofibromatosis (phaeochromocytoma)

Kidney palpation for signs of renal enlargement in 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: to detect radio-femoral delay in aortic coarctation

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Signs of Cushing's disease or acromegaly

Signs of thyroid disease

BMI = body mass index; BP = blood pressure; HMOD = hypertension-mediated organ damage.

#### 5.4 Assessment of hypertensionmediated organ damage

HMOD refers to structural or functional changes in arteries or end organs (heart, blood vessels, brain, eyes, and kidney) caused by an elevated BP, and is a marker of pre-clinical or asymptomatic CVD. 112 HMOD is common in severe or long-standing hypertension, but can also be found in less severe hypertension. With wider use of imaging, HMOD is becoming increasingly apparent in asymptomatic patients. 43 CV risk increases with the presence of HMOD, and more so when damage affects multiple organs. 16,113,114 Some types of HMOD can be reversed by antihypertensive treatment, especially when used early, but with long-standing hypertension, HMOD may become irreversible despite improved BP control. 115,116 Nevertheless, BP-lowering treatment is still important as it may delay the further progression of HMOD and will reduce the elevated CV risk of these patients. 116 Although poor technical provision and cost may limit the search for HMOD in some countries, it is recommended that basic screening for HMOD is performed in all hypertensive patients and more detailed assessment is performed when the presence of HMOD might influence treatment decisions. The various investigations to establish HMOD are shown in Table 15.

### 5.4.1 Using hypertension-mediated organ damage to help stratify risk in hypertensive patients

As discussed in section 3, hypertensive patients with documented CVD, diabetes, CKD, grade 3 hypertension, or marked cholesterol elevation (e.g. familial hypercholesterolaemia) are already at high or very high CV risk ( $\geq$ 10% risk of a fatal event). Thus, the presence of HMOD is unlikely to influence treatment, as these patients should

**Table 14** Routine workup for evaluation of hypertensive patients

Routine labo	oratory tests
Haemoglobin	and/or haematocrit
Fasting blood	glucose and glycated HbA <sub>1c</sub>
Blood lipids: to cholesterol	otal cholesterol, LDL cholesterol, HDL
Blood triglyce	rides
Blood potassi	um and sodium
Blood uric aci	d
Blood creatini	ne and eGFR
Blood liver fur	nction tests
•	microscopic examination; urinary protein by dip- deally, albumin:creatinine ratio
12-lead ECG	

eGFR = estimated glomerular filtration rate; ECG = electrocardiogram;  $HbA_{1c}$  = haemoglobin A1c.

Table 15 Assessment of hypertension-mediated organ damage

Basic screening tests for HMOD	Indication and interpretation	
12-lead ECG	Screen for LVH and other possible cardiac abnormalities, and to document heart rate and cardiac rhythm	
Urine albumin:creatinine ratio	To detect elevations in albumin excretion indicative of possible renal disease	
Blood creatinine and eGFR	To detect possible renal disease	
Fundoscopy	To detect hypertensive retinopathy, especially in patients with grade 2 or 3 hypertension	
More detailed screening for HMOD		
Echocardiography	To evaluate cardiac structure and function, when this information will influence treatment decisions	
Carotid ultrasound	To determine the presence of carotid plaque or stenosis, particularly in patients with cerebrovas- cular disease or vascular disease elsewhere	
Abdominal ultrasound and Doppler studies	<ul> <li>To evaluate renal size and structure (e.g. scarring) and exclude renal tract obstruction as possible underlying causes of CKD and hypertension</li> <li>Evaluate abdominal aorta for evidence of aneurysmal dilatation and vascular disease</li> <li>Examine adrenal glands for evidence of adenoma or phaeochromocytoma (CT or MRI preferred for detailed examination); see section 8.2 regarding screening for secondary hypertension</li> <li>Renal artery Doppler studies to screen for the presence of renovascular disease, especially the presence of asymmetric renal size</li> </ul>	
PWV	An index of aortic stiffness and underlying arteriosclerosis	
ABI	Screen for evidence of LEAD	
Cognitive function testing	To evaluate cognition in patients with symptoms suggestive of cognitive impairment	
Brain imaging	To evaluate the presence of ischaemic or haemorrhagic brain injury, especially in patients with a history of cerebrovascular disease or cognitive decline	

ABI = ankle-brachial index; CKD = chronic kidney disease; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HMOD = hypertension-mediated organ damage; LEAD = lower extremity artery disease; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; PWV = pulse wave velocity.

already receive lifestyle interventions, BP-lowering medications, statins, and in some cases antiplatelet therapy, to reduce their risk<sup>35</sup> (see section 9).

The main advantage of detecting HMOD is that it may reclassify a patient's SCORE risk assessment from low to moderate or from moderate to high risk.<sup>117</sup> The specific impact of HMOD<sup>114</sup> with regard to the reclassification of risk estimation according to the SCORE system has not been clearly defined. The SCORE system already takes account of the grade of hypertension as SBP is included in the risk calculation. Moreover, CKD and the presence of vascular disease on imaging are already specified as high or very high risk (*Table 5*). Conditioning of the risk score by the presence of HMOD will be most important in middle-aged patients with hypertension, many of whom will be at moderate-risk and at higher risk if HMOD is detected. Moreover, a risk-conditioning effect of HMOD will also be important in younger hypertensive patients who are invariably classified as low risk according to the SCORE system. In addition, detecting

HMOD in younger patients with grade 1 hypertension provides unequivocal evidence of hypertension-mediated damage and indicates a clear need for BP-lowering treatment in patients who may be reluctant to be treated. For the same reason, the presence of HMOD in a patient with high-normal BP would also provide a rationale to consider BP-lowering treatment.

Another important consideration is whether the presence of a specific manifestation of HMOD (e.g. LVH or CKD) might influence the selection of drug treatment for hypertension. This was considered important in the previous guidelines, <sup>17</sup> but is now considered less important. In patients more likely to have HMOD (i.e. those with high grade 1 or grade 2–3 hypertension), we now recommend initial treatment with a combination of two drugs, usually an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in combination with a calcium channel blocker (CCB) or thiazide-type diuretic, which would be the optimal treatment for all manifestations of HMOD (see section 7).

#### 5.5 Characteristics of hypertensionmediated organ damage

#### 5.5.1 The heart in hypertension

Chronically increased left ventricular (LV) workload in hypertensive patients can result in LVH, impaired LV relaxation, left atrial enlargement, an increased risk of arrhythmias, especially AF, and an increased risk of heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

#### 5.5.1.1 Electrocardiogram

A 12-lead electrocardiogram (ECG) should be part of the routine assessment in all hypertensive patients. The ECG is not a particularly sensitive method of detecting LVH and its sensitivity varies according to body weight. ECG LVH provides independent prognostic information, even after adjusting for other CV risk factors and echocardiographic LV mass. <sup>118</sup> In addition to LVH, the presence of a 'strain pattern' on an ECG is associated with increased risk. <sup>119</sup> The prevalence of ECG LVH increases with the severity of hypertension. <sup>120</sup> The most commonly used criteria to define ECG LVH are shown in *Table 16*.

The ECG cannot exclude LVH because it has poor sensitivity. When detailed information on cardiac structure and function will influence treatment decisions, echocardiography is recommended. When LVH is present on the ECG, it can be used to detect changes in LVH during follow-up in untreated and treated patients. <sup>121,122</sup>

#### 5.5.1.2 Transthoracic echocardiography in hypertension

Echocardiographic LVH is a potent predictor of mortality in both hypertensive patients and the general population, <sup>123,124</sup> and regression of echocardiographic LVH due to treatment of hypertension predicts an improved prognosis. <sup>125</sup> Two-dimensional transthoracic echocardiography (TTE) also provides information about LV geometry, left atrial volume, aortic root dimensions, LV systolic and diastolic function, pump performance, and output impedance. <sup>123,126,127</sup> Whether additional parameters other than evidence of increased LV mass and left atrial dilatation are useful to help stratify CV risk is uncertain. <sup>123,126,128</sup> The partition values recommended for the definition of LVH by echocardiography are shown in *Table 17*.

**Table 16** The most commonly used simple criteria and recognised cut-off points for definitions of electrocardiogram left ventricular hypertrophy

ECG voltage criteria	Criteria for LVH
S <sub>V1</sub> +R <sub>V5</sub> (Sokolow–Lyon criterion)	>35 mm
R wave in aVL	≥11 mm
S <sub>V3</sub> +R <sub>aVL</sub> (Cornell voltage) <sup>a</sup>	>28 mm (men)
Cornell duration product <sup>b</sup>	>20 mm (women)
	>2440 mm.ms

ECG = electrocardiogram; LVH = left ventricular hypertrophy.

Three-dimensional TTE is a more reliable method for quantitative analysis, <sup>129</sup> specifically for LV mass, <sup>130</sup> volumes, and ejection fraction, and has superior reproducibility to two-dimensional TTE but much less prognostic validation. <sup>131</sup> More detailed information on the use of echocardiography to assess the hypertensive heart is available. <sup>43</sup> Cardiac magnetic resonance is the gold standard for cardiac anatomical and functional quantification. <sup>132–134</sup>

Abnormal LV geometry in hypertensive patients is frequently associated with diastolic dysfunction, <sup>127,135</sup> which can be further evaluated by a combination of transmitral flow and tissue Doppler studies. <sup>136</sup> Left atrial size is also frequently increased in hypertensive patients and is associated with adverse CV events <sup>128,137</sup> and incident AF, <sup>138</sup> and is related to diastolic dysfunction. <sup>139,140</sup> During the diagnostic workup for secondary hypertension, a suprasternal view should also be performed for the identification of aortic coarctation. <sup>141</sup>

#### 5.5.2 The blood vessels in hypertension

#### 5.5.2.1 Carotid artery

Carotid intima-media thickness (IMT) quantified by carotid ultrasound, and/or the presence of plaques, predicts CV risk.  $^{42.142}$  This holds true both for the IMT value at the carotid bifurcations (reflecting primarily atherosclerosis) and for the IMT value at the level of the common carotid artery (reflecting primarily hypertension-related hypertrophy). A carotid IMT >0.9 mm is considered abnormal,  $^{143}$  but the upper limit of normality varies with age. The presence of a plaque can be identified by an IMT  $\geq 1.5$  mm, or by a focal increase in thickness of 0.5 mm or 50% of the surrounding carotid IMT value.  $^{144}$  Stenotic carotid plaques have a strong predictive value for both

Table 17 Echocardiographic definitions of left ventricular hypertrophy, concentric geometry, left ventricular chamber size, and left atrial dilatation

Parameter	Measure	Abnormality threshold
LVH	LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	>50 (men)
		>47 (women)
LVH <sup>a</sup>	LV mass/BSA (g/m <sup>2</sup> )	>115 (men)
		>95 (women)
LV concentric geometry	RWT	≥0.43
LV chamber size	LV end-diastolic	>3.4 (men)
	diameter/height (cm/m)	>3.3 (women)
Left atrial size	Left atrial volume/height <sup>2</sup>	>18.5 (men)
(elliptical)	(mL/m²)	>16.5 (women)

BSA = body surface area; LV = left ventricular; LVH = left ventricular hypertrophy; RWT = relative wall thickness.

<sup>&</sup>lt;sup>a</sup>Sum of limb and precordial lead voltage.

<sup>&</sup>lt;sup>b</sup>Product of Cornell voltage x QRS duration (mm.ms).

<sup>&</sup>lt;sup>a</sup>BSA normalization may be used in normal weight patients.

stroke and myocardial infarction, independent of traditional CV risk factors, <sup>42,142</sup> and confer superior prognostic accuracy for future myocardial infarction compared with IMT. <sup>145</sup> The presence of carotid plaques will automatically reclassify patients from intermediate to high risk; <sup>146,147</sup> however, routine carotid imaging is not recommended unless clinically indicated (i.e. presence of carotid bruit, previous TIA or cerebrovascular disease, or as part of the assessment of patients with evidence of vascular disease).

#### 5.5.2.2 Pulse wave velocity

Large artery stiffening is the most important pathophysiological determinant of isolated systolic hypertension and age-dependent increase in pulse pressure. Carotid-femoral pulse wave velocity (PWV) is the gold standard for measuring large artery stiffness. Peference values for PWV are available in healthy populations and patients at increased CV risk. PWV > 10 m/s is considered a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients. The additive value of PWV above and beyond traditional risk factors, including SCORE and the Framingham risk score, has been suggested by several studies. However, routine use of PWV measurement is not practical and is not recommended for routine practice.

#### 5.5.2.3 Ankle-brachial index

Ankle-brachial index (ABI) may be measured either with automated devices, or with a continuous wave Doppler unit and a BP sphygmomanometer. A low ABI (i.e. <0.9) indicates lower extremity artery disease (LEAD), is usually indicative of advanced atherosclerosis, <sup>152</sup> and has predictive value for CV events, <sup>153</sup> being associated with an almost two-fold greater 10 year CV mortality and major coronary event rate, compared with the overall rate in each Framingham category. <sup>153</sup> Even asymptomatic LEAD, detected by a low ABI, is associated in men with a high incidence of CV morbid and fatal events, approaching 20% in 10 years. <sup>153,154</sup> Routine use of ABI is not recommended in hypertensive patients, but should be considered in patients with symptoms or signs of LEAD, or in moderate-risk patients in whom a positive test would reclassify the patient as highrisk.

#### 5.5.3 The kidney in hypertension

Hypertension is the second most important cause of CKD after diabetes. Hypertension may also be the presenting feature of asymptomatic primary renal disease. An alteration of renal function is most commonly detected by an increase in serum creatinine. This is an insensitive marker of renal impairment because a major reduction in renal function is needed before serum creatinine rises. Furthermore, BP reduction by antihypertensive treatment often leads to an acute increase in serum creatinine by as much as 20–30%, especially with renin-angiotensin system (RAS) blockers, which has a functional basis and does not usually reflect manifest renal injury, but the long-term clinical significance is unclear. <sup>155,156</sup> The diagnosis of hypertension-induced renal damage is based on the finding of reduced renal function and/or the detection of albuminuria. CKD is classified according to estimated glomerular filtration rate (eGFR), calculated by the 2009 CKD-Epidemiology Collaboration formula. <sup>157</sup>

The albumin:creatinine ratio (ACR) is measured from a spot urine sample (preferably early morning urine), and is the preferred method

to quantify urinary albumin excretion. A progressive reduction in eGFR and increased albuminuria indicate progressive loss of renal function, and are both independent and additive predictors of increased CV risk and progression of renal disease. <sup>158</sup>

Serum creatinine, eGFR, and ACR should be documented in all hypertensive patients, and if CKD is diagnosed, repeated at least annually.  $^{159}$  One negative urinary dipstick test does not rule out albuminuria, in contrast to a normal ACR.  $^{160}$ 

#### 5.5.4 Hypertensive retinopathy

The prognostic significance of hypertensive retinopathy by fundoscopy has been well documented. <sup>161</sup> Detection of retinal haemorrhages, microaneurysms, hard exudates, cotton wool spots, and papilloedema is highly reproducible, indicates severe hypertensive retinopathy, and is highly predictive of mortality. <sup>161,162</sup> In contrast, evidence of arteriolar narrowing, either focal or general, and arteriovenous nicking at early stages of hypertensive retinopathy have less predictive value, <sup>163</sup> and limited interobserver and intraobserver reproducibility, even with experienced observers. <sup>164</sup> Fundoscopy should be performed in patients with grade 2 or 3 hypertension or hypertensive patients with diabetes, in whom significant retinopathy is more likely. Fundoscopy may be considered in other hypertensive patients. The increasing emergence of new techniques to visualize the fundus through smartphone technologies should increase the feasibility of more routine fundoscopy. <sup>165</sup>

#### 5.5.5 The brain in hypertension

Hypertension increases the prevalence of brain damage, of which transient ischaemic attack (TIA) and stroke are the most dramatic acute clinical manifestations. In the asymptomatic phase, brain damage can be detected by magnetic resonance imaging (MRI) as white matter hyperintensities, silent microinfarcts, (most of which are small and deep, i.e. lacunar infarctions), microbleeds, and brain atrophy. 166,167 White matter hyperintensities and silent infarcts are associated with an increased risk of stroke and cognitive decline due to degenerative and vascular dementia. 166-169 Availability and cost do not permit the widespread use of brain MRI for the evaluation of hypertensive patients, but white matter hyperintensity and silent brain infarcts should be sought in all hypertensive patients with neurological disturbances, cognitive decline, and, particularly, memory loss. 168,169 A family history of cerebral haemorrhage at middle age and early-onset dementia should prompt MRI. Cognitive impairment in older patients is, at least in part, hypertension-related, and cognitive evaluation tests should be considered in the clinical assessment of hypertensive patients with a history suggestive of early cognitive impairment. The Mini-Mental State Examination has been the most widely used method in clinical trials, but is now being superseded by more sophisticated cognitive tests that are more suitable for routine clinic visits. 170

# 5.6 Hypertension-mediated organ damage regression and cardiovascular risk reduction with antihypertensive treatment

As discussed above, HMOD assessment may play a role in stratifying the risk of patients with hypertension. In post hoc analyses, BP

treatment-induced regression of some (but not all) manifestations of asymptomatic HMOD, as a consequence of treatment, is associated with a reduction in CV risk, thereby providing additional information on the effectiveness of treatment in individual patients. 16,104,171 This has been best illustrated for the treatment-induced regression of LVH measured by either ECG or echocardiography. 125,172,173 A reduced incidence of CV events and slower progression of renal disease has been reported with a treatment-induced reduction in urinary protein excretion in both diabetic and non-diabetic patients. especially for microalbuminuria, <sup>174</sup> but results are discordant. <sup>175–179</sup> There is also evidence that treatment-induced changes in eGFR predict CV events 180 and progression to end-stage renal disease. 181,182 Two meta-analyses 183,184 failed to document any predictive value of treatment-induced reductions in carotid IMT for CV events. Evidence on the predictive power of treatment-induced changes on other measures of HMOD (PWV and ABI) are either limited or absent. Regression of HMOD might not be possible even when BP is controlled, particularly when HMOD is advanced, because some of the changes become irreversible.

The information available on the sensitivity and timing of changes in HMOD during antihypertensive treatment is summarized in *Table 18*. If, when, and how often the assessment of HMOD should be performed has not been validated in follow-up studies. HMOD can also develop during the course of antihypertensive treatment, <sup>185</sup> and this may be accompanied by increased risk. <sup>186–188</sup>

### 5.7 When to refer a patient with hypertension for hospital-based care

Hypertension is a very common condition and most patients with hypertension, in most healthcare systems, will be managed in the primary care setting. However, there are circumstances in which a referral for routine hospital-based evaluation and treatment may be required, keeping in mind that in some instances out-of-office or office-based care of hypertensive patients depends on the healthcare organization of a given country:

- Patients in whom secondary hypertension is suspected (see section 8.2)
- Younger patients (<40 years) with grade 2 or more severe hypertension in whom secondary hypertension should be excluded
- Patients with treatment-resistant hypertension (see section 8.1)
- Patients in whom more detailed assessment of HMOD would influence treatment decisions
- Patients with sudden onset of hypertension when BP has previously been normal
- Other clinical circumstances in which the referring doctor feels more specialist evaluation is required.

There are also rarer circumstances in which a patient with hypertension should be referred to hospital for emergency care, which will often require inpatient care (see section 8.3).

Table 18Sensitivity to detect treatment-induced changes, reproducibility and operator independence, time tochanges, and prognostic value of changes provided by markers of hypertension-mediated organ damage

Marker of HMOD	Sensitivity to changes	Reproducibility and operator independence	Time to changes	Prognostic value of the change
LVH by ECG	Low	High	Moderate (>6 months)	Yes
LVH by echocardiogram	Moderate	Moderate	Moderate (>6 months)	Yes
LVH by CMR	High	High	Moderate (>6 months)	No data
eGFR	Moderate	High	Very slow (years)	Yes
Urinary protein excretion	High	Moderate	Fast (weeks to months)	Moderate
Carotid IMT	Very low	Low	Slow (>12 months)	No
PWV	High	Low	Fast (weeks to months)	Limited data
Ankle-brachial ndex	Low	Moderate	Slow (>12 months)	Moderate

CMR = cardiac magnetic resonance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HMOD = hypertension-mediated organ damage; IMT = intimamedia thickness; LVH = left ventricular hypertrophy; PWV = pulse wave velocity.

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#### Clinical evaluation and HMOD assessment

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Heart		
12-lead ECG is recommended for all hypertensive patients. 120	1	В
<ul> <li>Echocardiography:</li> <li>Is recommended in hypertensive patients when there are ECG abnormalities or signs or symptoms of LV dysfunction. 42,134</li> </ul>	1	В
• May be considered when the detection of LVH may influence treatment decisions. <sup>42,134</sup>	Шь	В
Blood vessels		
Ultrasound examination of the carotid arteries:	ı	В
<ul> <li>May be considered for the detection of asymptomatic atherosclerotic plaques or carotid stenosis in patients with documented vascular disease elsewhere.<sup>42</sup></li> </ul>	ШЬ	В
Measurement of PWV may be considered for measuring arterial stiffness. 109,189	IIb	В
Measurement of ABI may be considered for the detection of advanced LEAD. 153,190	IIb	В
Kidney		
Measurement of serum creatinine and eGFR is recommended in all hypertensive patients. 180	1	В
Measurement of urine albumin:creatinine ratio is recommended in all hypertensive patients. 43,180	1	В
Renal ultrasound and Doppler examination should be considered in patients with impaired renal function, albuminuria, or for suspected secondary hypertension.	lla	С
Fundoscopy		
Is recommended in patients with grades 2 or 3 hypertension and all hypertensive patients with diabetes.	ı	С
May be considered in other hypertensive patients.	Шь	С
Brain		
In hypertensive patients with neurological symptoms and/or cognitive decline, brain MRI or CT should be considered for detecting brain infarctions, microbleeds, and white matter lesions. 168,169	lla	В

ABI = ankle—brachial index; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HMOD = hypertension-mediated organ damage; LEAD = lower extremity arterial disease; LV = left ventricular; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; PWV = pulse wave velocity; TIA = transient ischaemic attack.

### **6** Genetics and hypertension

A positive family history is a frequent feature in hypertensive patients, with the heritability estimated to vary between 35 and 50% in most studies. <sup>191,192</sup> However, hypertension is a highly heterogeneous disorder with a multifactorial aetiology. Several genomewide association studies and their meta-analyses have identified 120 loci that are associated with BP regulation, but together these only explain about 3.5% of the trait variance. <sup>193</sup> Several rare,

monogenic forms of hypertension have been described such as glucocorticoid-remediable aldosteronism, Liddle's syndrome, and others, where a single gene mutation fully explains the pathogenesis of hypertension and dictates the best treatment modality. <sup>194–196</sup> There are also inherited forms of phaeochromocytoma and paraganglioma, which are also rare causes of hypertension. <sup>197–200</sup> Outside of specialist clinics evaluating patients for these rare causes of secondary hypertension, there is no role for genetic testing in hypertension in routine clinical care.

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

Recommendations	Class <sup>a</sup>	Levelb
Genetic testing should be considered in specialist centres for patients suspected to have rare monogenic causes of secondary hypertension or for those with phaeochromocytoma. 198	lla	В
Routine genetic testing for hypertensive patients is not recommended.	ш	С

#### 7 Treatment of hypertension

#### 7.1 Beneficial effects of blood pressurelowering therapy in hypertension

There are two well-established strategies to lower BP: lifestyle interventions and drug treatment. Device-based therapy is also emerging, but is not yet proven as an effective treatment option. Lifestyle interventions can undoubtedly lower BP and in some cases CV risk (see section 7.4.1), but most patients with hypertension will also require drug treatment. The drug treatment of hypertension is founded on very solid evidence, underpinned by the largest number of outcomebased RCTs in clinical medicine. Meta-analyses of RCTs including several hundred thousand patients have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP is associated with significant reductions in all major CV events by  $\sim$ 20%, all-cause mortality by 10 - 15%, stroke by  $\sim$ 35%, coronary events by  $\sim$ 20%, and heart failure by ~40%. <sup>2,8</sup> These relative risk reductions are consistent, irrespective of baseline BP within the hypertensive range, the level of CV risk, comorbidities (e.g. diabetes and CKD), age, sex, and ethnicity. 2,201 The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed Chapter 44.7 Drug treatment of hypertension and Chapter 44.8 Device-based treatment for hypertension.

Relative outcome reductions calculated by two recent meta-analyses are similar to those provided by the original meta-analysis of the effects of BP lowering on outcomes in 1994.<sup>202</sup> Thus, the benefits of antihypertensive treatment have not been attenuated by the wide-spread concomitant prescription of lipid-lowering and antiplatelet therapies in contemporary medicine.

Another important objective of antihypertensive therapy is to reduce the development of CKD; however, the slow rate of decline in renal function in most hypertensive patients makes the demonstration of potential benefits of BP lowering difficult. Consequently, the protective effect of BP reduction on kidney function can be less obvious and has been restricted to patients with diabetes or CKD, in whom there is a faster rate of disease progression. <sup>203</sup> Some, but not all, RCTs have also shown a protective effective of BP lowering on

the progression of CKD towards end-stage renal disease in both diabetic and non-diabetic nephropathy.<sup>2</sup>

The recommendations that follow are based on outcome evidence from RCTs; however, it must be acknowledged that RCTs based on clinical outcomes have limitations, the most important of which are that the data are largely limited to older and high-risk patients, preferentially recruited to increase statistical power, and over a relatively short duration of follow-up, rarely beyond 5 years. This means that recommendations for life-long treatment for younger and lower risk patients are necessarily based on considerable extrapolation. Big data, now being collected by national health system registries, health insurance companies, and prolonged observational follow-up of RCTs, are becoming an important source of long-term information on the effects of chronic treatment, <sup>204</sup> which adds to that provided by observational studies over several decades. <sup>205–207</sup> Such evidence suggests that the benefit of continued treatment is maintained over decades. <sup>206</sup>

### 7.2. When to initiate antihypertensive treatment

#### 7.2.1 Recommendations in previous guidelines

All guidelines agree that patients with grade 2 or 3 hypertension should receive antihypertensive drug treatment alongside lifestyle interventions. <sup>208</sup> Guidelines are also consistent in recommending that patients with grade 1 hypertension and high CV risk or HMOD should be treated with BP-lowering drugs. There has been less consistency about whether BP-lowering drugs should be offered to patients with grade 1 hypertension and low–moderate CV risk or grade 1 hypertension in older patients (>60 years), or the need for BP-lowering drug treatment in patients with high–normal BP levels. <sup>17,209,210</sup> This uncertainty relates to the fact that low-risk patients with high–normal BP or grade 1 hypertension have rarely been included in RCTs, and that in older patients, RCTs have invariably recruited patients with at least grade 2 hypertension. New analyses and RCT data have become available in these important areas and are discussed below.

### 7.2.2 Drug treatment for patients with grade 1 hypertension at low moderate cardiovascular risk

Recent meta-analyses show significant treatment-induced reductions in CV events and mortality in patients with grade 1 hypertension. 8,201,211 However, the first of these analyses included a substantial number of patients who had grade 1 hypertension despite existing treatment, and were therefore likely to have had initial BPs above the grade 1 range. Furthermore, many of the patients had diabetes and were therefore at high CV risk.<sup>211</sup> The second metaanalysis, limited to RCTs in patients with grade 1 hypertension and low-moderate-risk (five RCTs, 8974 patients), demonstrated a significant reduction in all major CV events by BP-lowering drug treatment [combined stroke and coronary artery disease (CAD) reduced by 34%, and all-cause mortality by 19% for an SBP reduction of  $\sim$ 7 mmHg].8 A third analysis demonstrated a benefit of BP lowering in reducing death and CVD in patients with a baseline BP 140/90 mmHg or higher, but not when baseline BP was lower.<sup>201</sup> These findings have been supported by the results of a subgroup analysis of the

Heart Outcomes Prevention Evaluation (HOPE)-3 trial, showing a significant 27% reduction in major CV outcomes in patients at intermediate CV risk and baseline SBP values in the grade 1 hypertensive range [i.e. >143.5 mmHg (mean 154 mmHg)] when SBP was lowered by drug treatment by a mean of 6 mmHg. <sup>212</sup>

Based on these new data, this Task Force now recommends that lifestyle advice should be accompanied by BP-lowering drug treatment in patients with grade 1 hypertension at low-moderate CV risk.

### 7.2.3 Initiation of blood pressure-lowering drug treatment in older people with grade 1 hypertension

Discussion about the treatment of 'the elderly' or 'older' people has been complicated by the various definitions of older age used in RCTs. For example, older was defined as >60 years in the earliest trials, then as 65, 70, and finally  $75^{51}$  or 80 years<sup>213</sup> in later trials. Chronological age is often a poor surrogate for biological age, with consideration of frailty and independence influencing the likely tolerability of BP-lowering medications. For the purposes of this guideline, the 'old' are defined as  $\geq$ 65 years and the 'very old' as  $\geq$ 80 years. The previous Guidelines<sup>17</sup> noted that all available evidence on CV event reduction by BP lowering in older patients was obtained in patients whose baseline SBP was  $\geq$ 160 mmHg, and there is strong evidence that these patients should be offered BP-lowering drug treatment. <sup>210,214</sup>

Undoubtedly, there are RCTs showing outcome benefits with BP-lowering treatment in older patients whose baseline BP was in a lower SBP range, but these patients were often on background antihypertensive treatment, thus they cannot be defined as having true grade 1 hypertension. This is also the case for the data recently published from the SPRINT trial, which included a cohort of patients older than 75 years, in whom more intense BP lowering reduced the risk of major CV events and mortality.  $^{51,215}$  However, in most RCTs showing a protective effect of BP-lowering treatment in patients with an untreated baseline BP in the grade 1 hypertension range, older patients were well represented. This was further supported by the recent HOPE-3 trial, which showed beneficial effects of BP lowering on CV outcomes in patients, many with grade 1 hypertension (SBP >143 mmHg and mean BP = 154 mmHg), whose mean age was  $\sim\!66$  years, and in whom only 22% had prior treatment of hypertension.  $^{212}$ 

The evidence supports the recommendation that older patients (>65 years, including patients over 80 years) should be offered BP-lowering treatment if their SBP is ≥160 mmHg. There is also justification to now recommend BP-lowering treatment for old patients (aged >65 but not >80 years) at a lower BP (i.e. grade 1 hypertension; SBP = 140–159 mmHg).<sup>201</sup> BP-lowering drugs should not be withdrawn on the basis of age alone. It is well established that BP-lowering treatment withdrawal leads to a marked increase in CV risk. This was exemplified in older patients by a recent subgroup analysis of the Hypertension in the Very Elderly Trial (HYVET),<sup>213</sup> reporting that in patients aged ≥80 years, CV risk reduction was greatest in those who continued treatment rather than in those whose treatment was discontinued.<sup>216</sup> As stated above, all of the above recommendations relate to relatively fit and independent older patients,

because physically and mentally frail and institutionalized patients have been excluded in most RCTs of patients with hypertension.<sup>214</sup> Further details of the treatment of hypertension in older patients and very old patients is provided in section 8.8.

### 7.2.4 Initiation of blood pressure-lowering drug treatment in patients with high-normal blood pressure

The previous (2013) Guidelines<sup>17</sup> recommended not to initiate anti-hypertensive treatment in people with high–normal BP and low–moderate CV risk. This recommendation is further supported by new evidence:

- (1) In all RCTs (including SPRINT)<sup>51</sup> and meta-analyses<sup>2</sup> that have reported reduced major outcomes by lowering 'baseline' BP in the high—normal range, the 'baseline' BP was commonly measured on a background of antihypertensive treatment. Therefore, these studies do not provide evidence to support treatment initiation in patients without hypertension.<sup>8</sup>
- (2) The HOPE-3 trial,<sup>212</sup> in which only 22% of the patients at intermediate CV risk had background antihypertensive treatment, showed that BP-lowering treatment did not reduce the risk of major CV events in patients with baseline SBP values in the high–normal range.
- (3) A meta-analysis of 13 RCTs or RCT subgroups (involving 21 128 individuals) in patients at low-moderate CV risk and untreated baseline BP in the high-normal and normal range, showed no effect of BP-lowering treatment on any CV outcomes.<sup>217</sup>
- (4) Another recent analysis, including patients with high–normal BP, concluded that primary preventive BP lowering was associated with reduced risk for death and incident CVD if baseline SBP was 140 mmHg or higher, but at lower BP levels [i.e. high–normal BP (<140/90 mmHg)], treatment was not associated with any benefit in primary prevention.<sup>201</sup>
- (5) The situation may be different in very high-risk patients with a high-normal BP and established CVD. In a meta-analysis of 10 RCTs or RCT subgroups that also included individuals at high or very high CV risk, mostly with previous CVD and untreated high-normal and normal BP (n = 26 863), BP-lowering drug treatment, achieving an SBP reduction of 4 mmHg, reduced the risk of stroke but not any other CV events. <sup>217</sup> In another analysis of trials including people with previous CAD and a mean baseline SBP of 138 mmHg, treatment was associated with reduced risk for major CV events (relative risk 0.90; 95% confidence interval 0.84–0.97), but was not associated with an increased survival (relative risk 0.98; 95% confidence interval 0.89–1.07). <sup>201</sup> Thus, the benefit for treating people with high-normal BP appears marginal and, if present, appears to be restricted to those at very high CV risk and established CVD, especially CAD.

We recommend that patients with high—normal BP and low—moderate CV risk should be offered lifestyle advice, because this reduces their risk of progressing to established hypertension and may further reduce their CV risk. These patients should not be offered BP-lowering drug treatment. Nevertheless, based on the data from the HOPE-3 trial, drug treatment may be considered in these patients if

their BP is close to the hypertension diagnostic threshold of 140/90 mmHg, after a prolonged attempt to control BP with lifestyle changes.

BP-lowering drugs may be considered for patients with high-normal BP and established CVD, especially CAD. In these patients, monotherapy may be sufficient.

## 7.2.5 Should blood pressure-lowering drug treatment be initiated on the basis of blood pressure values or the level of total cardiovascular risk?

Two recent meta-analyses of RCTs<sup>8,218</sup> have shown that when BPlowering data are stratified according to CV risk, the relative risk reductions do not differ across the various risk strata; not surprisingly, the absolute risk reduction is greater with increasing baseline CV risk. These data have been taken as support for the hypothesis that BPlowering treatment should be based on CV risk and target those at greatest CV risk, irrespective of their BP.<sup>218</sup> However, it has recently been made that whereas patients at high or very high CV risk exhibit the greatest absolute reduction in CV outcomes with BP-lowering treatment, they also have the highest residual risk, which means failure of treatment to exert full protection.<sup>8</sup> It is the opinion of this Task Force that these data support earlier treatment of patients with SBP or DBP values >140/90 mmHg when their CV risk is still low-moderate, to prevent the accumulation of HMOD and a high incidence of late treatment failure (residual risk), which would otherwise occur if treatment was delayed by a purely CV risk-based approach. The most effective strategy to reduce risk is to prevent the development of high CV-risk situations with earlier intervention. The assessment of CV risk is at the core of the treatment strategy recommended by these Guidelines because of the frequent coexistence of multiple CV risk factors in hypertensive patients, and to inform the use of concomitant medications (e.g. statins, antiplatelet therapies, etc., see section 9) to reduce CV risk. We conclude that, in general, the decision to use BP-lowering treatment should not be based solely on the level of CV risk because even in patients at the highest risk (with established CVD), when baseline BP is below 140/90 mmHg, the benefits of BP-lowering treatment are at best marginal and most evident in patients with CAD at the upper end of the high-normal BP range. <sup>201</sup>

### 7.2.6 Initiation of blood pressure-lowering drug treatment

In patients with grade 2 or 3 hypertension, it is recommended that BP-lowering drug treatment should be initiated alongside lifestyle interventions. In patients with grade 1 hypertension at high risk or with HMOD, drug treatment should also be initiated simultaneously with lifestyle interventions. In lower-risk patients with grade 1 hypertension, BP-lowering drug treatment should be initiated after 3–6 months if BP is not controlled by lifestyle interventions alone (Figure 3). Recommended BP thresholds for the initiation of antihypertensive drug treatment are shown in Table 19.

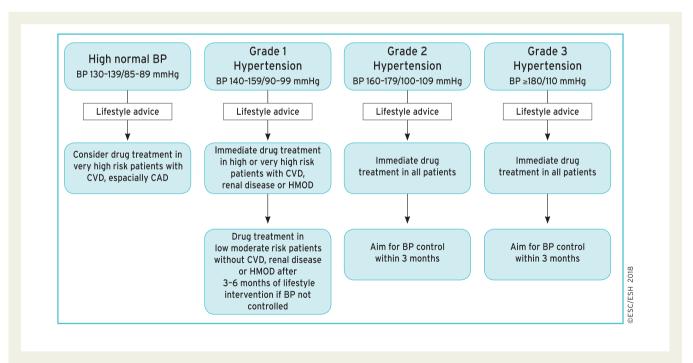


Figure 3 Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels. BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage.

#### Initiation of hypertension treatment according to office BP

Recommendations	Class <sup>a</sup>	Levelb
Prompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneous with the initiation of lifestyle changes. <sup>2,8</sup>	1	А
In patients with grade 1 hypertension:  • Lifestyle interventions are recommended to determine if this will normalize BP. 219	п	В
• In patients with grade 1 hypertension at low–moderate-risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention. 211,212	ı	А
• In patients with grade 1 hypertension and at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions. 211,212	1	А
In fit older patients with hypertension (even if aged >80 years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is $\geq$ 160 mmHg. $^{210,220,221}$	1	А
BP-lowering drug treatment and lifestyle intervention are recommended for fit older patients ( $>65$ years but not $>80$ years) when SBP is in the grade 1 range ( $140-159$ mmHg), provided that treatment is well tolerated. <sup>212</sup>	1	А
Antihypertensive treatment may also be considered in frail older patients if tolerated. 215	IIb	В
Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥80 years, is not recommended, provided that treatment is well tolerated. <sup>213</sup>	Ш	А
In patients with high–normal BP (130–139/85–89 mmHg):	ı	А
<ul> <li>Lifestyle changes are recommended. 17,35</li> <li>Drug treatment may be considered when their CV is very high due to established CVD, especially CAD. 217</li> </ul>	IIb	A

BP = blood pressure; CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure.

In patients with grade 1 hypertension and at low-moderate-risk, drug treatment may be preceded by a prolonged period of lifestyle intervention to determine if this approach will normalize BP. The duration of the lifestyle intervention alone will depend on the level of BP within the grade 1 range, i.e. the likelihood of achieving BP control with lifestyle intervention alone, and the opportunities for significant lifestyle change in individual patients.

Table 19 Summary of office blood pressure thresholds for treatment

Age group	Office SBP treatment threshold (mmHg)				Office DBP treatment threshold (mmHg)	
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18 - 65 years	≥140	≥140	≥140	≥140 <sup>a</sup>	≥140 <sup>a</sup>	≥90
65 - 79 years	≥140	≥140	≥140	≥140 <sup>a</sup>	≥140 <sup>a</sup>	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	≥90

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

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<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

<sup>&</sup>lt;sup>a</sup>Treatment may be considered in these very high-risk patients with high-normal SBP (i.e. SBP 130–140 mmHg).

#### 7.3 Blood pressure treatment targets

### 7.3.1 New evidence on systolic blood pressure and diastolic blood pressure treatment targets

The 2013 ESH/ESC hypertension Guidelines<sup>17</sup> recommended an office BP treatment target of <140/90 mmHg, regardless of the number of comorbidities and level of CV risk. The Guidelines specifically stated that evidence from RCTs, meta-analyses, and *post hoc* analysis of large-scale RCTs all showed no obvious incremental benefit of lowering BP to <130/80 mmHg. Since then, new information has emerged from *post hoc* analyses of large outcome trials in patients at high CV risk, <sup>222–224</sup> registries in patients with coronary disease, and, more importantly, new RCTs and meta-analyses of all available RCT evidence. In the *post hoc* RCT analyses and registry data, compared with a target SBP of between 130 mmHg and 139 mmHg, lowering SBP to <130 mmHg was, in general, associated with no further benefit on major CV events, except perhaps for further reductions in the risk of stroke. A consistent finding was that reducing SBP to <120 mmHg increased the incidence of CV events and death.

A recent RCT relevant to the issue of target BP is SPRINT, which compared two different SBP targets (<140 or <120 mmHg) in >9000 patients at high CV risk, but excluded patients with diabetes or previous stroke. More intensive BP-lowering treatment (achieved SBP 121 vs. 136 mmHg) was associated with a 25% reduction in major CV events and a 27% reduction in all-cause death (but no significant reduction in stroke or myocardial infarction).<sup>51</sup> This outcome unquestionably provides strong support for the beneficial effects of more vs. less intensive BP-lowering treatment strategies in higher risk patients. However, this RCT does not clarify the optimal BP target because the method used for office BP measurement in SPRINT (unattended automatic measurement) had not been used in any previous RCTs that provide the evidence base for the treatment of hypertension.<sup>225</sup> This is because unattended automated office BP measurement results in lower BP values, relative to conventional office BP measurement, due to the absence of the white-coat effect. 52,54 Thus, it has been suggested that the BP values reported in SPRINT may correspond to conventional office SBPs in the 130 – 140 and 140-150 mmHg ranges in the more vs. less intensive BPlowering groups, respectively.

Some new information on SBP and DBP targets for drug treatment has been provided by two recent, large meta-analyses of RCTs of BP lowering. In the first of these meta-analyses, achieved SBP was stratified according to three SBP target ranges (149–140 mmHg, 139–130 mmHg, and <130 mmHg). Lowering SBP to <140 mmHg reduced the relative risk of all major CV outcomes (including mortality); similar benefits were seen when SBP was lowered to <130 mmHg (average 126 mmHg). Importantly, the latter was also true when the achieved SBP in the comparator group was 130–139 mmHg. Stratification of RCTs for achieved DBP, to either 89–80 mmHg or <80 mmHg, also showed a reduction in all types of CV outcomes compared with higher DBP values.  $^{226}$ 

The second meta-analysis, which also included the SPRINT trial,<sup>2</sup> noted that every 10 mmHg reduction in SBP reduced the rate of major CV events and death for baseline SBP values >160 mmHg to

baseline values between 130 and 139 mmHg, implying benefit at achieved SBP values of <130 mmHg. Furthermore, a benefit of a 10 mmHg reduction in SBP was also reported for patients with a baseline SBP of <130 mmHg, thereby achieving values <120 mmHg. However, there were far fewer patients in these subgroups, and this last set of data will have been heavily influenced by the unusually low BP values in the SPRINT trial, due to the method of BP measurement (see above). Importantly, this analysis showed consistent benefit from intensive BP lowering in patients at all levels of risk, including those with and without existing CVD, stroke, diabetes, and CKD.

Finally, in the first meta-analysis, <sup>226</sup> the incremental benefit of BP lowering on events progressively decreased as the target BP was lowered. Furthermore, an additional meta-analysis by the same group found that permanent treatment discontinuation because of treatment-related adverse effects was significantly higher in those targeted to lower BP values. <sup>227</sup> Therefore, advocating more intensive BP-lowering targets for all has to be viewed in the context of an increased risk of treatment discontinuation due to adverse events, which might offset, in part or completely, the limited incremental reduction in CV risk.

Whilst considering BP targets, it is important to acknowledge that <50% of patients treated for hypertension currently achieve a target office SBP of <140 mmHg.<sup>11,12</sup> This is a major missed opportunity for CVD prevention in millions of people across the world.

This Task Force recommends that when BP-lowering drugs are used, the first objective should be to lower BP to <140/90 mmHg in all patients. Provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients, although in some groups the evidence is less compelling. In older patients (>65 years), SBP should be targeted to between 130 and 140 mmHg, and DPB to <80 mmHg. Treated SBP should not be targeted to <120 mmHg.

Importantly, we specify a target range because the lower safety boundary assumes greater importance when BP is targeted to lower levels. Furthermore, in general, when SBP is lowered to <120 mmHg in patients included in RCTs (i.e. older and higher-risk patients, often with comorbidities and CVD), the risk of harm appears to increase and outweigh the benefits.  $^{222}$ 

### 7.3.2 Blood pressure targets in specific subgroups of hypertensive patients

7.3.2.1. Diabetes mellitus

RCTs in type 1 diabetes mellitus demonstrate that BP-lowering treatment has a renoprotective effect, <sup>228</sup> but because these patients tend to be younger, previous RCTs have had inadequate power to study CV outcomes and to establish optimal BP targets.

In contrast, there have been many BP-lowering treatment RCTs, either exclusively dedicated to patients with type 2 diabetes or hypertension trials that have included a large cohort of patients with type 2 diabetes. Most of these RCTs have shown that BP lowering to <140/85 mmHg is beneficial in patients with type 2 diabetes and hypertension. However, the results have been less clear about

whether a lower BP target is associated with further benefits. The evidence can be summarized as follows:

- i. A large RCT in patients with type 2 diabetes has shown that an achieved SBP of <135 mmHg, compared with  $\sim$ 140 mmHg, was associated with a significant reduction in cardiovascular and all-cause mortality.  $^{229}$
- ii. Evidence from another large RCT in patients with type 2 diabetes showed that, compared with patients with an on-treatment SBP of  $\sim$ 135 mmHg, reducing SBP to 121 mmHg did not reduce CV morbidity and mortality or all-cause death, but substantially reduced the risk of stroke.  $^{230}$
- iii. Although one recent meta-analysis concluded that most of the benefit associated with BP lowering was obtained at higher BP targets (i.e. <150 mmHg but not <140 mmHg),<sup>231</sup> other large meta-analyses have confirmed that in type 2 diabetes, lowering SBP to <140 mmHg is associated with reductions in all major CV events.<sup>1,232–234</sup>
- iv. Two of the meta-analyses concluded that the overall benefit of lowering BP in patients with type 2 diabetes (unlike patients without type 2 diabetes) largely disappears when SBP is lowered to <130/80 mmHg, <sup>1,235</sup> except for the continuing incremental benefit on stroke.
- v. Similar evidence for stroke benefit from lower achieved SBP has also been reported from *post hoc* analysis of diabetic patients in the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study. In addition, reanalysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD)<sup>230</sup> trial in type 2 diabetes, after removing the interaction from the intensive glucose-lowering arm and thereby limiting the analysis to BP-lowering effects, showed an overall reduction in CV events with intensive SBP lowering to <130 mmHg.<sup>236</sup>
- vi. Further recent analysis of the ACCORD trial has shown that reducing SBP to <120 mmHg was associated with increased risk of major CV events. <sup>236</sup>
- vii. With regard to DBP, earlier evidence suggested a benefit on major CV events when DBP was lowered to <85 mmHg.<sup>237,238</sup> More recently, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial,<sup>229</sup> the benefits on CV outcomes was observed at diastolic pressures of 75 mmHg. This is consistent with evidence from the meta-analyses cited above, that it is safe and effective to lower DBP to <80 mmHg in patients with type 2 diabetes.

In summary, In patients with diabetes receiving BP-lowering drugs, it is recommended that office BP should be targeted to an SBP of 130 mmHg,  $^{229}$  and lower if tolerated. In older patients (aged  $\geq\!65$  years) the SBP target range should be 130–140 mmHg $^{213}$  if tolerated. SBP should not be lowered to <120 mmHg and DBP should be lowered to <80 mmHg. Attention should also be given to the consistency of BP control, because visit-to-visit BP variability is associated with increased CV and renal disease risk. Furthermore, CV protection has been found to be greater when BP control is accompanied by fewer visit-to-visit BP variations.  $^{239-241}$ 

#### 7.3.2.2. Older patients

The definition of 'older' is complex. As populations age, there is increasingly wide variation between a patient's chronological age and their functional status, ranging from fit, active, and independent, through to frail and dependent. The anticipated benefits vs. potential harm of BP treatment in older patients will be influenced by the patient's ability to tolerate treatment and their health and functional status. For the purposes of these Guidelines, 'older' patients are defined as those aged >65 years.

In the 2013 ESH/ESC hypertension Guidelines, the target SBP for older hypertensive patients was set at 140–150 mmHg because this was the range of systolic values achieved by major outcome trials demonstrating a beneficial effect of antihypertensive treatment in these patients. A similar SBP target was suggested by the HYVET trial, in which treating to an SBP target of <150 mmHg (achieving a mean SBP of 144 mmHg) in the very old (>80 years) demonstrated significant reductions in mortality, fatal stroke, and heart failure, with the caveat that the 'very old' patients in this study were active and independent. More recent evidence supports a lower SBP target for older patients (>65 years):

- (1) The SPRINT trial included a high proportion of patients over the age of 75 years (*n* = 2636) and demonstrated that more intensive BP-lowering treatment (mean achieved BP = 124/62 mmHg) significantly reduced the risk of major CV events, heart failure, and all-cause death (all by >30%) compared with standard treatment (mean achieved BP = 135/67 mmHg).<sup>215</sup> It has been noted above that the BP measurement technique used in SPRINT generated lower values than those provided by the conventional office BP measurement.<sup>225,242</sup> Consequently, the SBP of 124 mmHg achieved in the intensively treated older patients in the SPRINT trial most probably reflects a conventional office SBP range of 130–139 mmHg.
- (2) Although HYVET and most other RCTs in older patients have recruited relatively fit and independent patients, the SPRINT study also suggested that there are benefits of more intensive treatment being extended to older patients who are at the frailer end of the spectrum of patients meeting the recruitment criteria, with reduced gait speed.<sup>215</sup>

Based on the new data, the targets suggested by the previous Guidelines now appear too conservative for many old and very old patients, especially those who are active and independent. Consequently, we recommend that in older patients treated for hypertension, BP should be lowered to <140/80 mmHg, but not below an SBP of 130 mmHg. Importantly, the impact of BP-lowering on the well-being of the patient should be closely monitored, because the increased risk of adverse events (e.g. injurious falls) with lower BP values could be more pronounced in older patients in the real-life setting than in the closely monitored conditions of RCTs. Further details on the approach to treatment of the frail older patient are discussed in section 8.8.

7.3.2.3 Office vs. home and ambulatory blood pressure targets

No outcome-based RCT has used ABPM or HBPM to guide the treatment of hypertension. Thus, ABPM and HBPM BP targets are based on extrapolation from observational data rather than on outcome trials. Although we do not provide formal ABPM or HBPM BP targets for treated patients, it should be noted that:

- (1) In population studies, the difference between office and out-of-office BP levels decreases as office BP decreases, to a point of around 115 120/70 mmHg, at which office and 24 h ABPM mean BP values are usually similar.<sup>54</sup>
- (2) This convergence has also been confirmed in treated patients<sup>243</sup> in whom the difference between office BP and ambulatory BP values diminishes and becomes negligible at an SBP of approximately 120 mmHg.
- (3) In treated patients, a target office SBP of 130 mmHg might therefore correspond to a slightly lower mean 24 h SBP, i.e. approximately 125 mmHg.
- (4) Although there are no available data, the home SBP target, to be equivalent to an office SBP target of 130 mmHg, might also be lower than 130 mmHg.

#### Office BP treatment targets in hypertensive patients

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients and, provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. <sup>2.8</sup>	1	A
In patients <65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients. <sup>c</sup> 2,215,229	1	A
In older patients (aged ≥65 years) receiving BP-lowering drugs:  ■ It is recommended that SBP should be targeted to a BP range of 130–139 mmHg. <sup>2,235,244</sup>	-	A
<ul> <li>Close monitoring of adverse effects is recommended.</li> </ul>	- 1	С
<ul> <li>These BP targets are recommended for patients at any level of CV risk and in patients with and without established CVD.<sup>2,8</sup></li> </ul>	1	A
A DBP target of <80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities. 226,235	lla	В

BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

#### 7.4 Treatment of hypertension

#### 7.4.1 Lifestyle changes

Heathy lifestyle choices can prevent or delay the onset of hypertension and can reduce CV risk. <sup>17,35</sup> Effective lifestyle changes may be sufficient to delay or prevent the need for drug therapy in patients with grade 1 hypertension. They can also augment the effects of BP-lowering therapy, but they should never delay the initiation of drug therapy in patients with HMOD or at a high level of CV risk. A major drawback of lifestyle modification is the poor persistence over time. <sup>245,246</sup> The recommended lifestyle measures that have been shown to reduce BP are salt restriction, moderation of alcohol consumption, high consumption of vegetables and fruits, weight reduction and maintaining an ideal body weight, and regular physical activity. <sup>17</sup> In addition, tobacco smoking has an acute prolonged pressor effect that may raise daytime ambulatory BP, but smoking cessation and other lifestyle measures are also important beyond BP (i.e. for CVD and cancer prevention). <sup>35</sup>

#### 7.4.2 Dietary sodium restriction

There is evidence of a causal relationship between sodium intake and BP, and excessive sodium consumption (>5 g sodium per day, e.g. one small teaspoon of salt per day) has been shown to have a pressor effect and be associated with an increased prevalence of hypertension and the rise in SBP with age.<sup>247</sup> Conversely, sodium restriction has been shown to have a BP-lowering effect in many trials. A recent meta-analysis of these trials showed that a reduction of  $\sim$ 1.75 g sodium per day (4.4 g salt/day) was associated with a mean 4.2/2.1 mmHg reduction in SBP/DBP, with a more pronounced effect (-5.4/ -2.8 mmHg) in people with hypertension. <sup>248</sup> The beneficial effect of a reduced sodium intake on BP tends to diminish with time, in part due to poor dietary persistence. The BP-lowering effect of sodium restriction is greater in black people, in older patients, and in patients with diabetes, metabolic syndrome, or CKD.<sup>249</sup> In people with treated hypertension, effective sodium restriction may reduce the number or dose of BP-lowering drugs that are necessary to control BP. 250,251

The effect of reduced dietary sodium on CV events remains unclear. 252-255 Prospective cohort studies have reported an overall increased risk of mortality and CV events on high sodium intake. However, they also reported that reducing sodium intake below a certain level (about 3 g of sodium per day) further reduced BP, but paradoxically was associated with an increased risk of all-cause and CV mortalities in both the general population and in hypertensive people, suggesting a J-curve phenomenon.<sup>256</sup> The mechanism of this apparent increased risk at low sodium intake is not well understood and might be confounded by reverse causality. There is no evidence from epidemiological studies that very low sodium intake may cause harm.<sup>257</sup> Although a few trials and meta-analyses suggest that reducing salt intake from high to moderate is accompanied by a lower risk of CV events, 254,255,258 to date, no prospective RCT has provided definitive evidence about the optimal sodium intake to minimize CV events and mortality. Increased potassium intake is associated with BP reduction and may have a protective effect, thereby modifying the association between sodium intake, BP, and CVD.<sup>259</sup>

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

<sup>&</sup>lt;sup>c</sup>Less evidence is available for this target in low-moderate-risk patients.

Globally, usual sodium intake is between 3.5–5.5 g per day (which corresponds to 9 - 12 g of salt per day), with marked differences between countries and even between regions within countries. We recommend sodium intake to be limited to approximately 2.0 g per day (equivalent to approximately 5.0 g salt per day) in the general population and to try to achieve this goal in all hypertensive patients. Effective salt reduction is not easy and there is often poor appreciation of which foods contain high salt levels. Advice should be given to avoid added salt and high-salt foods. A reduction in population salt intake remains a public health priority but requires a combined effort between the food industry, governments, and the public in general, as 80% of salt consumption involves hidden salt in processed foods.

#### 7.4.3 Moderation of alcohol consumption

There is a long-established positive linear association between alcohol consumption, BP, the prevalence of hypertension, and CVD risk. Binge drinking can have a strong pressor effect. The Prevention and Treatment of Hypertension Study (PATHS) investigated the effects of alcohol reduction on BP; the intervention group had a modest 1.2/0.7 mmHg lower BP than the control group at the end of the 6 month period. A Mendelian randomization meta-analysis of 56 epidemiological studies suggested that reduction of alcohol consumption, even for light—moderate drinkers, might be beneficial for CV health. Hypertensive men who drink alcohol should be advised to limit their consumption to 14 units per week and women to 8 units per week (1 unit is equal to 125 mL of wine or 250 mL of beer). Alcohol-free days during the week and avoidance of binge drinking a realso advised.

#### 7.4.4 Other dietary changes

Hypertensive patients should be advised to eat a healthy balanced diet containing vegetables, legumes, fresh fruits, low-fat dairy products, wholegrains, fish, and unsaturated fatty acids (especially olive oil), and to have a low consumption of red meat and saturated fatty acids. <sup>262–264</sup> The Mediterranean diet includes many of these nutrients and foods, with a moderate consumption of alcohol (mostly wine with meals). A number of studies and meta-analyses <sup>262–265</sup> have shown that the Mediterranean diet is associated with a reduction in CV events and all-cause mortality. An RCT in high-risk individuals on the Mediterranean diet over 5 years showed a 29% CV risk reduction compared with a low-fat control diet, and a 39% reduction in stroke. <sup>265</sup> The Mediterranean diet also significantly reduced ambulatory BP, blood glucose, and lipid levels. <sup>266</sup> The diet should be

accompanied by other lifestyle changes such as physical exercise and weight loss.<sup>35</sup>

With regard to coffee consumption, caffeine has been shown to have an acute pressor effect. Nevertheless, coffee consumption is associated with CV benefits, as highlighted by a recent systematic review of prospective cohort studies including more than 1 million participants and 36 352 CV events. Moreover, green or black tea consumption may also have a small but significant BP-lowering effect. 268,269

Regular consumption of sugar-sweetened soft drinks has been associated with overweight, metabolic syndrome, type 2 diabetes, and higher CV risk. The consumption of these drinks should be discouraged.  $^{35}$ 

Thus, adopting a healthy and balanced diet may assist in BP reduction and also reduce CV risk.

#### 7.4.5 Weight reduction

Excessive weight gain is associated with hypertension, and reducing weight towards an ideal body weight decreases BP.<sup>270</sup> In a metaanalysis, the mean SBP and DBP reductions associated with an average weight loss of 5.1 kg were 4.4 and 3.6 mmHg, respectively.<sup>271</sup> Both overweight and obesity are associated with an increased risk of CV death and all-cause mortality. Weight reduction is recommended in overweight and obese hypertensive patients for control of metabolic risk factors, but weight stabilization may be a reasonable goal for many. The Prospective Studies Collaboration 272 concluded that mortality was lowest at a body mass index (BMI) of approximately 22.5 - 25 kg/m<sup>2</sup>, whereas a more recent meta-analysis concluded that mortality was lowest in subjects with overweight. 273,274 Although the optimal BMI is unclear, maintenance of a healthy body weight (BMI of approximately 20-25 kg/m<sup>2</sup> in people <60 years of age; higher in older patients) and waist circumference (<94 cm for men and <80 cm for women) is recommended for non-hypertensive individuals to prevent hypertension, and for hypertensive patients to reduce BP.<sup>35</sup> Weight loss can also improve the efficacy of antihypertensive medications and the CV risk profile. Weight loss should employ a multidisciplinary approach that includes dietary advice, regular exercise, and motivational counselling.<sup>35,275</sup> Furthermore, short-term results are often not maintained over the long-term. Weight loss can also be promoted by anti-obesity drugs and, to a greater degree, bariatric surgery, which appears to decrease CV risk in severely obese patients. Further details are available in a recent document of the ESH and the European Association for the Study of Obesity. 276

#### 7.4.6 Regular physical activity

Physical activity induces an acute rise in BP, especially SBP, followed by a short-lived decline in BP below baseline. Epidemiological studies suggest that regular aerobic physical activity may be beneficial for both the prevention and treatment of hypertension, and to lower CV risk and mortality. A meta-analysis of RCTs, which rely on selfreported exercise and are by necessity unblinded, has shown that aerobic endurance training, dynamic resistance training, and isometric training reduce resting SBP and DBP by 3.5/2.5, 1.8/3.2, and 10.9/6.2 mmHg, respectively, in general populations. 277 Endurance training, but not other types of training, reduces BP more in hypertensive participants (8.3/5.2 mmHg). Regular physical activity of lower intensity and duration lowers BP less than moderate- or high-intensity training, but is associated with at least a 15% decrease in mortality in cohort studies. 278,279 This evidence suggests that hypertensive patients should be advised to participate in at least 30 min of moderateintensity dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5–7 days per week. Performance of resistance exercises on 2-3 days per week can also be advised. For additional benefit in healthy adults, a gradual increase in aerobic physical activity to 300 min a week of moderate intensity or 150 min a week of vigorousintensity aerobic physical activity, or an equivalent combination thereof, is recommended.<sup>35</sup> The impact of isometric exercises on BP and CV risk is less well established.<sup>280</sup>

#### 7.4.7 Smoking cessation

Smoking is a major risk factor for CVD and cancer. Although the rate of smoking is declining in most European countries, especially in men, it is still common in many regions and age groups, and overall the prevalence remains high at 20-35% in Europe. 281 There is also evidence suggesting ill-health effects of passive smoking.<sup>282</sup> Studies using ABPM have shown that both normotensive subjects and untreated hypertensive smokers present higher daily BP values than non-smokers.<sup>283</sup> No chronic effect of smoking has been reported for office BP,<sup>284</sup> which is not lowered by smoking cessation. Smoking is second only to BP in contributing risk to the global burden of disease, and smoking cessation is probably the single most effective lifestyle measure for the prevention of CVD, including stroke, myocardial infarction, and PAD. 285,286 Therefore, the history of tobacco use should be established at each patient visit and hypertensive smokers should be counselled regarding smoking cessation.

Brief advice from a physician has a small but significant effect of 1-3% over and above the unassisted 12 month quit rate. <sup>287</sup> This can be improved by the use of pharmacological measures, with varenicline and combination nicotine replacement therapy being superior to bupropion or single nicotine replacement therapy. <sup>288</sup> In comparison with placebo, nicotine replacement therapy or treatment with buproprion doubles the chance of quitting, whilst varenicline or combination nicotine replacement therapy triples the chance of quitting. Combining behavioural support with pharmacotherapy increases the chance of success by 70-100% compared with brief advice alone. <sup>289</sup>

### Lifestyle interventions for patients with hypertension or high-normal $\ensuremath{\mathbf{BP}}$

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Salt restriction to <5 g per day is recommended. <sup>248,250,255,258</sup>	ı	A
It is recommended to restrict alcohol consumption to:  • Less than 14 units per week for men.  • Less than 8 units per week for women. <sup>35</sup>	1	A
It is recommended to avoid binge drinking.	Ш	С
Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended. 262,265	ı	A
Body-weight control is indicated to avoid obesity (BMI >30 kg/m <sup>2</sup> or waist circumference >102 cm in men and >88 cm in women), as is aiming at healthy BMI (about 20–25 kg/m <sup>2</sup> ) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk. <sup>262,271,273,290</sup>	ı	A
Regular aerobic exercise (e.g. at least 30 min of moderate dynamic exercise on 5–7 days per week) is recommended. <sup>262,278,279</sup>	ı	A
Smoking cessation, supportive care, and referral to smoking cessation programs are recommended. 286,288,291	1	В

BMI = body mass index; BP = blood pressure; CV = cardiovascular.

## 7.5. Pharmacological therapy for hypertension

#### 7.5.1 Drugs for the treatment of hypertension

Most patients will require drug therapy in addition to lifestyle measures to achieve optimal BP control. In the previous Guidelines, five major drug classes were recommended for the treatment of hypertension: ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like diuretics such as chlortalidone and indapamide), based on: (i) proven ability to reduce BP; (ii) evidence from placebo-controlled studies that they reduce CV events; and (iii) evidence of broad equivalence on overall CV morbidity and mortality, with the conclusion that benefit from their use predominantly derives from BP lowering. These conclusions have since been confirmed by

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence mostly based on the effect on BP and/or CV risk profile.

recent meta-analyses. <sup>1,2,217,292</sup> These meta-analyses have reported cause-specific differences on outcomes between some drugs (e.g. less stroke prevention with beta-blockers, and less heart failure prevention with CCBs); however, overall, major CV outcomes and mortality were similar with treatment based on initial therapy with all five major classes of treatment. These Guidelines thus recommend that the same five major classes of drugs should form the basis of antihypertensive therapy. There are compelling or possible contraindications for each class of drug (*Table 20*) and preferential use of some drugs for some conditions, as discussed below. There is also evidence that there are differences in the persistence and discontinuation rates of the major drug classes. <sup>293,294</sup>

Other classes of drugs have been less widely studied in event-based RCTs or are known to be associated with a higher risk of adverse effects [e.g. alpha-blockers, centrally acting agents, and mineralocorticoid receptor antagonists (MRAs)]. These are useful additions to the antihypertensive armamentarium in patients whose BP cannot be controlled by proven combinations of the aforementioned major drug classes.

converting enzyme inhibitors and angiotensin receptor blockers)

Both ACE inhibitors and ARBs are among the most widely used classes of antihypertensive drugs. They have similar effectiveness<sup>295,296</sup> as each other and other major drug classes on major CV events and mortality outcomes.<sup>2,292</sup> ARBs are associated with significantly lower treatment discontinuation rates for adverse events than those of all other antihypertensive therapies,<sup>297</sup> and similar rates to placebo.<sup>294</sup> ACE inhibitors and ARBs should not be combined for the treatment of hypertension because there is no added benefit on outcomes and an excess of renal adverse events.<sup>298,299</sup> Dual combina-

tion of RAS blockers also led to the premature cessation of another trial due to adverse events, <sup>291</sup> when a renin inhibitor, aliskiren, was

combined with either an ACE inhibitor or an ARB in people with dia-

betes. This result halted further research into the clinical utility of alis-

kiren for BP treatment.

7.5.1.1. Blockers of the renin—angiotensin system (angiotensin-

Both ACE inhibitors and ARBs reduce albuminuria more than other BP-lowering drugs and are effective at delaying the progression of diabetic and non-diabetic CKD.<sup>217</sup> A recent meta-analysis shows

Table 20 Compelling and possible contraindications to the use of specific antihypertensive drugs

Drug	Contraindication	ons
	Compelling	Possible
Diuretics (thiazides/thiazide-like, e.g. chlortha- lidone and indapamide)	• Gout	<ul> <li>Metabolic syndrome</li> <li>Glucose intolerance</li> <li>Pregnancy</li> <li>Hypercalcaemia</li> <li>Hypokalaemia</li> </ul>
Beta-blockers	Asthma     Any high-grade sinoatrial or atrioventricular block     Bradycardia (heart rate <60 beats per min)	<ul><li>Metabolic syndrome</li><li>Glucose intolerance</li><li>Athletes and physically active patient</li></ul>
Calcium antagonists (dihydropyridines)		Tachyarrhythmia Heart failure (HFrEF, class III or IV) Pre-existing severe leg oedema
Calcium antagonists (verapamil, diltiazem)	<ul> <li>Any high-grade sinoatrial or atrioventricular block</li> <li>Severe LV dysfunction (LV ejection fraction &lt;40%)</li> <li>Bradycardia (heart rate &lt;60 beats per min)</li> </ul>	Constipation
ACE inhibitors	<ul> <li>Pregnancy</li> <li>Previous angioneurotic oedema</li> <li>Hyperkalaemia (potassium &gt;5.5 mmol/L)</li> <li>Bilateral renal artery stenosis</li> </ul>	Women of child-bearing potential without reliable contraception
ARBs	<ul> <li>Pregnancy</li> <li>Hyperkalaemia (potassium &gt;5.5 mmol/L)</li> <li>Bilateral renal artery stenosis</li> </ul>	Women of child-bearing potential without reliable contraception

 $ACE = angiotensin-converting\ enzyme;\ ARB = angiotensin\ receptor\ blocker;\ HFrEF = heart\ failure\ with\ reduced\ ejection\ fraction;\ LV = left\ ventricular.$ 

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that RAS blockers are the only antihypertensive agents for which evidence is available of a reduced risk of end-stage renal disease. <sup>217</sup>

ACE inhibitors and ARBs also appear effective in preventing or regressing HMOD, such as LVH and small artery remodelling, for an equivalent reduction in BP.<sup>292</sup> Both drugs reduce incident AF, which may be related to improved LV function and more effective LV structural regression.<sup>292</sup> ACE inhibitors and ARBs are also indicated post-myocardial infarction and in patients with chronic HFrEF, which are frequent complications of hypertension.

ACE inhibitors are associated with a small increased risk of angioneurotic oedema, especially in people of black African origin and, in such patients, when RAS blockers are used, an ARB may be preferred.

### 7.5.1.2. Calcium channel blockers

CCBs are widely used for the treatment of hypertension and have similar effectiveness as other major drug classes on BP, major CV events, and mortality outcomes.<sup>2,292</sup> CCBs have a greater effect on stroke reduction than expected for the BP reduction achieved, but may also be less effective at preventing HFrEF. 2,292 However, in antihypertensive treatment trials, emergent heart failure is the event considered. Though clinically a very relevant event, it is a difficult endpoint to quantify precisely, either because symptoms and signs are relatively non-specific or because oedema due to CCBs may result in misdiagnosis. Comparison with diuretics may also be difficult because fluid loss may mask signs and symptoms of incipient heart failure rather than preventing it. CCBs have also been compared with other antihypertensive agents in HMOD-based trials, and are reported to be more effective than beta-blockers in slowing the progression of carotid atherosclerosis, and in reducing LVH and proteinuria.<sup>17</sup>

CCBs are a heterogeneous class of agents. Most RCTs demonstrating the benefits of CCBs on outcomes have used dihydropyridines (especially amlodipine). A smaller number of RCTs have compared non-dihydropyridines (verapamil and diltiazem) with other drugs, and meta-analyses evaluating the two subclasses (vs. other drugs) have not shown substantial differences in effectiveness. <sup>292</sup>

# 7.5.1.3. Thiazide/thiazide-like diuretics (e.g. chlorthalidone and indapamide)

Diuretics have remained the cornerstone of antihypertensive treatment since their introduction in the 1960s. Their effectiveness in preventing all types of CV morbidities and mortality has been confirmed in RCTs and meta-analyses.<sup>300</sup> Diuretics also appear to be more effective than other drug classes in preventing heart failure.<sup>292</sup> There has been debate about whether thiazide-like diuretics such as chlorthalidone and indapamide should be given preference over classical thiazide diuretics (e.g. hydrochlorothiazide and bendrofluazide), but their superiority on outcomes has never been tested in head-to-head RCTs. Chlorthalidone and indapamide have been used in a number of RCTs showing CV benefits, and these agents are more potent per milligram than hydrochlorothiazide in lowering BP, with a longer duration of action compared with hydrochlorothiazide and no evidence of a greater incidence of side effects. 301 Lower dose thiazidelike diuretics (typical of modern antihypertensive treatment regimens) also have more evidence from RCTs demonstrating reductions in CV events and mortality, when compared with lower dose thiazide diuretics.<sup>302</sup> That said, hydrochlorothiazide, alone or in

combination with a potassium-sparing agent, has also been used in BP-lowering RCTs, with positive results. 303 A recent meta-analysis of placebo-controlled studies based on thiazides, chlorthalidone, and indapamide reported similar effects on CV outcomes of the three types of diuretics.<sup>300</sup> Therefore, in the absence of evidence from direct comparator trials and recognizing that many of the approved single-pill combinations (SPCs) are based on hydrochlorothiazide (see below), we recommend that thiazides, chlorthalidone, and indapamide can all be considered suitable antihypertensive agents. Both thiazide and thiazide-like diuretics can reduce serum potassium and have a side effect profile that is less favourable than RAS blockers, which may account for their association with a higher rate of treatment discontinuation.<sup>293,300</sup> They also exhibit dysmetabolic effects that increase insulin resistance and the risk of new-onset diabetes. Potassium may attenuate these effects, 304 and a recent study has shown that the adverse effect of thiazides on glucose metabolism may be reduced by the addition of a potassium-sparing diuretic. 305 Both thiazides and thiazide-like agents are less effective antihypertensive agents in patients with a reduced GFR (eGFR <45 mL/min) and become ineffective when the eGFR is <30 mL/min. In such circumstances, loop diuretics such as furosemide (or torasemide) should replace thiazides and thiazide-like diuretics to achieve an antihypertensive effect.

### 7.5.1.4. Beta-blockers

RCTs and meta-analyses demonstrate that when compared with placebo, beta-blockers significantly reduce the risk of stroke, heart failure, and major CV events in hypertensive patients. 300 When compared with other BP-lowering drugs, beta-blockers are usually equivalent in preventing major CV events, except for less effective prevention of stroke, which has been a consistent finding. 1,2,217 It is possible that the difference originated from small differences in achieved BP (including central SBP<sup>108</sup> between different drug treatments), to which cerebrovascular events may be especially sensitive. RCTs based on HMOD have also indicated that beta-blockers are somewhat less effective than RAS blockers and CCBs in preventing or regressing LVH, carotid IMT, aortic stiffness, and small artery remodelling. 17 In addition, a mortality benefit post-myocardial infarction is uncertain in patients without LV dysfunction.<sup>306</sup> Beta-blockers, as well as diuretics, and particularly their combination, are also associated with increased risk of new-onset diabetes in predisposed subjects (mostly those with the metabolic syndrome). They also exhibit a somewhat less favourable side effect profile than that of RAS blockers, with a higher rate of treatment discontinuation when assessed in real-life conditions.<sup>293</sup> Beta-blockers have been shown to be particularly useful for the treatment of hypertension in specific situations such as symptomatic angina, for heart rate control, post-myocardial infarction, HFrEF, and as an alternative to ACE inhibitors or ARBs in younger hypertensive women planning pregnancy or of child-bearing potential.

Finally, beta-blockers are not a homogeneous class. In recent years, the use of vasodilating beta-blockers—such as labetalol, nebivolol, celiprolol, and carvedilol—has increased. Studies on nebivolol have shown that it has more favourable effects on central BP, aortic stiffness, endothelial dysfunction, etc. It has no adverse effect on the risk of new-onset diabetes and a more favourable side effect profile than classical beta-blockers, 307,308 including less adverse effects on sexual

function. Bisoprolol, carvedilol, and nebivolol have been shown to improve outcomes in RCTs in heart failure;  $^{136}$  however, there are no RCTs reporting patient outcomes with these beta-blockers in hypertensive patients.

### 7.5.1.5. Other antihypertensive drugs

Centrally active drugs were widely used in the earliest decades of antihypertensive treatment when other treatments were not available, but are less frequently used now, principally because of their poorer tolerability relative to the newer major classes of drugs. The alphablocker doxazosin was effective in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) as third-line therapy (with no increase in the risk of heart failure),<sup>309</sup> and was more effective than placebo but less effective than spironolactone at lowering BP in resistant hypertension in the Prevention And Treatment of Hypertension With Algorithm-based therapY-2 (PATHWAY-2) study. 310 Alpha-blockers may also be required in specific indications (e.g. the treatment of symptomatic prostatic hypertrophy). Antihypertensive drugs, other than the major classes already discussed above, are no longer recommended for the routine treatment of hypertension, and are primarily reserved for add-on therapy in rare cases of drug-resistant hypertension where all other treatment options have failed.

# 7.5.2 Drug treatment strategy for hypertension

Guidelines have generated a variety of different strategies to initiate and escalate BP-lowering medication to improve BP control rates. In previous Guidelines, the emphasis was on initial use of different monotherapies, increasing their dose, or substituting for another monotherapy. However, increasing the dose of monotherapy produces little additional BP lowering and may increase the risk of adverse effects, whilst switching from one monotherapy to another is frustrating, time consuming, and often ineffective. For these reasons, more recent Guidelines have increasingly focused on the steppedcare approach, initiating treatment with different monotherapies and then sequentially adding other drugs until BP control is achieved. Despite this, BP control rates have remained poor worldwide. As shown by recent observations, irrespective of the world region, whether high- or low-income economies, or the level of sophistication of healthcare provision, only  $\sim$ 40% of patients with hypertension are treated; of these, only  $\sim$ 35% are controlled to a BP of <140/ 90 mmHg.<sup>12</sup> This failure to achieve BP control in most hypertensive patients, despite numerous iterations of previous Guidelines, suggests that these treatment strategies are not working and that a different approach is needed. This Task Force believes that one of the most important issues to address in these Guidelines is 'how do we improve BP control in treated patients?'. This has become an even more pressing matter because, based on new evidence, current Guidelines are recommending more stringent BP targets (on-treatment values of  $\leq$  130/80 mmHg in the general population and  $\leq$  140/ 90mmHg in older hypertensive people), which will make the achievement of BP control even more challenging.

Several reasons need to be considered to identify why the current treatment strategy has failed to achieve better BP control rates:

(1) Efficacy of pharmacological therapies. Are the best available treatments, in whatever combination, incapable of controlling BP in most patients? The evidence from RCTs demonstrating that BP control can be achieved in most recruited patients, and that no more than 5-10% of these patients exhibit resistance to the selected treatment regimen, suggests that ineffective drug therapy is not the source of the problem.

- (2) **Physician or treatment inertia.** (i.e. failure to adequately uptitrate treatment). Evidence suggests that inertia<sup>311</sup> contributes to suboptimal BP control, with many patients remaining on monotherapy and/or suboptimal doses, despite inadequate BP control.<sup>12</sup>
- (3) **Patient adherence to treatment.** Evidence is accumulating that adherence is a much more important factor than previously recognised. Studies using urine or blood assays for the presence or absence of medication have shown that adherence to treatment is low. This is supported by studies in the general population in which adherence to treatment, based on prescription refilling, was <50% of the treatment in half of the patients. Poor adherence has also be shown to be associated with increased CV risk in various studies (see section 10).
- (4) Insufficient use of combination treatment. BP is a multiregulated variable depending on many compensating pathways. Consequently, combinations of drugs, working through different mechanisms, are required to reduce BP in most people with hypertension. Thus, monotherapy is likely to be inadequate therapy in most patients. Indeed, almost all patients in RCTs have required combinations of drugs to control their BP.<sup>314</sup>
- (5) Complexity of current treatment strategies. There is also evidence that adherence to treatment is adversely affected by the complexity of the prescribed treatment regimen. In a recent study, adherence to treatment was strongly influenced by the number of pills that a patient was prescribed for the treatment of hypertension.<sup>315</sup> Non-adherence was usually <10% with a single pill, rising to ~20% with two pills, ~40% with three pills, and very high rates of partial or complete non-adherence in patients receiving five or more pills.<sup>315</sup>

The above considerations suggest that the most effective evidence-based treatment strategy to improve BP control is one that: (i) encourages the use of combination treatment in most patients, especially in the context of lower BP targets; (ii) enables the use of SPC therapy for most patients, to improve adherence to treatment; and (iii) follows a treatment algorithm that is simple, applies to all patients, and is pragmatic, with the use of SPC therapy as initial therapy for most patients, except those with BP in the high—normal range and in frail older patients (see below).

### 7.5.2.1. Drug combinations for hypertension treatment

Among the large number of RCTs of antihypertensive therapy, only a few have directly compared different two-drug combinations, with systematic use of the two combinations in both arms. In other trials, treatment was initiated using monotherapy in either arm and another drug (and sometimes more than one drug) was added, usually in a non-randomized fashion, according to a pre-specified treatment algorithm. In a few trials, the design precluded the use of what might be considered optimal combinations because multiple monotherapies were being evaluated [e.g. the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), where the addon therapy to either a diuretic, CCB, ACE inhibitor, or alpha-blocker was a beta-blocker, clonidine, or reserpine]. 316

With this caveat, *Table 21* shows that a variety of drug combinations have been used in at least one active arm of placebo-controlled trials and have been associated with significant benefit on major CV events. In trials comparing different regimens (*Table 22*), all combinations have been used in a larger or smaller proportion of patients, without major differences in benefits. The only exceptions are two trials in which a large proportion of the patients received either an ARB–diuretic combination, or CCB–ACE inhibitor combination, with both regimens being superior to a beta-blocker–diuretic combination in reducing CV outcomes. However, in six other trials (with seven comparisons), beta-blockers followed by diuretics or

diuretics followed by beta-blockers were not associated with a significantly different risk of any CV outcome, <sup>233,234,316,319–321</sup> and the beta-blocker diuretic combination was significantly more effective than placebo in three trials. <sup>322–324</sup> It should be mentioned that the beta-blocker–diuretic combination may result in more cases of new-onset diabetes in susceptible individuals compared with other combinations. <sup>325</sup> A rarely used combination of thiazide and potassium-sparing diuretic (amiloride) has also been shown to be equivalent to CCB-based treatment, <sup>310,326</sup> and was recently reported to be associated with fewer metabolic adverse effects compared with thiazide alone (less hypokalaemia and glucose intolerance). <sup>305</sup>

**Table 21** Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. placebo or monotherapy)

Trial	Comparator	Type of patients	SBP difference (mmHg)	Outcomes [change in relative risk (%)]		
ACE inhibitor and diuretic combination						
PROGRESS <sup>27</sup>	Placebo	Previous stroke or TIA	-9	-28% strokes (P <0.001)		
ADVANCE <sup>229</sup>	Placebo	Diabetes	-5.6	-9% micro/macrovascular events ( $P = 0.04$ )		
HYVET <sup>220</sup>	Placebo	Hypertensive; ≥80 years	-15	-34% CV events ( <i>P</i> <0.001)		
ARB and diuretic combination						
SCOPE <sup>330</sup>	Diuretic + placebo	Hypertensive; ≥70 years	-3.2	-28% non-fatal strokes (P = 0.04)		
CCB and diuretic combination						
FEVER <sup>331</sup>	Diuretic + placebo	Hypertensive	-4	-27% CV events (P <0.001)		
ACE inhibitor and CCB of	combination					
Syst-Eur <sup>332</sup>	Placebo	Older with ISH	-10	-31% CV events ( <i>P</i> <0.001)		
Syst-China <sup>333</sup>	Placebo	Older with ISH	-9	−37% CV events ( <i>P</i> <0.004)		
Beta-blocker and diuretic	c combination					
Coope and Warrender <sup>322</sup>	Placebo	Older hypertensive	-18	-42% strokes (P < 0.03)		
SHEP <sup>323</sup>	Placebo	Older with ISH	-13	-36% strokes (P < 0.001)		
STOP-H <sup>324</sup>	Placebo	Older hypertensive	-23	-40% CV events (P = 0.003)		
STOP-H 2 <sup>334</sup>	ACE inhibitor or conventional antihypertensive	Hypertensive	0	NS difference in CV events		
Combination of two RAS	blockers/ACE inhibite	or + ARB or RAS blocke	r + renin inhibito	or)		
ONTARGET <sup>299</sup>	ACE inhibitor or ARB	High-risk patients		More renal events		
ALTITUDE <sup>291</sup>	ACE inhibitor or ARB	High-risk diabetic patients		More renal events		

ACE = angiotensin-converting enzyme; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron – MR Controlled Evaluation; ALTITUDE = Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CV = cardiovascular; FEVER = Felodipine Event Reduction; HYVET = Hypertension in the Very Elderly Trial; ISH = isolated systolic hypertension; NS = non-significant; ONTARGET = Ongoing Telmissartan Alone and in combination with Ramipril Global Endpoint trial; PROGRESS = perindopril protection against recurrent stroke study; RAS = renin-angiotensin system; SBP = systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SHEP = Systolic Hypertension in the Elderly Program; STOP-H = Swedish Trial in Old Patients with Hypertension; Syst-China = Systolic Hypertension in Europe; TIA = transient ischaemic attack.

Table 22 Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination (combinations vs. other combinations)

Trial	Comparator	Type of patients	SBP difference (mmHg)	Outcomes [change in relative risk (%)]
ACE inhibitor and	diuretic combination			
CAPPP <sup>335</sup>	BB + diuretic	Hypertensive	+3	+5% CV events (NS)
ACCOMPLISH <sup>327</sup>	ACE inhibitor + CCB	Hypertensive with risk factors	+1	+21% CV events (P < 0.001)
ARB and diuretic	combination			
LIFE <sup>317</sup>	BB + diuretic	Hypertensive with LVH	-1	-26% stroke ( <i>P</i> <0.001)
CCB and diuretic	combination			
ELSA <sup>336</sup>	BB + diuretic	Hypertensive	0	NS difference in CV events
CONVINCE <sup>233</sup>	BB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
VALUE <sup>337</sup>	ARB + diuretic	High-risk hypertensive	-2.2	-3% CV events (P = NS)
COPE <sup>338</sup>	CCB + BB	Hypertensive	+0.7	NS difference in CV events or stroke
ACE inhibitor and	CCB combination			
NORDIL <sup>339</sup>	BB + diuretic	Hypertensive	+3	NS difference in CV events
INVEST <sup>340</sup>	BB + diuretic	Hypertensive with CAD	0	NS difference in CV events
ASCOT <sup>318</sup>	BB + diuretic	Hypertensive with risk factors	-3	-16% CV events ( <i>P</i> <0.001)
ACCOMPLISH <sup>327</sup>	ACE inhibitor + diuretic	Hypertensive with risk factors	-1	-21% CV events (P < 0.001)
Beta-blocker and	diuretic combination			
CAPPP <sup>335</sup>	ACE inhibitor + diuretic	Hypertensive	-3	-5% CV events (P = NS)
LIFE <sup>317</sup>	ARB + diuretic	Hypertensive with LVH	+1	+26% stroke ( <i>P</i> <0.001)
ALLHAT <sup>316</sup>	ACE inhibitor + BB	Hypertensive with risk factors	-2	NS difference in CV events
ALLHAT <sup>316</sup>	CCB + BB	Hypertensive with risk factors	-1	NS difference in CV events
CONVINCE <sup>233</sup>	CCB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
NORDIL <sup>339</sup>	ACE inhibitor + CCB	Hypertensive	-3	NS difference in CV events
INVEST <sup>340</sup>	ACE inhibitor + CCB	Hypertensive with CAD	0	NS difference in CV events
ASCOT <sup>318</sup>	ACE inhibitor + CCB	Hypertensive with risk factors	+3	+16% CV events (P < 0.001)
Beta-blocker and	CCB combination			
COPE <sup>329</sup>	ARB + CCB	Hypertensive	+0.8	NS difference in CV events or stroke
ARB and CCB cor	nbination			
COPE <sup>329</sup>	CCB + diuretic	Hypertensive	-0.7	NS difference in CV events or stroke
COPE <sup>329</sup>	CCB + BB	Hypertensive	-0.8	NS difference in CV events or stroke
COLM <sup>328</sup>	ARB + diuretic	Older hypertensive	0	NS difference in CV events

ACCOMPLISH = Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB = angiotensin receptor blocker; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; BB = beta-blocker; CAD = coronary artery disease; CAPPP = Captopril Prevention Project; CCB = calcium channel blocker; COLM = Combination of OLMesartan and a calcium channel blocker or diuretic in Japanese elderly hypertensive patients; CONVINCE = Controlled Onset Verapamil Investigation of Cardiovascular Points; COPE = Combination Therapy of Hypertension to Prevent Cardiovascular Events; CV = cardiovascular; ELSA = European Lacidipine Study on Atherosclerosis; INVEST = International Verapamil-Trandolapril Study; LIFE = Losartan Intervention For Endpoint reduction in hypertension; LVH = left ventricular hypertrophy; NORDIL = Nordic Diltiazem; NS = non-significant; SBP = systolic blood pressure; VALUE = Valsartan Antihypertensive Long-term Use Evaluation.

Three outcome trials directly compared two different combinations, each involving a combination of a RAS blocker (ACE inhibitor or ARB) and a CCB with other combinations. In the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, the ACE inhibitor—CCB combination was superior to the same ACE inhibitor in combination with a thiazide diuretic at preventing major CV outcomes, despite no apparent BP difference between the two arms. This finding was not confirmed in the Combination of OLMesartan and a CCB or diuretic in Japanese older hypertensive patients (COLM) and Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trials, which reported no significant differences in CV events when a RAS blocker–CCB combination was compared with a RAS blocker—thiazide diuretic combination, but both of these trials had insufficient statistical power.

Based on the results of outcome RCTs and recent meta-analyses, and evidence of BP-lowering effectiveness, all five major drug classes can, in principle, be combined with one another, except for ACE inhibitors and ARBs, whose concomitant use may lead to no additional benefit but increased adverse effects and is thus discouraged. We recommend that the treatment of hypertension should be preferentially based on combinations of an ACE inhibitor or ARB with a CCB and/or a thiazide/thiazide-like diuretic. These combinations are now widely available in a single pill and in a range of doses, facilitating simplification of treatment, flexible prescribing, and uptitration from lower to higher doses. Combination therapy that includes an ACE inhibitor or ARB with either a CCB or thiazide/thiazide-like diuretic are complementary because both CCBs or diuretics activate the RAS, which will be counteracted by their combination with an ACE inhibitor or ARB. These combinations will also limit potential adverse effects associated with diuretic or CCB monotherapy, reducing the risk of hypokalaemia due to diuretics and reducing the prevalence of peripheral oedema due to CCBs. These combinations also ensure that the RAS is inhibited as part of the treatment strategy, which is an important consideration for many patient groups (e.g. diabetes, LVH,

Other combinations, such as CCB + diuretic, also have evidence from RCTs supporting their use. These are much less widely available as SPCs and do not include blockade of the RAS, which may be desirable in many patient groups.

Beta-blockers in combination should be preferentially used when there is a specific clinical indication for their use (e.g. in patients with symptomatic angina, for patients requiring heart rate control, post-myocardial infarction, chronic HFrEF, and as an alternative to ACE inhibitors or ARBs in younger hypertensive women planning pregnancy or of child-bearing potential). SPCs of beta-blockers with an ACE inhibitor, CCB, or diuretic are available.

# 7.5.2.2 Rationale for initial two-drug combination therapy for most patients

As discussed above and with the emphasis in these Guidelines on achieving a BP target in most patients of <130/80 mmHg, the majority of patients will require combination therapy. Initial combination therapy is invariably more effective at BP lowering than monotherapy, indeed even low-dose combination therapy is usually more effective than maximal dose monotherapy.<sup>341</sup> Furthermore, the combination of medications targeting multiple mechanisms, such as blocking the

RAS as well as inducing vasodilatation and/or diuresis, reduces the heterogeneity of the BP response to initial treatment and provides a steeper dose response than is observed with escalating doses of monotherapy.<sup>342</sup> Finally, two-drug combinations as initial therapy have been shown to be safe and well tolerated, with no or only a small increase in the risk of hypotensive episodes,<sup>341</sup> even when given to patients with grade 1 hypertension,<sup>343</sup> in which adverse events leading to treatment discontinuation are infrequent.<sup>294</sup>

Although no RCT has compared major CV outcomes between initial combination therapy and monotherapy, observational evidence suggests that the time taken to achieve BP control is an important determinant of clinical outcomes, especially in higher risk patients, with a shorter time to control associated with lower risk.<sup>344</sup> Furthermore, there is evidence from the more general hypertensive population that, compared with patients on initial monotherapy, those who start treatment with a two-drug combination exhibit more frequent BP control after 1 year. 341,345 This is probably because initial combination treatment is associated with a better long-term adherence to the prescribed treatment regimen<sup>346</sup> and because initial two-drug administration prevents therapeutic inertia (i.e. reluctance or failure to upgrade treatment from one to more drugs when BP is uncontrolled).<sup>347</sup> Studies from very large hypertension cohorts in usual care have shown that initial combination treatment results in reduced treatment discontinuation and a lower risk of CV events than initial monotherapy followed by the traditional stepped-care approach. 312,346 The usual-care settings for these studies may be especially relevant to study the true impact of treatment strategies on adherence and therapeutic inertia, because this can be difficult to replicate in a conventional RCT in which the motivation of the clinical staff and patients, and the monitoring of treatment, are very different from usual care. In this regard, the outcome of these real-life studies of the impact of initial combination therapy on adherence, BP control, and CV outcomes may be especially relevant.<sup>348</sup>

A consideration in the current Guidelines was to persist with the current stepped-care approach to BP treatment, which has been interpreted as recommending monotherapy as initial therapy for most patients, reflecting current practice. In fact, the previous Guidelines did acknowledge the possibility of initial combination therapy for patients with grade 2 or 3 hypertension, or patients at high or very high risk. In other words, initial monotherapy was only recommended for grade 1 hypertension and low- or moderate-risk patients. Thus, in reality, the shift in emphasis in this new guidance is subtle. However, normalizing the concept of initiating therapy with a two-drug combination for most patients with hypertension is likely to have a major effect on clinical practice and the speed and quality of BP control. We acknowledge that some low- or moderate-risk patients with grade 1 hypertension may achieve their BP target with monotherapy, but this is unlikely in patients with an initial SBP >150 mmHg who would require a BP reduction of  $\geq$ 20 mmHg. Moreover, the possibility of starting with a low-dose combination of two antihypertensive drugs, even in grade 1 hypertensive patients with low-moderate-risk, is supported by the reduction of CV events obtained by combination therapy in the upper tertile (grade 1 hypertension) in the HOPE-3 trial.<sup>212</sup> In patients with high-normal BP and a high CV risk or in frail older patients, treatment initiation with monotherapy may be appropriate in the former because only a small BP reduction may be required to achieve the BP target, and in the

latter because in older patients baroreflex sensitivity is frequently impaired and the risk of hypotension is greater.

7.5.2.3 Uptitration of treatment to three-drug combination therapy Studies suggest that two-drug combination therapy will control BP in approximately two-thirds of patients. The patients whose BP is not controlled by two-drug combination therapy, the logical option is to increase treatment to three-drug combination therapy: usually a RAS blocker, a CCB, and a diuretic. Studies suggest that a three-drug combination should control BP in >80% of patients. This rate of BP control is much greater than the current rate of BP control across Europe in treated hypertensive patients. We do not recommend three-drug combinations as initial therapy.

# 7.5.2.4 Rationale for single-pill combination therapy as usual therapy for hypertension

The 2013 ESH/ESC Guidelines <sup>17</sup> favoured the use of combinations of two antihypertensive drugs in a single pill, because reducing the number of pills to be taken daily improves adherence and increases the rate of BP control. 346,351 This recommendation is endorsed by the current Guidelines. It is further supported by data from recent studies using various methods to assess adherence to treatment, including the quantification of antihypertensive drugs in urine and blood, 352,353 and estimates such as pill counting or prescription refills, which, although indirect, allow the measurement of adherence on a prolonged basis, thereby accounting for its time-variable nature. 347,354 These studies have unequivocally shown a direct inverse relationship between the number of pills and the likelihood of adherence. This approach is now facilitated by the availability of several SPCs with a range of dosages, which eliminates the often-stated disadvantage of SPC therapy (i.e. the inability to increase the dose of one drug independently of the other). It is also convenient that the most widely available SPCs mirror the major drug class combinations recommended by these Guidelines. The major advantage of an SPC as the usual therapeutic approach for hypertension is that patients can progress from 1, 2, or 3 drug treatments whilst remaining on a simple treatment regimen with a single pill throughout, increasing the likelihood of adherence to therapy and achieving BP control. Such an approach has the potential to double BP control rates in treated patients from the present low level of  $\sim$ 40%. Although, at present, the availability of two-drug SPCs is largely limited to a RAS blocker with either a CCB or diuretic, it would be desirable to see the development of an expanded range of low-cost SPCs in different drug formulations, tailored to different clinical requirements.

Polypills have also emerged as SPCs (i.e. a fixed-dose combination of one or more antihypertensive agents with a statin and low-dose aspirin), with the rationale that hypertensive patients are often at sufficient CV risk to benefit from statin therapy. Studies of bioequivalence suggest that when combined in the polypill, different agents maintain all or most of their expected effect. Furthermore, studies performed in the setting of secondary prevention, particularly in patients with a previous myocardial infarction, have shown that use of the polypill is accompanied by a better adherence to treatment compared with separate medications. The ESC Guidelines for the management of myocardial infarction suggest that the use of the polypill may be considered to improve long-term adherence to prescribed therapy (class Ilb, level B). No data are available for primary prevention in

patients with hypertension. Nevertheless, the advantage of treatment simplification and adherence suggests that use of the polypill may be considered in patients with hypertension as substitution therapy, when the need and effectiveness of each polypill component has been previously established by their administration in separate tablets. 355

### 7.5.2.5 Further uptitration of antihypertensive therapy

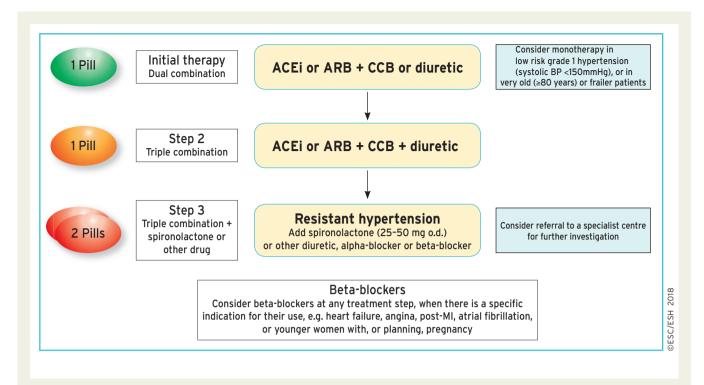
When BP remains uncontrolled with three-drug combination therapy, the patient is classified as having resistant hypertension, assuming that secondary causes of hypertension and poor adherence to treatment have been excluded, and that the elevation in BP has been confirmed by repeated office BP measurement, ABPM, or HBPM (see section 8.1). Such patients should be considered for specialist evaluation. Additional treatment options include the addition of low-dose spironolactone (25 - 50 mg daily)<sup>310</sup> or another additional diuretic therapy [higherdose amiloride 10 - 20 mg daily,<sup>357</sup> higher dose thiazide or thiazide-like diuretics, loop diuretics in patients with significant renal impairment (eGFR <45 mL/min/m²), beta-blockers, alpha-blockers, centrally acting agents (e.g. clonidine), or, rarely, minoxidil] (see section 8.1).

### 7.5.3 The drug treatment algorithm for hypertension

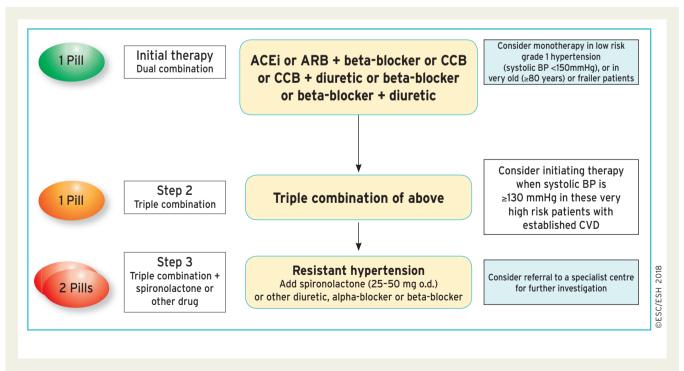
Reflecting on the evidence above, and recognizing the urgent need to address the factors contributing to the poor control of BP in treated hypertensive patients (see section 7.5.1), this drug treatment algorithm has been developed to provide a simple and pragmatic treatment recommendation for the treatment of hypertension, based on a few key recommendations:

- The initiation of treatment in most patients with an SPC comprising two drugs, to improve the speed, efficiency, and predictability of BP control
- (2) Preferred two-drug combinations are a RAS blocker with a CCB or a diuretic. A beta-blocker in combination with a diuretic or any drug from the other major classes is an alternative when there is a specific indication for a beta-blocker, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.
- (3) Use monotherapy for low-risk patients with stage 1 hypertension whose SBP is <150 mmHg, very high-risk patients with high–normal BP, or frail older patients.
- (4) The use of a three-drug SPC comprising a RAS blocker, a CCB, and a diuretic if BP is not controlled by a two-drug SPC.
- (5) The addition of spironolactone for the treatment of resistant hypertension, unless contraindicated (see section 8.1.4).
- (6) The use of other classes of antihypertensive drugs in the rare circumstances in which BP is not controlled by the above treatments.
- (7) Information on availability and recommended doses of individual drugs, as well as SPCs and free combinations, can be found in national formularies.

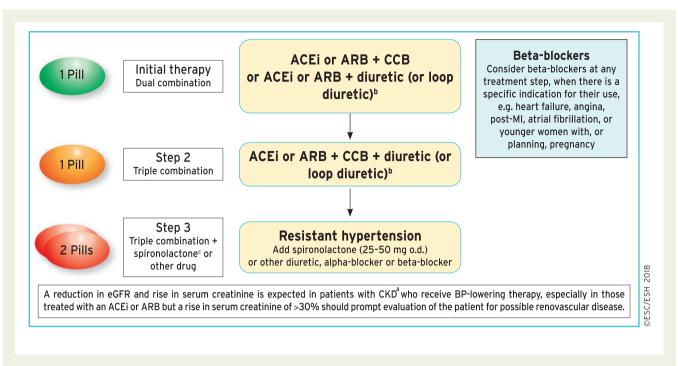
This treatment algorithm focuses on the five major classes of drugs: ACE inhibitors, ARBs, CCBs, thiazide or thiazide-like diuretics, and beta-blockers. The algorithm recommends initial therapy for most patients with a two drug-combination, ideally as an SPC. Variations from the core drug treatment algorithm for uncomplicated hypertension shown in *Figure 4* are specified in *Figures 5* to 8. Recommended BP target ranges for treated hypertension are shown in *Table 23*.



**Figure 4 Core drug treatment strategy for uncomplicated hypertension.** The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.



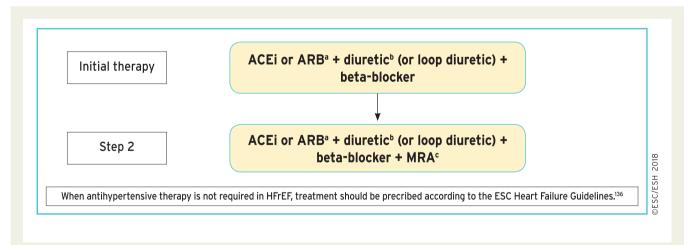
**Figure 5 Drug treatment strategy for hypertension and coronary artery disease.** ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CVD = cardiovascular disease; o.d. = omni die (every day).



**Figure 6 Drug treatment strategy for hypertension and chronic kidney disease.** ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; o.d. = omni die (every day).

<sup>a</sup>CKD is defined as an eGFR <60 mL/min/1.72 m<sup>2</sup> with or without proteinuria.

<sup>&</sup>lt;sup>c</sup>Caution: risk of hyperkalaemia with spironolactone, especially when eGFR is <45 mL/min/1.72 m<sup>2</sup> or baseline K<sup>+</sup>  $\geq$ 4.5 mmol/L.



**Figure 7 Drug treatment strategy for hypertension and hear failure with reduced ejection fraction.** Do not use non-dihydropyridine CCBs (e.g. verapamil or diltiazem). ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; ESC = European Society of Cardiology; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.
<sup>a</sup>Consider an angiotensin receptor/neprilysin inhibitor instead of ACEi or ARB per ESC Heart Failure Guidelines. <sup>136</sup>

 $<sup>^{</sup>b}$ Use loop diuretics when eGFR is <30 mL/min/1.72 m $^{2}$ , because thiazide/thiazide-like diuretics are much less effective/ineffective when eGFR is reduced to this level.

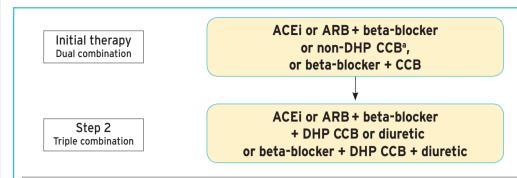
<sup>&</sup>lt;sup>b</sup>Diuretic refers to thiazide/thiazide-like diuretic. Consider a loop diuretic as an alternative in patients with oedema.

<sup>&</sup>lt;sup>c</sup>MRA (spironolactone or eplerenone).

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Add oral anticoagulation when indicated according to the CHA2DS2-VASc score, unless contraindicated.

<sup>a</sup>Routine combination of beta-blockers with non-dihydropyridine CCBs (e.g. verapamil or diltiazem) is not recommended due to a potential marked reduction in heart rate.

Figure 8 Drug treatment strategy for hypertension and atrial fibrillation. ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CCB = calcium channel blocker;  $CHA_2DS_2-VASc = CHA_2DS_2-VASc = Cardiac$  failure, Hypertension, Age  $\geq$ 75 (Doubled), Diabetes, Stroke (Doubled) – Vascular disease, Age 65–74 and Sex category (Female); DHP = dihydropyridine. aNon-DHP CCB (non-DHP CCB, e.g. verapamil or diltiazem).

Table 23 Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)				Office DBP treatment target range (mmHg)	
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke <sup>a</sup> /TIA	
18 - 65 years	Target to 130 or lower if tolerated Not <120	Target to 130 or lower if tolerated Not <120	Target to <140 to 130 if tolerated	Target to 130 or lower if tolerated Not <120	Target to 130 or lower if tolerated Not <120	70–79
65 - 79 years <sup>b</sup>	Target to 130-139 if tolerated	Target to 130-139	Target to 130-139 if tolerated	Target to 130-139 if tolerated	Target to 130-139 if tolerated	70–79
≥80 years <sup>b</sup>	Target to 130-139 if tolerated	Target to 130-139	Target to 130-139	Target to 130-139 if tolerated	Target to 130-139 if tolerated	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

The drug treatment strategy for patients with hypertension should be based on the algorithm shown (Figures 4 to 8), unless there are contraindications to these drugs (Table 20), or

concomitant conditions or diseases are present that require specific modification of the drugs, as outlined in the recommendations below.

<sup>&</sup>lt;sup>a</sup>Refers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

<sup>&</sup>lt;sup>b</sup>Treatment decisions and blood pressure targets may need to be modified in older patients who are frail and independent.

# Drug treatment strategy for hypertension

Recommendations	Class <sup>a</sup>	Levelb
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies. <sup>2</sup>	1	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used. 233,318,327,329,341–345	1	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control. 300,341	1	А
It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg). 342,346,351	1	В
It is recommended that if BP is not controlled <sup>c</sup> with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC. <sup>349,350</sup>	1	A
It is recommended that if BP is not controlled <sup>c</sup> with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker. <sup>310</sup>	1	В
The combination of two RAS blockers is not recommended. <sup>291,298,299</sup>	Ш	А

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CV = cardiovascular; RAS = renin-angiotensin system; RCT = randomized controlled trial; SBP = systolic blood pressure; SPC = single-pill combination.

# 7.6 Device-based hypertension treatment

Various device-based therapies have emerged, principally targeted at the treatment of resistant hypertension. These are discussed below.

# 7.6.1 Carotid baroreceptor stimulation (pacemaker and stent)

Carotid baroreceptor stimulation or baroreflex amplification therapy—externally via an implantable pulse generator or internally via an implantable device designed to increase the strain on the carotid bulb—can lower BP in patients with resistant hypertension. An RCT with the first generation of an implantable pulse generator showed sustained BP-lowering efficacy (and sympathetic nervous system inhibition), but with some concerns about procedural and longer term safety. A second-generation unilateral device has been developed to improve safety and sustained efficacy. A propensity scorematched comparison of the first- and second-generation systems revealed that BP at 12 months post-implantation was similar, with a better safety profile for the second-generation device. <sup>359</sup> However, no RCT is currently available with this second-generation device. Another consideration is that implantation is costly and requires a

complex surgical intervention. This has led to the development of an endovascular carotid baroreflex amplification device using a dedicated stent-like device designed to stretch the carotid bulb and increase baroreflex sensitivity. Preliminary data in humans have shown evidence of BP-lowering efficacy of this new approach, but data from ongoing RCTs are needed to definitively understand its longer-term efficacy and safety.

### 7.6.2 Renal denervation

The rationale for renal denervation lay with the importance of sympathetic nervous system influences on renal vascular resistance, renin release, and sodium reabsorption, <sup>361</sup> the increased sympathetic tone to the kidney and other organs in hypertensive patients, <sup>361</sup> and the pressor effect of renal afferent fibres documented in experimental animals. <sup>362</sup> Catheter-based renal denervation using radiofrequency, ultrasound, or perivascular injection of neurotoxic agents such as alcohol has been introduced as a minimally invasive treatment option for patients with resistant hypertension. <sup>363</sup> However, the clinical evidence in support of renal denervation as an effective BP-lowering technique is conflicting. Several observational studies and national and international registries <sup>364</sup> support the BP-lowering efficacy of

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

<sup>&</sup>lt;sup>c</sup>Adherence should be checked.

renal denervation originally reported in the Symplicity HTN-1 and HTN-2 trials.<sup>365</sup> A reduction in sympathetic activity following renal denervation has also been observed. 366 However, two RCTs with a sham procedure control<sup>367,368</sup> failed to document the superiority of renal denervation compared with the sham procedure in reducing BP, but did confirm the safety of the procedure. Another RCT, the Renal Denervation for Hypertension (DENERHTN) trial, 369 showed the superiority of renal denervation in combination with optimized pharmacotherapy compared with pharmacotherapy alone. The PRAGUE-15 study<sup>370</sup> documented similar effects between renal denervation and optimized pharmacotherapy (mainly by adding spironolactone) with respect to BP-lowering efficacy; however, the latter was associated with more side effects and high discontinuation rates. Beyond resistant hypertension, interim data in the first 80 patients treated with renal denervation but with no background antihypertensive therapy showed a modest effect of renal denervation vs. sham control on 24 h ambulatory BP after 3 months. 366 This study

Evaluating the efficacy of renal denervation has been challenging because the procedure needs to be applied to a population with a high probability of BP response. This is complicated by (i) the complex pathophysiology of hypertension, (ii) the lack of clinically applicable measures of sympathetic activity, (iii) the absence of predictors of the long-term BP response following renal denervation, and (iv) the absence of reliable markers of procedural success to immediately establish whether denervation has been achieved.<sup>371</sup> There is evidence indicating that isolated systolic hypertension, characterized by increased aortic stiffness, is associated with a limited response to renal denervation<sup>372,373</sup> and baroreceptor stimulation (see above). Except for rare problems related to the catheterization procedure (access site complications, vessel dissection, etc.), no major complications or deterioration of renal function have been reported.

Major uncertainties remain as to the clinical role of renal denervation outside of clinical studies, which should be performed in carefully selected patients at specialist hypertension centres and by experienced operators.

# 7.6.3 Creation of an arteriovenous fistula

The central iliac arteriovenous anastomosis creates a fixed-calibre (4 mm) conduit between the external iliac artery and vein using a stentlike nitinol device (ROX arteriovenous coupler). 374,375 Device deployment can be verified and is reversible, resulting in the diversion of arterial blood (0.8-1 L/min) into the venous circuit with immediate, verifiable reductions in BP. 374,375 The BP-lowering effect of arteriovenous anastomosis was first observed in a study of patients with chronic obstructive pulmonary disease (COPD), in whom a moderate improvement in the 6 min walking test was shown. <sup>376</sup> In the ROX CONTROL HTN trial, patients with resistant hypertension were randomized to receive either standard care or insertion of an arteriovenous coupler in combination with standard care.<sup>377</sup> At 6 months, office and ambulatory BP were significantly reduced in the coupler group compared with the control group. Some important safety aspects need to be considered. Ipsilateral venous stenosis, which needed venoplasty and/or stenting, occurred in 29% of patients. There were no reports of right heart failure or high-output cardiac failure after device implantation over the short-term, but longer follow-up is clearly needed. 377,378

### 7.6.4 Other devices

The carotid body is located at the bifurcation of the common carotid. It is innervated by nerve fibres from the vagus nerve through the cervical ganglion and the carotid sinus nerve. The Stimulation of the carotid body drives sympathetic tone, resulting in an increase in BP and minute ventilation. Surgical resection of the carotid body is associated with reductions in BP and sympathetic overactivity in patients with heart failure. Devices for endovascular carotid body modification by ultrasound-guided ablation have been developed and are currently under investigation.

In summary, device-based therapy for hypertension is a fast-moving field. Further sham-controlled studies are needed before device-based therapies can be recommended for the routine treatment of hypertension outside of the framework of clinical trials.

Recommendation	Classa	Level <sup>b</sup>
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available. 367,368	ш	В

# 8 Hypertension in specific circumstances

# 8.1 Resistant hypertension

# 8.1.1 Definition of resistant hypertension

Hypertension is defined as resistant to treatment when the recommended treatment strategy fails to lower office SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively, and the inadequate control of BP is confirmed by ABPM or HBPM in patients whose adherence to therapy has been confirmed. The recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs, which should include a diuretic, typically an ACE inhibitor or an ARB, and a CCB. Pseudo-resistant hypertension (see below) and secondary causes of hypertension should also have been excluded (see section 8.2). The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed Chapter 44.9 Hypertension in specific conditions/ co-morbidities and Chapter 44.10 Hypertension in special situations.

Prevalence studies of resistant hypertension have been limited by variation in the definition used, and reported prevalence rates range from 5-30% in patients with treated hypertension. After applying a strict definition (see above) and having excluded causes of pseudoresistant hypertension (see section 8.1.2), the true prevalence of resistant hypertension is likely to be <10% of treated patients. Patients with resistant hypertension are at higher risk of HMOD, CKD, and premature CV events.  $^{382}$ 

### 8.1.2 Pseudo-resistant hypertension

Several possible causes of pseudo-resistant hypertension should be evaluated and ruled out before concluding that the patient has resistant hypertension:

- (1) **Poor adherence to prescribed medicines** is a frequent cause of pseudo-resistant hypertension, occurring in ≤50% of patients assessed by therapeutic drug monitoring, and is directly related to the number of tablets prescribed<sup>315</sup> (see section 10).
- (2) White-coat phenomenon (in which office BP is elevated but BP is controlled at ABPM or HBPM) is not uncommon in these patients, hence the recommendation to confirm office hypertension with ABPM or HBPM before confirming the diagnosis of resistant hypertension.
- (3) **Poor office BP measurement technique**, including the use of cuffs that are too small relative to the arm circumference, can result in a spurious elevation of BP.
- (4) Marked brachial artery calcification, especially in older patients with heavily calcified arteries.
- (5) Clinician inertia, resulting in inadequate doses or irrational combinations of BP-lowering drug therapies.

### Other causes of resistant hypertension

- (1) Lifestyle factors, such as obesity or large gains in weight, excessive alcohol consumption, and high sodium intake.
- (2) Intake of vasopressor or sodium-retaining substances, drugs prescribed for conditions other than hypertension, some herbal

- remedies, or recreational drug use (cocaine, anabolic steroids, etc.) (see *Table 24*).
- (3) Obstructive sleep apnoea (usually, but not invariably, associated with obesity).
- (4) Undetected secondary forms of hypertension (see section 8.2).
- (5) Advanced HMOD, particularly CKD or large-artery stiffening.

Resistant hypertension is associated with older age (especially >75 years), male sex, black African origin, higher initial BP at diagnosis of hypertension, highest BP ever reached during the patient's lifetime, frequent outpatient visits, obesity, diabetes, atherosclerotic disease and HMOD, CKD, and a Framingham 10 year coronary risk score >20%. 383,384

### 8.1.3 Diagnostic approach to resistant hypertension

Diagnosis of resistant hypertension requires detailed information about:

- The patient's history, including lifestyle characteristics, alcohol and dietary sodium intake, interfering drugs or substances, and sleep history.
- (2) The nature and dosing of the antihypertensive treatment.
- (3) A physical examination, with a particular focus on determining the presence of HMOD and signs of secondary hypertension.
- (4) Confirmation of treatment resistance by out-of-office BP measurements (i.e. ABPM or HBPM).

Table 24 Resistant hypertension characteristics, secondary causes, and contributing factors (adapted from reference<sup>385</sup>)

Characteristics of patients with resistant hypertension	Causes of secondary resistant hypertension	Drugs and substances that may cause raised BP
Older age (especially >75 years) Obesity More common in black people Excess dietary sodium intake High baseline BP and chronicity of uncontrolled hypertension	More common causes  Primary hyperaldosteronism  Atherosclerotic renovascular disease  Sleep apnoea  CKD	Prescribed drugs  Oral contraceptives  Sympathomimetic agents (e.g. decongestants in proprietary cold remedies)  Non-steroidal anti-inflammatory drugs  Cyclosporin  Erythropoietin  Steroids (e.g. prednisolone and hydrocortisone)  Some cancer therapies
<ul> <li>Concomitant disease</li> <li>HMOD: LVH and/or CKD</li> <li>Diabetes</li> <li>Atherosclerotic vascular disease</li> <li>Aortic stiffening and isolated systolic hypertension</li> </ul>	<ul> <li>Uncommon causes</li> <li>Phaeochromocytoma</li> <li>Fibromuscular dysplasia</li> <li>Aortic coarctation</li> <li>Cushing's disease</li> <li>Hyperparathyroidism</li> </ul>	Non-prescription drugs  Recreational drugs (e.g. cocaine, amphetamines, and anabolic steroids)  Excessive liquorice ingestion  Herbal remedies (e.g. ephedra and ma huang)

BP = blood pressure; CKD = chronic kidney disease; HMOD = hypertension-mediated organ damage; LVH = left ventricular hypertrophy.

(5) Laboratory tests to detect electrolyte abnormalities (hypokalaemia), associated risk factors (diabetes), organ damage (advanced renal dysfunction), and secondary hypertension.

(6) Confirmation of adherence to BP-lowering therapy.

Patients should be screened for a secondary cause of hypertension, especially primary aldosteronism<sup>386</sup> or atherosclerotic renal artery stenosis, particularly in older patients or patients with CKD. Poor adherence to treatment should be considered, but its identification may be challenging in routine clinical practice.<sup>387</sup> Some methods are easy to use but of limited value (e.g. standardized questionnaires), whereas others, such as drug screening of urine or blood, show considerable promise but are not yet widely available.<sup>388</sup> Other methods include the measurement of BP after directly observed treatment intake,<sup>389</sup> which has been used in clinical trials,<sup>390</sup> but may be more difficult to implement in routine clinical practice.

### 8.1.4 Treatment of resistant hypertension

Effective treatment combines lifestyle changes (especially the reduction of sodium intake), discontinuation of interfering substances, and the sequential addition of antihypertensive drugs to the initial triple therapy. Ultimately, replacing all current drugs by a simpler treatment regimen using SPC treatment is recommended to reduce pill burden and improve adherence to treatment. The optimal drug treatment of resistant hypertension has been poorly studied. The most effective strategy seems to be additional diuretic treatment to decrease volume overload, together with the restriction of salt intake, particularly in patients with CKD. BP control may be improved by increasing the dose of the existing diuretic or by switching to a more potent thiazide-like diuretic (chlorthalidone or indapamide). A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is <30 mL/ min. Although resistant hypertension may show a BP reduction if the existing diuretic dose is further increased, most patients require the administration of additional drugs. There is growing evidence to suggest that the fourth-line treatment should involve a blockade of the biological effects of aldosterone through the use of MRAs<sup>391</sup> (spironolactone up to 50 mg/day), as shown in the PATHWAY 2 study<sup>357</sup> and supported by other studies and their meta-analysis. 392-394 Not all patients will be able to tolerate spironolactone due to antiandrogenic side effects resulting in breast tenderness or gynaecomastia (in  $\sim$ 6%), impotence in men, and menstrual irregularities in women. Moreover, the efficacy and safety of spironolactone for the treatment of resistant hypertension has not yet been established in patients with significant renal impairment. As such, the use of spironolactone for resistant hypertension should usually be restricted to patients with an eGFR ≥45 mL/min and a plasma potassium concentration of 4.5 mmol/L. Moreover, electrolytes and eGFR should be monitored soon after initiation and at least annually thereafter. On theoretical grounds, alternative additional diuretic therapy to spironolactone (when it is not tolerated due to androgen-like side effects) could include the MRA eplerenone (50-100 mg/day). Amiloride (10-20 mg/day) has recently been shown to be as effective as spironolactone 25-50 mg daily) in reducing BP in the PATHWAY2 study.<sup>357</sup> It is emphasized that the same cautions about the use of these agents should be considered in patients with reduced eGFR and baseline potassium levels >4.5 mmol/L. The PATHWAY-2 study also evaluated bisoprolol (5 - 10 mg/day) or doxazosin modified

release (4-8 mg/day) as alternatives to spironolactone. Neither was as effective as spironolactone, but they did reduce BP significantly vs. placebo when added to background treatment in resistant hypertension.  $^{310}$  Thus, bisoprolol and doxazosin have an evidence base for the treatment of resistant hypertension when spironolactone is contraindicated or not tolerated. Direct vasodilators, such as hydralazine or minoxidil, are infrequently used because they may cause severe fluid retention and tachycardia.

New BP-lowering drugs (nitric oxide donors, vasopressin antagonists, aldosterone synthase inhibitors, neutral endopeptidase inhibitors, and endothelin antagonists) are all under investigation. 388

# Resistant hypertension

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when:  • Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively; and  • The inadequate control of BP has been confirmed by ABPM or HBPM; and  • After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.	ı	С
Recommended treatment of resistant hypertension is:  Reinforcement of lifestyle measures, especially sodium restriction. 395  Addition of low-dose spironolactone to existing treatment; 310,392,394  Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone, amiloride, a higher-dose thiazide/thiazide-like diuretic, or a loop diuretic; 357  Or the addition of bisoprolol or doxazosin. 310	ı	В

ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; DBP = diastolic blood pressure; HBPM = home blood pressure monitoring.

°When spironolactone is not tolerated, replace with amiloride or eplerenone. The use of these drugs should be restricted to patients with an estimated glomerular filtration rate  $\geq$ 45 mL/min and a plasma potassium concentration of  $\leq$  4.5 mmol/L, because of the risk of hyperkalaemia.

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

bLevel of evidence.

 $<sup>^{\</sup>rm d}$ A loop diuretic should replace thiazides/thiazide-like diuretics if the estimated glomerular filtration rate is <30 mL/min.

# 8.2 Secondary hypertension

Secondary hypertension is hypertension due to an identifiable cause, which may be treatable with an intervention specific to the cause. A high index of suspicion and early detection of secondary causes of hypertension are important because interventions may be curative, especially in younger patients [e.g. corrective surgery for aortic coarctation, renal angioplasty in younger patients with renal artery fibromuscular dysplasia, reversal of an endocrine cause of hypertension (e.g. by removal of an adrenal adenoma), or drug treatment of a monogenic disorder affecting a specific drug-sensitive ion channel (e.g. selective use of amiloride in Liddle's syndrome)]. Interventions that treat the cause of secondary hypertension later in life are less likely to be curative (i.e. remove the need for antihypertensive medication) because longstanding hypertension results in vascular and other organ damage that sustains the elevated BP, but intervention is still important because it will often result in much better BP control with less medication.

The prevalence of secondary hypertension is reported to be  $5-15\%^{396}$  of people with hypertension. Screening all hypertensive patients for secondary hypertension is not feasible or cost-effective; however, there are some general patient characteristics that suggest those more likely to have secondary hypertension and in whom screening should be considered after confirming that BP is elevated with ABPM (*Table 25*).

It is beyond the scope of these Guidelines to describe the detailed clinical management of specific causes of secondary hypertension. However, the commoner causes of secondary hypertension, clinical history, and screening tests are described in *Table 26*, and the typical age distribution of these causes of secondary hypertension is shown in *Table 27*. Review of these tables demonstrates that most screening can be undertaken with blood and urine tests, abdominal ultrasound, and echocardiography. Referral to a specialist centre is recommended for additional investigations to confirm a suspected diagnosis of secondary hypertension and for clinical management. Other causes of secondary

hypertension due to drugs and substances, and rarer monogenic causes, are described below and are summarized in *Tables 28 and 29*.

# 8.2.1 Drugs and other substances that may cause secondary hypertension

Medications and other substances may cause a sufficient increase in BP to raise the suspicion of secondary hypertension<sup>397</sup> (*Table 28*). Consequently, a careful drug history is important when considering a diagnosis of secondary hypertension. Moreover, other commonly used drugs such as non-steroidal anti-inflammatory drugs or glucocorticoids can antagonize the BP-lowering effect of antihypertensive medications in patients treated for hypertension, and may contribute to a loss of BP control.

# 8.2.2 Genetic causes of secondary hypertension

Genetic causes of secondary hypertension are usually due to singlegene disorders (see section 6). 194,195 They are rare but important causes of secondary hypertension because identifying the cause can point to a specific drug treatment (*Table 29*). 194,195 Common features of these genetic disorders are that they usually present with hypertension in children, adolescents, or young adults, and most monogenic disorders induce hypertension by increasing the renal tubular reabsorption of sodium. Thus, they are usually associated with a suppressed plasma renin concentration (PRC) or plasma renin activity (PRA), which is unusual in younger patients and especially those treated with antihypertensive medications (e.g. RAS blockers, CCBs, or diuretics), that would be expected to increase PRC or PRA. Thus, the finding of a suppressed PRC or PRA, especially whilst taking these drugs, should raise the suspicion of secondary hypertension due a salt-retaining state. Importantly, beta-blockers in particular, but also non-steroidal anti-inflammatory drugs, alpha-methyl dopa, or clonidine, suppress PRC and PRA. These drugs should be discontinued (if clinically feasible) for at least 2 weeks before measuring PRC or PRA.

 Table 25
 Patient characteristics that should raise the suspicion of secondary hypertension

# Characteristic Younger patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood Acute worsening hypertension in patients with previously documented chronically stable normotension Resistant hypertension (see section 8.1) Severe (grade 3) hypertension or a hypertension emergency (see section 8.3) Presence of extensive HMOD Clinical or biochemical features suggestive of endocrine causes of hypertension or CKD

CKD = chronic kidney disease; HMOD = hypertension-mediated organ damage.

Symptoms suggestive of phaeochromocytoma or family history of phaeochromocytoma

Table 26 Common causes of secondary hypertension

Cause	Prevalence in hypertensive patients	Suggestive symptoms and signs	Screening Investigations
Obstructive sleep apnoea	5–10%	Snoring; obesity (can be present in non- obese); morning headache; daytime somnolence	Epworth score and ambulatory polygraphy
Renal parenchymal disease	2–10%	Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD	Plasma creatinine and electrolytes, eGFR; urine dipstick for blood and pro- tein, urinary albumin:creatinine ratio; renal ultrasound
Renovascular disease			
Atherosclerotic renovascular disease	1–10%	Older; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit	Duplex renal artery Doppler or CT angiography or MR angiography
Fibromuscular dysplasia		Younger; more common in women; abdominal bruit	
Endocrine causes			
Primary Aldosteronism	5 - 15%	Mostly asymptomatic; muscle weakness (rare)	Plasma aldosterone and renin, and aldosterone:renin ratio; hypokalaemia (in a minority): note hypokalaemia can depress aldosterone levels
Phaeochromocytoma	<1%	Episodic symptoms (the 5 'Ps'): paroxysmal hypertension, pounding headache, perspiration, palpitations, and pallor; labile BP; BP surges precipitated by drugs (e.g. betablockers, metoclopramide, sympathomimetics, opioids, and tricyclic antidepressants)	Plasma or 24 h urinary fractionated metanephrines
Cushing's syndrome	<1%	Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use	24 h urinary-free cortisol
Thyroid disease (hyper- or hypothyroidism)	1 - 2%	Signs and symptom of hyper- or hypothyroidism	Thyroid function tests
Hyperparathyroidism	<1%	Hypercalcaemia, hypophosphataemia	Parathyroid hormone, Ca <sup>2+</sup>
Other causes			
Coarctation of the aorta	<1%	Usually detected in children or adolescence; different BP (≥20/10 mmHg) between upper—lower extremities and/or between right—left arm and delayed radial-femoral femoral pulsation; low ABI interscapular ejection murmur; rib notching on chest X-ray	Echocardiogram

ABI = ankle-brachial index; BP = blood pressure; CKD = chronic kidney disease; CT = computed tomography; eGFR = estimated glomerular filtration rate; MR = magnetic resonance; PAD = peripheral artery disease.

Table 27 Incidence and typical causes of secondary hypertension according to age

Age group	Per cent with underlying cause	Typical causes
Young children (<12 years)	70 - 85	<ul><li>Renal parenchymal disease</li><li>Coarctation of the aorta</li><li>Monogenic disorders</li></ul>
Adolescents (12–18 years)	10–15	<ul><li>Renal parenchymal disease</li><li>Coarctation of the aorta</li><li>Monogenic disorders</li></ul>
Young adults (19–40 years)	5–10	<ul> <li>Renal parenchymal disease</li> <li>Fibromuscular dysplasia (especially in women)</li> <li>Undiagnosed monogenic disorders</li> </ul>
Middle-aged adults (41–65 years)	5–15	<ul> <li>Primary aldosteronism</li> <li>Obstructive sleep apnoea</li> <li>Cushing's syndrome</li> <li>Phaeochromocytoma</li> <li>Renal parenchymal disease</li> <li>Atherosclerotic renovascular disease</li> </ul>
Older adults (>65 years)	5–10	<ul> <li>Atherosclerotic renovascular disease</li> <li>Renal parenchymal disease</li> <li>Thyroid disease</li> </ul>

 Table 28
 Medications and other substances that may increase blood presssure

Medication/substance			
Oral contraceptive pill	Especially oestrogen containing; cause hypertension in $\sim$ 5% of women, usually mild but can be severe		
Diet pills	For example, phenylpropanolamine and sibutramine		
Nasal decongestants	For example, phenylephrine hydrochloride and naphazoline hydrochloride		
Stimulant drugs	Amphetamine, cocaine, and ecstasy; these substances usually cause acute rather than chronic hypertension		
Liquorice	Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism		
Immunosuppressive medications	For example, cyclosporin A (tacrolimus has less effect on BP and rapamycin has almost no effect on BP) and steroids (e.g. corticosteroids and hydrocortisone)		
Antiangiogenic cancer therapies	Antiangiogenic drugs such as VEGF inhibitors (e.g. bevacizumab), tyrosine kinase inhibitors (e.g. sunitinib), and sorafenib have been reported to increase BP		
Other drugs and substances that may raise BP	Anabolic steroids, erythropoietin, non-steroidal anti-inflammatory drugs, and herbal remedies (e.g. ephedra and ma huang)		

 $\mbox{BP = blood pressure; VEGF = vascular endothelial growth factor.} \label{eq:BP}$ 

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Table 29 Rare genetic causes of secondary hypertension

Condition	Phenotype	Mechanism and effect
Liddle syndrome	Hypokalaemia, metabolic alkalosis, low PRA or PRC, low PAC	Increased renal tubular ENaC activity: responds to treatment with amiloride
Apparent mineralocorticoid excess	Hypokalaemia, metabolic alkalosis, low PRA or PRC, low PAC	Decreased 11β-dehydrogenase isoenzyme 2
Gordon syndrome	Hyperkalaemia, metabolic acidosis, low PRA or PRC, low PAC	Overactivity of sodium chloride cotransporter
Geller syndrome	Pregnancy-exacerbated hypertension, low PRA or PRC, low PAC	Agonist effect of progesterone on the mineralocorticoid receptor
Glucocorticoid remediable hypertension	Hypokalaemia, metabolic alkalosis, low PRC or PRA, and increased PAC	Chimeric CYP11β1 to CYP11β2 gene: response to treatment with glucocorticoids

ENaC = epithelial sodium channel; PAC = plasma aldosterone concentration; PRA = plasma renin activity; PRC = plasma renin concentration.

# 8.3 Hypertension urgencies and emergencies

Hypertension emergencies are situations in which severe hypertension (grade 3) is associated with acute HMOD, which is often life-threatening and requires immediate but careful intervention to lower BP, usually with intravenous (i.v.) therapy.<sup>398</sup> The rate and magnitude of an increase in BP may be at least as important as the absolute level of BP in determining the magnitude of organ injury.<sup>399</sup> Typical presentations of a hypertension emergency are:

- Patients with malignant hypertension, characterized by severe hypertension (usually grade 3) associated with funduscopic changes (flame haemorrhages and/or papilloedema), microangiopathy, and disseminated intravascular coagulation, and can be associated with encephalopathy (in about 15% of cases), 400 acute heart failure, and acute deterioration in renal function. The hallmark of this condition is small artery fibrinoid necrosis in the kidney, retina, and brain. The term 'malignant' reflects the very poor prognosis for this condition if untreated. 401–404
- Patients with severe hypertension associated with other clinical conditions who are likely to require an urgent reduction of BP, e.g. acute aortic dissection, acute myocardial ischaemia. or acute heart failure.
- Patients with sudden severe hypertension due to phaeochromocytoma, associated with organ damage.
- Pregnant women with severe hypertension or preeclampsia (see section 8.9.1).

The most common emergency symptoms will depend of the organs affected but may include headache, visual disturbances, chest pain, dyspnoea, dizziness, and other neurological deficits. In patients with hypertensive encephalopathy, the presence of somnolence, lethargy, tonic clonic seizures, and cortical blindness may precede a loss of consciousness; however, focal neurological lesions are rare and should raise the suspicion of stroke.

**Acute stroke**, especially intracerebral haemorrhage, when associated with severe hypertension has often been termed a

**Table 30** Diagnostic workup for patients with a suspected hypertension emergency

Common tests for all potential causes
Fundoscopy is a critical part of the diagnostic workup
12-lead ECG
Haemoglobin, platelet count, fibrinogen
Creatinine, eGFR, electrolytes, LDH, haptoglobin
Urine 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.

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hypertension emergency, but a more cautious approach is now recommended for acute BP lowering in the emergency setting of acute stroke (see section 8.15).

The term 'hypertension urgency' has also been used to describe severe hypertension in patients presenting to the emergency department in whom there is no clinical evidence of acute HMOD. 405 Whilst these patients require BP reduction, they do not usually require admission to hospital, and BP reduction is best achieved with oral medication according to the drug treatment algorithm presented in Figure 4. However, these patients will require urgent outpatient review to ensure that their BP is coming under control.

Acute and severe increases in BP can sometimes be precipitated by ingestion of sympathomimetics such as meta-amphetamine or cocaine. This can result in a hypertension emergency when there is evidence of acute HMOD.

It is emphasized that many patients in an emergency department with acute pain or distress may experience an acute elevation in BP that will be restored to normal when the pain and distress are relieved, rather than requiring any specific intervention to

For patients with a suspected hypertension emergency, a diagnostic workup is shown in Table 30.

### 8.3.1 Acute management of hypertensive emergencies

Apart from acute BP lowering in stroke, there are no RCTs evaluating different treatment strategies for hypertensive emergencies. The key considerations in defining the treatment strategy are:

(1) Establishing the target organs that are affected, whether they require any specific interventions other than BP lowering, and

- whether there is a precipitating cause for the acute rise in BP that might affect the treatment plan (e.g. pregnancy);
- (2) The recommended timescale and magnitude of BP lowering required for safe BP reduction;
- The type of BP-lowering treatment required. With regard to drug treatment, in a hypertension emergency, i.v. treatment with a drug with a short half-life is ideal to allow careful titration of the BP response to treatment in a higher dependency clinical area with facilities for continuous haemodynamic monitoring.

Recommended drug treatments for specific hypertension emergencies <sup>398,406</sup> are shown in *Table 31* and an expanded range of possible drug choices<sup>398</sup> is shown in *Table 32*. Rapid uncontrolled BP lowering is not recommended as this can lead to complications.<sup>397</sup>

Although i.v. drug administration is recommended for most hypertension emergencies, oral therapy with ACE inhibitors, ARBs, or beta-blockers is sometimes very effective in malignant hypertension because the renin system is activated by renal ischaemia. However, low initial doses should be used because these patients can be very sensitive to these agents and treatment should take place in hospital. Further comprehensive details on the clinical management of hypertension emergencies are available.<sup>398</sup>

### 8.3.2 Prognosis and follow-up

The survival of patients with hypertension emergencies has improved dramatically over past decades, 407 but these patients remain at high risk<sup>408,409</sup> and should be screened for secondary hypertension (see section 8.2). After discharge from hospital, when BP has reached a safe and stable level on oral therapy, we recommend frequent, at least monthly, visits in a specialized setting until the optimal target BP is achieved and long-term specialist follow-up thereafter.

Table 31 Hypertensive emergencies requiring immediate blood pressure lowering with intravenous drug therapy

Clinical presentation	Timeline and target for BP reduction	First-line treatment	Alternative
Malignant hypertension with or without acute renal failure	Several hours Reduce MAP by 20–25%	Labetalol Nicardipine	Nitroprusside Urapidil
Hypertensive encephalopathy	Immediately reduce MAP by 20–25%	Labetalol, nicardipine	Nitroprusside
Acute coronary event	Immediately reduce SBP to <140 mmHg	Nitroglycerine, labetalol	Urapidil
Acute cardiogenic pulmonary oedema	Immediately reduce SBP to <140 mmHg	Nitroprusside or nitroglycerine (with loop diuretic)	Urapidil (with loop diuretic)
Acute aortic dissection	Immediately reduce SBP to <120 mmHg AND heart rate to <60 bpm	Esmolol and nitroprusside or nitroglycerine or nicardipine	Labetalol OR metoprolol
Eclampsia and severe pre- eclampsia/HELLP	Immediately reduce SBP to <160 mmHg AND DBP to <105 mmHg	Labetalol or nicardipine and magnesium sulfate	Consider delivery

BP = blood pressure; bpm = beats per min; DBP = diastolic blood pressure; HELLP = haemolysis, elevated liver enzymes, and low platelets; i.v. = intravenous; MAP = mean arterial pressure; SBP = systolic blood pressure.

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Table 32 Drug types, doses, and characteristics for treatment of hypertension 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	2.5–5mg i.v. bolus over 2 minutes - may be repreated every 5 minutes to a maximum dose of 15mg	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 15 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
Nitroglycerine	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	1–2 min	10-30 min	0.5–1 mg/kg i.v. bolus OR 50–300 μg/kg/min as i.v. infusion		Tachyarrhythmias, chest pain

AV = atrioventricular; BP = blood pressure; i.v. = intravenous.

# 8.4 White-coat hypertension

As discussed in section 4, white-coat hypertension is defined as an elevated office BP despite a normal out-of-office BP. White-coat hypertension may be present in many people with an increased office BP, with a maximum in grade 1 hypertension, and very old people (>50%). Compared with normotensive people, white-coat hypertension is associated with an increased prevalence of dysmetabolic risk factors and asymptomatic organ damage. It is also associated with a greater risk of developing type 2 diabetes and sustained hypertension,

as well as an overall increased risk of CV events. <sup>68,410–412</sup> It is recommended that people with white-coat hypertension should have an accurate assessment of their CV risk profile, including a search for HMOD. Office and out-of-office BP (both home and ambulatory BP) should be measured frequently, e.g. no less than every 2 years. Treatment should consider lifestyle changes to reduce the elevated CV risk. <sup>85,86,89</sup>

Whether or not patients with white-coat hypertension should receive antihypertensive drugs is unresolved. In white-coat

hypertension, antihypertensive drugs have been shown to effectively and persistently lower office BP, with no concomitant reduction (indeed, even a small increase) of ambulatory BP values. 413,414 Whether these BP changes lead to CV protection has not been investigated with adequately powered outcome studies and remains unknown. However, it should be considered that people with whitecoat hypertension have inevitably been well represented in trials documenting the protective effect of antihypertensive drugs, 415 particularly those addressing conditions in which white-coat hypertension is more common, such as grade 1 hypertension or hypertension in older patients. In a recent subanalysis of the HYVET trial of the very old with hypertension, white-coat hypertension was reported to account for 55% of the trial population. 416 Thus, antihypertensive drug treatment cannot definitively be excluded for patients with white-coat hypertension and may be considered, in particular, in white-coat hypertensive people with a higher CV risk profile, such as those with HMOD, an uncertain out-of-office BP normality pattern (i.e. ambulatory but not home BP normality or vice versa), or a persistent office BP elevation at repeated visits. 417-420 No CV risk excess has been reported in patients in whom white-coat hypertension results from treatment-dependant normalization of out-of-office BP only. 418,421 Thus, whether this condition benefits from an uptitration of the existing drug treatment regimen (to also achieve office BP normalization) remains to be determined.

# 8.5 Masked hypertension

As reported in section 4.7.2, masked hypertension is defined in people whose BP is normal in the office but elevated on out-of-office BP measurements. Such people usually have dysmetabolic risk factors and asymptomatic organ damage, which are substantially more frequent than in people who are truly normotensive. 93,410-412,422 The challenge is how to diagnose masked hypertension, because most hypertension screening programmes use office BP measurement, which is normal in these people. Masked hypertension is commoner in younger rather than older individuals, and in those with an office BP in the borderline hypertension range (i.e. 130 - 139/80 - 89 mmHg). It is uncommon in people whose office BP is <130/80 mmHg. Masked hypertension is associated with progression to sustained office hypertension, increased frequency of developing type 2 diabetes, and the presence of HMOD. The long-term risk of fatal and non-fatal CV events approaches that of patients with sustained hypertension. <sup>68,81,93,95,423</sup> Patients with masked hypertension should have an accurate initial assessment of their CV risk profile. CV risk factors (including organ damage and ideally both home and ambulatory BP) should then be periodically monitored. Factors contributing to the out-of-office BP elevation (e.g. smoking) should be discouraged and lifestyle interventions implemented to improve out-of-office BP levels. The impact of antihypertensive drug treatment on CV outcomes in people with masked hypertension has never been studied. Nevertheless, treatment with BP-lowering medication should be considered because these patients are at high CV risk, often have HMOD, and the adverse prognostic importance of out-ofoffice BP elevations has been well documented. 68,74

# 8.6 Masked uncontrolled hypertension

MUCH occurs in some treated patients in whom the office BP appears controlled to recommended BP targets, but BP is elevated and thus uncontrolled according to out-of-office BP measurements

(ABPM or HBPM).<sup>84</sup> Registry-based studies in Spain have suggested that MUCH occurs in as many as 30% of treated hypertensive patients,<sup>84</sup> and is more common with comorbidities such as diabetes and CKD and in those at highest risk. Moreover, MUCH was more commonly due to poorly controlled nocturnal rather than daytime pressures on ABPM. Presently, no data are available from outcome trials for patients with MUCH; however, mindful of their high CV risk, treatment uptitration should be considered to ensure that that both office and out-of-office BP are controlled.<sup>84</sup>

# Management of white coat and masked hypertension

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In white-coat hypertensive patients, it is recommended to implement lifestyle changes aimed at reducing CV risk as well as regular follow-up with periodic out-of-office BP monitoring.	ı	С
In patients with white-coat hypertension:  • Drug treatment may be considered in people with evidence of HMOD or in whom CV risk is high or very high.	Шь	С
Routine drug treatment is not indicated.	Ш	С
Management of masked hypertension		
Recommendations		
In masked hypertension, lifestyle changes are recommended to reduce CV risk, with regular follow-up, including periodic out-of-office BP monitoring.	ı	С
Antihypertensive drug treatment should be considered in masked hypertension to normalize the out-of-office BP, based on the prognostic importance of out-of-office BP elevation.	lla	С
Antihypertensive drug uptitration should be considered in treated patients whose out-of-office BP is not controlled (i.e. masked uncontrolled hypertension), because of the high CV risk of these patients.	lla	С

 $\mbox{BP} = \mbox{blood pressure; } \mbox{CV} = \mbox{cardiovascular; } \mbox{HMOD} = \mbox{hypertension-mediated}$  organ damage.

# 8.7 Hypertension in younger adults (age <50 years)

The prevalence of hypertension increases with age. Most hypertension across the age span is due to systolic hypertension; however, elevations of DBP and isolated diastolic hypertension, when they occur,

<sup>&</sup>lt;sup>a</sup>Class of recommendation

bLevel of evidence.

are more common in younger rather than older patients.<sup>211</sup> There is a greater likelihood of detecting secondary hypertension in younger patients (<50 years), where the prevalence of secondary hypertension may be as high as 10% and should be considered, especially in those with more severe hypertension (see section 3).

All younger adults with grade 2 or more severe hypertension should be offered lifestyle advice and drug treatment, as well as highrisk younger adults with grade 1 hypertension (i.e. with HMOD, CVD, diabetes, CKD, or those at high CVD risk, although CV risk is often underestimated in younger adults over shorter-term projections, such as 10 years).<sup>35</sup>

There is controversy about whether younger adults with uncomplicated grade 1 hypertension should be treated because of the obvious difficulty in conducting conventional clinical outcome trials in younger adults in whom the outcomes only occur after many years. 424 There is little doubt that treating stage 1 hypertension in older patients, even those at low-moderate-risk, reduces CV morbidity and mortality. 425 Moreover, long-term epidemiological studies have demonstrated a clear relationship between BP and longer-term risk of CV events and mortality in young adults with a BP >130/80 mmHg. 424,426 Furthermore, earlier treatment 23 can prevent more severe hypertension 427 and the development of HMOD, which may not be completely reversible with later treatment. Thus, despite the absence of RCT evidence demonstrating the benefits of antihypertensive treatment in younger adults with uncomplicated grade 1 hypertension, treatment with BP-lowering drugs may be considered prudent. If a decision is taken not to offer treatment or treatment is declined, lifestyle advice should be prescribed, and longer-term follow-up is essential as BP will invariably rise. In younger patients with hypertension treated with BP-lowering medication, office BP should be reduced to ≤ 130/80 mmHg if treatment is well tolerated. Other interventions, e.g. statins or antiplatelet therapy, should also be considered for higher-risk patients (see section 7.2.5).

# 8.7.1 Isolated systolic hypertension in the young

Some young, healthy people, and men in particular, may present with isolated grade 1 systolic hypertension (i.e. brachial SBP ≥140 - 159 mmHg and a normal DBP <90 mmHg), and this may be associated with a normal central aortic SBP due to excessive peripheral systolic pressure amplification. 428 It is unclear whether isolated systolic hypertension in the context of a normal aortic pressure is benign. A recent examination of prospective data from the Chicago Heart Association Detection Project found that young men with isolated systolic hypertension had a CV risk similar to that of individuals with high-normal BP and that isolated systolic hypertension in the young was closely associated with smoking. 429 On the basis of current evidence, these young individuals should receive recommendations on lifestyle modification (particularly cessation of smoking); whether they should receive drug treatment is unclear, but they do require longer-term follow-up as many will develop sustained hypertension.430

# 8.8 Hypertension in older patients (age $\geq$ 65 years)

The prevalence of hypertension increases with age, with a prevalence of  $\sim$ 60% over the age of 60 years and  $\sim$ 75% over the age of 75 years.

For the purposes of these Guidelines, older is defined as  $\geq$ 65 years and the very old as  $\geq$ 80 years.

For many years, advanced age has been a barrier to the treatment of hypertension because of concerns about potential poor tolerability, and even harmful effects of BP-lowering interventions in people in whom mechanisms preserving BP homeostasis and vital organ perfusion may be more frequently impaired. This approach is not appropriate, because evidence from RCTs has shown that in old and very old patients, antihypertensive treatment substantially reduces CV morbidity and CV and all-cause mortality<sup>220,431</sup> (see section 7). Moreover, treatment has been found to be generally well tolerated. However, older patients are more likely to have comorbidities such as renal impairment, atherosclerotic vascular disease, and postural hypotension, which may be worsened by BP-lowering drugs. Older patients also frequently take other medications, which may negatively interact with those used to achieve BP control. A further important caveat is that RCTs have not included very frail patients, dependent patients, and patients with postural hypotension. It is thus uncertain whether, and to what extent, such patients would benefit from BPlowering treatment in the context of their comorbidities and reduced life expectancy. Thus, in older hypertensive patients, treatment presents more difficulties than in younger people, because the decision to treat hypertension must take into account the patient's clinical condition, concomitant treatments, and frailty. That said, age alone must never be a barrier to treatment because high BP is an important risk factor even at the most advanced ages. Furthermore, a recent study of a cohort of older patients from the general population (thus including those with frailty) has shown that better adherence to antihypertensive treatment was associated with a reduced risk of CV events and mortality, even when age was >85 years (mean 90 years).432

It is recommended that older patients are treated according to the treatment algorithm outlined in section 7. In very old patients, it may be appropriate to initiate treatment with monotherapy. In all older patients, when combination therapy is used, it is recommended that this is initiated at the lowest available doses. In all older patients, and especially very old or frail patients, the possible occurrence of postural BP should be closely monitored and symptoms of possible hypotensive episodes checked by ABPM. Unless required for concomitant diseases, loop diuretics and alpha-blockers should be avoided because of their association with injurious falls. 433,434 Renal function should be frequently assessed to detect possible increases in serum creatinine and reductions in eGFR as a result of BP-related reductions in renal perfusion. When treated, BP should be lowered to a systolic value of 130-139 mmHg and a diastolic value of <80 mmHg if tolerated. Treated SBP values of <130 mmHg should be avoided. A key emphasis in treating older patients, and especially the very old, is to carefully monitor for any adverse effects or tolerability problems associated with BP-lowering treatment, keeping in mind that adverse effects can be more frequent than reported in RCTs, in which specific medical expertise and close patient supervision may minimize adverse effects and tolerability problems.

An important consideration is frail, dependent older patients, including those with orthostatic hypotension. These have been excluded from RCTs. The SPRINT trial showed the benefits of BP-lowering treatment being extended to recruited patients who were at the frailer end of the spectrum, including those with reduced gait

speed.<sup>215</sup> This suggests that the benefit of treatment is not limited to fit and independent older patients; however, to what extent BP-lowering treatment benefits the very frail<sup>214</sup> and institutionalized patients remains to be determined.

In some patients, the best achievable BP may be higher than the recommended target, but it should be recognised that any amount of BP lowering is likely to be worthwhile and associated with a reduced risk of major CV events (especially stroke and heart failure) and mortality.

# 8.9 Women, pregnancy, oral contraception, and hormone-replacement therapy

# 8.9.1 Hypertension and pregnancy

Hypertensive disorders in pregnancy affect 5–10% of pregnancies worldwide and remain a major cause of maternal, foetal, and neonatal morbidity and mortality. Maternal risks include placental abruption, stroke, multiple organ failure, and disseminated intravascular coagulation. The foetus is at high risk of intrauterine growth retardation (25% of cases of pre-eclampsia), prematurity (27% of cases of pre-eclampsia), and intrauterine death (4% of cases of pre-eclampsia).

# 8.9.1.1 Definition and classification of hypertension in pregnancy

The definition of hypertension in pregnancy is based on office BP values, SBP  $\geq$ 140 mmHg and/or DBP  $\geq$ 90 mmHg, <sup>436,437</sup> and is classified as mild (140–159/90–109 mmHg) or severe ( $\geq$ 160/110 mmHg), in contrast to the conventional hypertension grading.

Hypertension in pregnancy is not a single entity but comprises:

- **Pre-existing hypertension:** precedes pregnancy or develops before 20 weeks of gestation, and usually persists for more than 6 weeks post-partum and may be associated with proteinuria.
- **Gestational hypertension:** develops after 20 weeks of gestation and usually resolves within 6 weeks post-partum.
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.
- **Pre-eclampsia:** gestational hypertension with significant proteinuria (>0.3 g/24 h or ≥30 mg/mmol ACR). It occurs more frequently during the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or with pre-existing hypertension, renal disease, or diabetes. It is often associated with foetal growth restriction due to placental insufficiency and is a common cause of prematurity. The only cure for pre-eclampsia is delivery. As proteinuria may be a late manifestation of pre-eclampsia, it should be suspected when *de novo* hypertension is accompanied by headache, visual disturbances, abdominal pain, or abnormal laboratory tests, specifically low platelets and/ or abnormal liver function.
- Antenatally unclassifiable hypertension: this term is used when BP is first recorded after 20 weeks of gestation and it is unclear if hypertension was pre-existing. Reassessment 6 weeks post-partum will help distinguish pre-existing from gestational hypertension.

### 8.9.1.2 Blood pressure measurement in pregnancy

BP in pregnancy should be measured in the sitting position (or the left lateral recumbent during labour) with an appropriately sized arm cuff at heart level and using Korotkoff V for DBP. Manual auscultation remains the gold standard for BP measurement in pregnancy, because automated

devices tend to under-record the BP and are unreliable in severe preeclampsia. Only validated devices should be used in pregnancy. A39 ABPM is superior to office BP measurement for the prediction of pregnancy outcome. ABPM devices recommended for use in pregnancy are more accurate than those used for office measurement or HBPM. ABPM helps avoid unnecessary treatment of white-coat hypertension, and is useful in the management of high-risk pregnant women with hypertension and those with diabetic or hypertensive nephropathy.

### 8.9.1.3 Investigation of hypertension in pregnancy

Basic laboratory investigations recommended for monitoring pregnant hypertensive women include urine analysis, blood count, haematocrit, liver enzymes, serum creatinine, and serum uric acid (increased in clinically evident pre-eclampsia). Hyperuricaemia in hypertensive pregnancies identifies women at increased risk of adverse maternal and foetal outcomes.<sup>441</sup>

All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia. A dipstick test of  $\geq 1+$  should prompt evaluation of ACR in a single spot urine sample and a value <30 mg/mmol can reliably rule out proteinuria in pregnancy.  $^{442}$ 

In addition to basic laboratory tests, the following investigations may be considered:

- Ultrasound investigation of the kidneys and adrenals, and plasma or urinary fractionated metanephrine assays in pregnant women with a history suggestive of phaeochromocytoma.
- Doppler ultrasound of uterine arteries (performed after 20 weeks of gestation) to detect those at higher risk of gestational hypertension, pre-eclampsia, and intrauterine growth retardation.
- A soluble fms-like tyrosine kinase 1:placental growth factor ratio of  $\leq$  38 can be used to exclude the development of pre-eclampsia in the next week when suspected clinically. 444

### 8.9.1.4 Prevention of hypertension and pre-eclampsia

Women at high or moderate-risk of pre-eclampsia should be advised to take 100-150 mg of aspirin daily from weeks 12-36. High risk of pre-eclampsia includes any of the following:

- Hypertensive disease during a previous pregnancy
- CKD
- Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- Type 1 or type 2 diabetes
- Chronic hypertension.

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

- First pregnancy
- Age ≥40 years
- Pregnancy interval of >10 years
- BMI of ≥35 kg/m<sup>2</sup> at first visit
- Family history of pre-eclampsia
- Multiple pregnancy.

# 8.9.1.5 Clinical management of hypertension in pregnancy

Mild hypertension of pregnancy (BP 140159/90109 mmHg). The goal of drug treatment of hypertension in pregnancy is to reduce

maternal risk; however, the agents selected must be safe for the foetus. The benefits of drug treatment for mother and foetus in hypertension in pregnancy have not been extensively studied, with the best data from a single trial using alpha-methyldopa, performed 40 years ago. 446–448 A further study suggested that tighter vs. less tight control of BP in pregnancy showed no difference in the risk of adverse perinatal outcomes and overall serious maternal complications. However, secondary analysis suggested that tighter control of BP may reduce the risk of developing more severe hypertension and pre-eclampsia. 446

Most women with pre-existing hypertension and normal renal function will not have severe hypertension and are a low risk for developing complications during pregnancy. Indeed, some of these women may be able to withdraw their medication in the first half of pregnancy because of the physiological fall in BP. Despite the paucity of evidence, European Guidelines <sup>17,449,450</sup> have recommended initiating drug treatment:

- (1) In all women with persistent elevation of BP ≥150/95 mmHg;
- (2) In women with gestational hypertension (with or without proteinuria), pre-existing hypertension with the superimposition of gestational hypertension, or hypertension with subclinical HMOD, when BP is >140/90 mmHg.

Women with pre-existing hypertension may continue their current antihypertensive medication, but ACE inhibitors, ARBs, and direct renin inhibitors are contraindicated due to adverse foetal and neonatal outcomes. Methyldopa, labetalol, and CCBs are the drugs of choice. Beta-blockers may induce foetal bradycardia; consequently, if used, their type and dose should be carefully selected, with atenolol best avoided. Diuretic therapy is generally avoided because plasma volume is reduced in women who develop pre-eclampsia.

There are no data to define the optimal BP treatment target in pregnant women. Nevertheless, for pragmatic reasons, if treatment is initiated it is important to suggest a treatment target to calibrate how much treatment to give. A BP target of <140/90 is suggested for pregnant women receiving antihypertensive therapy.

Severe hypertension of pregnancy (≥160/110 mmHg). There is no agreed definition of severe hypertension, with values ranging between 160–180 mmHg/>110 mmHg. The 2018 ESC Task Force on cardiovascular disease during pregnancy<sup>435</sup> considers an SBP ≥170 mmHg or DBP ≥110 mmHg an emergency in a pregnant woman, who should be immediately admitted to hospital for treatment. The selection of the antihypertensive drug and its route of administration depends on the expected time of delivery. Pharmacological treatment with i.v. labetalol, oral methyldopa, or CCB should be initiated. Intravenous hydralazine is no longer the drug of choice as it is associated with more perinatal adverse effects than other drugs. However, hydralazine is still used when other treatment regimens fail to achieve adequate BP control. Intravenous urapidil can also be considered.

In hypertensive crises, i.e. in patients with eclampsia or severe preeclampsia (with or without haemolysis, elevated liver enzymes, and low platelets syndrome), hospitalization and BP-lowering therapy is essential, and delivery needs to be considered after the maternal condition has stabilized. 435 Intravenous magnesium sulfate is recommended for the prevention of eclampsia and treatment of seizures. The consensus is to lower BP to <160/105 mmHg to prevent acute hypertensive complications in the mother. Both labetalol and nicardipine have shown to be safe and effective for the treatment of severe pre-eclampsia if i.v. BP-lowering therapy is necessary. 452 In both cases, monitoring of foetal heart rate is necessary. To prevent foetal bradycardia, the cumulative dose of labetalol should not exceed 800 mg/24 h. Intravenous sodium nitroprusside is contraindicated in pregnancy because of an increased risk of foetal cyanide poisoning. The drug of choice when pre-eclampsia is associated with pulmonary oedema is nitroglycerin (glyceryl trinitrate), given as an i.v. infusion of 5 μg/min, and gradually increased every 3–5 min to a maximum dose of 100 µg/min.

Delivery is indicated (i) urgently in pre-eclampsia with visual disturbances or haemostatic disorders, and (ii) at 37 weeks in asymptomatic women.  $^{453}$ 

**Blood pressure post-partum.** Post-partum hypertension is common in the first week. Any drug recommended can be used according to the hypertension treatment algorithm shown in *Figure 4*, with the caveats: (i) methyldopa should be avoided because of the risk of post-partum depression and (ii) consideration should be given to drug choice in breastfeeding women.

# 8.9.1.6 Hypertension and breastfeeding

All antihypertensive drugs taken by the nursing mother are excreted into breast milk. Most are present at very low concentrations except for propranolol and nifedipine, with breast milk concentrations similar to those in maternal plasma. Reference to prescribing information in breastfeeding women is important.

8.9.1.7 Risk of recurrence of hypertensive disorders in a subsequent pregnancy

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the higher the risk of recurrence in a subsequent pregnancy.

8.9.1.8 Long-term cardiovascular consequences of gestational hypertension

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension, stroke, and ischaemic heart disease in later adult life. Lifestyle modifications are indicated to avoid complications in subsequent pregnancies and to reduce maternal CV risk in the future. Therefore, annual visits to a primary care physician to check BP and metabolic factors are recommended for these patients.

Further detail on the management of hypertension and other CV disorders in pregnancy is available.  $^{435}$ 

### Management of hypertension in pregnancy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In women with gestational hypertension, pre-existing hypertension superimposed by gestational hypertension, or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended when SBP is $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg.	ı	С
In all other cases, initiation of drug treatment is recommended when SBP is $\geq$ 150 mmHg or DBP is $\geq$ 95 mmHg.	1	С
Methyldopa, labetalol, and CCBs are recommended as the drugs of choice for the treatment of hypertension in pregnancy. 447,448	ı	B (methyldopa)
	1	C (labetalol or CCBs)
ACE inhibitors, ARBs, or direct renin inhibitors are not recommended during pregnancy.	III	С
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and admission to hospital is recommended.	1	С
In severe hypertension, drug treatment with i.v. labetalol, oral methyldopa, or nifedipine is recommended.	1	С
The recommended treatment for hypertensive crisis is i.v. labetalol or nicardipine and magnesium.	1	С
In pre-eclampsia associated with pulmonary oedema, nitroglycerin given as an i.v. infusion is recommended.	ı	С
In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks. <sup>453</sup>	ı	В
It is recommended to expedite delivery in pre-eclampsia with adverse conditions, such as visual disturbances or haemostatic disorders.	1	С

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; i.v. = intravenous; SBP = systolic blood pressure.

### 8.9.2 Oral contraceptive pills and hypertension

Combined oestrogen-progesterone oral contraceptive pills can be associated with a small but significant increase in BP and the development of hypertension in about 5% of users. 456,457 BP usually decreases promptly following cessation of these pills; consequently, BP should be monitored before and during oral contraceptive pill treatment. The rise in BP appears to be related to the oestrogen content and may be less likely with the progestogen-only oral contraceptive pill. Older studies have demonstrated a relationship between the oral contraceptive pill and venous thrombosis and venous thromboembolism, and, to a lesser extent, myocardial infarction (especially with concomitant smoking history) and stroke. 458 More recent studies with newer-generation oral contraceptive pills have reported conflicting results. Thus, the use of oral contraceptives should consider the risks and benefits for the individual patient. Changes in BP should be carefully evaluated with follow-up readings.<sup>459</sup> Concomitant CV risk factors (e.g. smoking history) should be assessed and oral contraceptive pill use is not recommended if BP is elevated. In such patients, alternative forms of contraception should be offered. Discontinuation of combined oestrogen-progestin oral contraceptives in women with hypertension may improve their BP control.460

### 8.9.3 Hormone-replacement therapy and hypertension

Cross-sectional studies have long established that menopause doubles the risk of developing hypertension, even after adjusting for factors such as age and BMI. He although hormone-replacement therapy contains oestrogens, there is no convincing evidence that significant rises in BP will occur in otherwise normotensive menopausal women due to this therapy, or that BP will increase further due to hormone-replacement therapy in menopausal hypertensive women. Hormone-replacement therapy and selective oestrogen receptor modulators should not be used for primary or secondary prevention of CVD. In summary, current evidence suggests that the use of hormone-replacement therapy is not associated with an increase in BP. Moreover, it is not contraindicated in women with hypertension, and women with hypertension may be prescribed hormone-replacement therapy as long as BP levels can be controlled by antihypertensive medication.

# **8.10 Hypertension in different ethnic groups**

In comparison with the non-black population, hypertension is more prevalent in the black population living in Europe,  $^{463}$  similarly to that reported for the USA.  $^{464}$  As for the European white population, the

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

black European population is heterogenous in nature, 463 although in almost all European countries the largest ethnic group originates from the Sub-Saharan African region. 463 Hypertension epidemiology, diagnosis, and treatment have been thoroughly studied in black (i.e. Afro-American) US patients, 464 in contrast to the much scarcer database available for European black people, and thus we extrapolate from US data. However, this extrapolation requires some caution as differences between the North American and the European black population exist, especially with regard to socioeconomic status, CV risk, 465,466 and the response to antihypertensive drug treatment. 467 BP-related HMOD, as well as CV and renal complications, are more common and severe in black patients compared with age-matched white patients at any BP level. 464 Black hypertensive patients exhibit a similar proportional reduction of CV and renal events in response to BP-lowering treatment as white patients, with somewhat different treatment modalities. However, to achieve an effective BP reduction and BP control, salt restriction is particularly important in black patients, in whom it may lead to greater BP falls and more favourably impact on the effectiveness of BP-lowering drug treatment. 468 Hypertensive black patients also show a reduced antihypertensive response to RAS-blocker monotherapy, whereas they usually respond more effectively to thiazide or thiazide-like diuretics and CCBs, 316,469,470 which in black patients may be combined with each other or with a RAS blocker, making the latter more effective. Angioedema appears more common with ACE inhibitors in black patients, which may favour the preferred use of ARBs in this population. Despite some progress in recent years, data on hypertension prevalence, management, and control in European black patients (and in other immigrant populations such as European individuals from South Asia) are still scarce, 463,471 which makes this field an important area for future research. There is no evidence that the BP response to treatment in other ethnic groups differs from that reported in the general population in Europe.

# Hypertension in ethnic groups

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that a two-drug combination, usually as an SPC, is used as initial therapy for most black patients. <sup>c</sup>	1	C
In black patients, initial antihypertensive treatment should include a diuretic or a CCB, either in combination or with a RAS blocker. <sup>d</sup> 316,469	ı	В
In other ethnic groups, BP-lowering treatment may be based on the core treatment algorithm (see <i>Figure 4</i> ).	ПР	С

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; RAS = renin-angiotensin system; SPC = single-pill combination.

# 8.11 Hypertension in diabetes mellitus

High BP is a common feature of type 1 and, particularly, type 2 diabetes. Moreover, masked hypertension and a blunted nocturnal fall in BP are not infrequent in people with diabetes. Recording 24 h ABPM in apparently normotensive people with diabetes may be a useful diagnostic procedure, especially in those with HMOD. Substantial evidence supports the benefits of BP reduction 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, 231,235 retinopathy, and albuminuria. Diabetic neuropathy has never been included as an outcome in RCTs of BP-lowering treatment.

When considering treatment for hypertension, it is important to exclude significant postural hypotension, which can be marked in people with diabetes due to autonomic neuropathy. <sup>235</sup> Initiation of antihypertensive drug therapy is recommended when the office BP is >140/90 mmHg. Alongside lifestyle interventions, treatment should usually be initiated with a two-drug combination of an ACE inhibitor or ARB with a CCB or thiazide/thiazide-like diuretic, and treatment escalated according to the recommended treatment algorithm (see section 7). This approach ensures that the treatment strategy includes an ACE inhibitor or ARB, which has been shown to reduce albuminuria and the appearance or progression of diabetic nephropathy more effectively than other drug classes. <sup>235</sup> Combination of an ACE inhibitor with an ARB is contraindicated because it is accompanied by an excess of renal adverse events. <sup>298,473,474</sup>

Recent RCTs have shown that some antidiabetes agents (the selective inhibitors of sodium glucose cotransporter 2 in the kidney) can reduce office and ambulatory BP by several mmHg,  $^{475,476}$  and that this occurs even when people are treated with antihypertensive drugs. This may help improve BP control (see below), which is especially difficult in diabetes,  $^{477}$  and may reduce the progression of CKD $^{478-481}$  (see also section 8.12).

There has been considerable debate about the target BP that should be achieved in people with diabetes (see section 7). We recommend that in people with diabetes, the first objective should be to lower BP to <140/80 mmHg, aiming at an SBP of 130 mmHg. Provided that the treatment is well tolerated, treated SBP values of <130 mmHg should be considered because of the benefits on stroke prevention. Achieved SBP values of <120 mmHg should always be avoided. BP targets for renoprotection for patients with diabetic kidney disease are discussed in section 8.12.

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

<sup>&</sup>lt;sup>c</sup>Except in patients with low grade 1 hypertension or frail older patients, in whom initial treatment with a single drug may be more appropriate.

<sup>&</sup>lt;sup>d</sup>Angioedema is more common with ACE inhibitors and thus ARBs may be preferred.

# Treatment strategies in people with diabetes

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Antihypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg. <sup>1,226,235,482</sup>	ı	A
In people with diabetes receiving BP-lowering drugs it is recommended:  To target SBP to 130 mmHg and <130mmHg if tolerated, but not <120 mmHg. 1,231,235	1	A
<ul> <li>In older people (aged ≥65 years aged), to target to an SBP range of 130–139 mmHg. <sup>1,205,235</sup></li> </ul>	1	A
<ul> <li>To target the DBP to &lt;80 mmHg, but not &lt;70 mmHg.</li> </ul>	1	С
It is recommended to initiate treatment with a combination of a RAS blocker with a CCB or thiazide/thiazide-like diuretic. c 1,175,205	1	A
Simultaneous administration of two RAS blockers, e.g. an ACE inhibitor and ARB, is not indicated. <sup>291,298,299</sup>	ш	A

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; RAS = renin-angiotensin system; SBP = systolic blood pressure.

<sup>c</sup>When eGFR <30 mL/min/1.73 m<sup>2</sup>, avoid thiazide/thiazide-like diuretics and consider using a loop diuretic when a diuretic is required.

# 8.12 Hypertension and chronic kidney disease

Hypertension is a major risk factor for the development and progression of CKD, irrespective of the cause of CKD. In patients with CKD, resistant hypertension, masked hypertension, and elevated night-time BP are common, and are associated with a lower eGFR, higher levels of albuminuria, and HMOD. 483,484

The effects of lowering BP in patients with CKD have been the subject of many meta-analyses. A recent meta-analysis has shown that BP lowering significantly reduced end-stage renal disease in

patients with CKD, but only in those with albuminuria and without any beneficial effect on CV events. However, a more recent and larger meta-analysis has shown a significant reduction in all-cause mortality following BP reduction in patients with CKD.

Reduction of albuminuria has also been considered as a therapeutic target. Analyses of data from RCTs have reported that changes in urinary albumin excretion are predictors of renal and CV events. However, there are also studies in which treatment that was less effective at reducing albuminuria was more effective at reducing CV events and vice versa. Thus, whether reducing albuminuria per se is a proxy for CVD prevention remains unresolved.

Patients with CKD should receive lifestyle advice, especially sodium restriction, and drug treatment when their office BP is >140/90 mmHg. Achieving recommended BP targets in CKD usually requires combination therapy, which should be initiated as a combination of a RAS blocker with a CCB or diuretic in these patients. The combination of two RAS blockers is not recommended. <sup>291</sup> Loop diuretics should replace thiazide diuretics when the estimated GFR is <30 mL/min/1.73 m<sup>2</sup>.

The evidence with respect to BP targets in patients with CKD is complex. In patients with non-diabetic CKD, one meta-analysis showed that the slowest progression on CKD was obtained with a treated SBP in the range of 110 - 119 mmHg in patients with albuminuria >1 g/day.  $^{487}$  In contrast, in patients with a proteinuria <1 g/day, the lowest risk of developing CKD (not CV risk) was obtained with an SBP of <140 mmHg.  $^{487}$  Another systematic review failed to demonstrate that a BP target of <130/80 mmHg improved clinical outcomes more than a target of <140/90 mmHg in non-diabetic CKD.  $^{488}$  In a large retrospective cohort containing 398 419 treated hypertensive patients (30% with diabetes), the nadir SBP and DBP for the lowest risk of end-stage renal disease and mortality were 137 and 71 mmHg, respectively, with a clear increase in mortality risk at SBP <120 mmHg.  $^{489}$ 

Current evidence suggests that in patients with CKD, BP should be lowered to <140/90 mmHg and towards 130/80 mmHg. Lifestyle advice, especially sodium restriction, may be especially effective at aiding BP lowering in patients with CKD. Because BP lowering reduces renal perfusion pressure, it is expected and not unusual for eGFR to be reduced by 10 - 20% in patients treated for hypertension. Thus, careful monitoring of blood electrolytes and eGFR is essential, but clinicians should not be alarmed by the anticipated decline in GFR when treatment is initiated. This decline usually occurs within the first few weeks of treatment and stabilizes thereafter. If the decline in GFR continues or is more severe, the treatment should be stopped, and the patient investigated to determine the presence of renovascular disease.

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

# The rapeutic strategies for treatment of hypertension in $\ensuremath{\mathsf{CKD}}$

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication. 9,203,485	ı	A
In patients with diabetic or non-diabetic CKD:  • It is recommended to lower SBP to a range of 130–139 mmHg. 9,487,489	ı	A
<ul> <li>Individualized treatment should be con- sidered according to its tolerability and impact on renal function and electrolytes.</li> </ul>	lla	С
RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria. 487,489	ı	А
A combination of a RAS blocker with a CCB or a diuretic <sup>c</sup> is recommended as initial therapy. <sup>175</sup>	1	A
A combination of two RAS blockers is not recommended. <sup>298</sup>	ш	A

BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAS = renin-angiotensin system; SBP = systolic blood pressure.

# 8.13 Hypertension and chronic obstructive pulmonary disease

Hypertension is the most frequent comorbidity in patients with COPD, and coincidence of the two diseases may affect 2.5% of the adult population. Patients with hypertension and COPD are at particularly high CV risk. Both conditions share similar environmental risks and, in addition, hypoxia may exacerbate risk. Preatment of COPD with anticholinergic agents and long-acting beta-2 adrenoceptor agonists may adversely affect the CV system (increase heart rate and BP). The presence of COPD also has an impact on the selection of antihypertensive drugs, which should consider their effects on pulmonary function. Concern has been predominantly directed to the use of beta-blockers, although there is evidence that in COPD these drugs maintain their CV-protective

effects. <sup>492,493</sup> Beta-blockers may negatively affect the reduced basal lung function in patients with COPD, diminish the effectiveness of emergency beta-agonist administration, reduce the benefit of long-acting beta-agonist treatment, and make the discrimination of asthma and COPD more difficult. That said, when tolerated, the use of cardiac beta1-selective beta-blockers in patients with COPD has proven to be safe in different settings, including hypertension. <sup>494</sup> It should also be noted that diuretics may decrease the plasma level of potassium (in addition to the hypokalaemic effects of glucocorticoids and beta2-adrenoceptor agonists), worsen carbon dioxide retention (including metabolic alkalosis-related hypoxia in hypoventilated patients), increase haematocrit, and deteriorate mucus secretion in bronchi. Therefore, in general, diuretics are not recommended for widespread use in hypertensive patients with COPD. <sup>490,495</sup>

In conclusion, management of hypertensive patients with COPD should include lifestyle changes, among which cessation of smoking is essential. CCBs, ARBs or ACEIs, or the CCB/RAS blocker combination are recommended as the initial drugs of choice. If the BP response is poor, or depending on other comorbidities, thiazides or thiazide-like diuretics and beta1-selective beta-blockers can be considered.

# 8.14 Hypertension and heart disease

# 8.14.1 Coronary artery disease

There are strong epidemiological relationships between CAD and hypertension. The INTERHEART study showed that  $\sim\!50\%$  of the population-attributable risk of a myocardial infarction can be accounted for by lipids, with hypertension accounting for  $\sim\!25\%.^{10}$  Another registry-based study of over 1 million patients showed that ischaemic heart disease (angina and myocardial infarction) accounted for most (43%) of the CVD-free years of life lost due to hypertension from the age of 30 years.  $^7$ 

More compelling is the beneficial effect of BP treatment on reducing the risk of myocardial infarction. A recent meta-analysis of RCTs of antihypertensive therapy showed that for every 10 mmHg reduction in SBP, CAD was reduced by 17%.<sup>2</sup> A similar risk reduction has been reported by others with more intensive BP control.<sup>496</sup> The benefits of reducing cardiac events are also evident in high-risk groups, such as those with diabetes.<sup>231,425</sup>

There remains some inconsistency over the optimal BP target in hypertensive patients with overt CAD, and especially whether there is a I-curve relationship between achieved BP and CV outcomes in CAD. 497-500 A recent analysis 501 of 22 672 patients with stable CAD who were treated for hypertension found that, after a median follow-up of 5.0 years, an SBP of ≥140 mmHg and a DBP of ≥80 mmHg were each associated with increased risk of CV events. An SBP of <120 mmHg was also associated with increased risk, as was a DBP of <70 mmHg. Similar findings were also reported from another analysis of RCT data evaluating the relationships between achieved BP and risks of CV outcomes.<sup>222</sup> Whether a J-curve phenomenon exists in patients with CAD who have been revascularized remains uncertain. Other analyses do not support the existence of a J-curve, even in hypertensive patients at increased CV risk.<sup>239</sup> For example, in patients with CAD and initially free from congestive heart failure enrolled in ONTARGET, a BP reduction from baseline over the

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

 $<sup>^{\</sup>circ}$ In case of eGFR <30 mL/min/1.73 m $^{2}$ , avoid thiazide/thiazide-like diuretics and consider using a loop diuretic if required.

examined BP range had little effect on the risk of myocardial infarction and predicted a lower risk of stroke. Thus, a target BP of approximately <130/80 mmHg in patients with CAD appears safe and can be recommended, but achieving a BP <120/80 mmHg is not recommended.

In hypertensive patients with CAD, beta-blockers and RAS blockers may improve outcomes post-myocardial infarction. <sup>503</sup> In patients with symptomatic angina, beta-blockers and calcium antagonists are the preferred components of the drug treatment strategy.

# Therapeutic strategies in hypertensive patients with CAD

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients with CAD receiving BP-lowering drugs, it is recommended:		
• To target SBP to ≤ 130 mmHg if tolerated, but not <120 mmHg. <sup>2,496</sup>	1	A
<ul> <li>In older patients (aged ≥65 years), to target to an SBP range of 130–140 mmHg.<sup>2,496</sup></li> </ul>	-	A
<ul> <li>To target DBP to &lt;80 mmHg, but not &lt;70 mmHg.</li> </ul>	1	С
In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment. 503	ı	A
In patients with symptomatic angina, beta- blockers and/or CCBs are recommended. <sup>503</sup>	1	A

BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; DBP = diastolic blood pressure; RAS = renin—angiotensin system; SBP = systolic blood pressure.

# 8.14.2 Left ventricular hypertrophy and heart failure

Hypertension is the leading risk factor for the development of heart failure,<sup>7</sup> and most patients with heart failure will have an antecedent history of hypertension. This may be a consequence of CAD, which results in HFrEF. Hypertension also causes LVH, which impairs LV

relaxation (so-called diastolic dysfunction) and is a potent predictor of heart failure, even when LV systolic function is normal and there is no preceding myocardial infarction (HFpEF). Hypertension-dependent fibrosis and structural alteration of large and small arteries (microvascular disease) also contribute.

Treating hypertension has a major impact on reducing the risk of incident heart failure and heart failure hospitalization, especially in old and very old patients.  $^{51,213,316}$  This has been observed using diuretics, beta-blockers, ACE inhibitors, or ARBs, with CCBs being less effective in comparative trials.  $^{504}$ 

Reducing BP can also lead to the regression of LVH, which has been shown to be accompanied by a reduction of CV events and mortality. The magnitude of LVH regression is associated with baseline LV mass, duration of therapy, the SBP reduction, 505,506 and the drugs used, with ARBs, ACE inhibitors, and CBBs causing more effective LVH regression than beta-blockers 173 or diuretics.

In patients with HFrEF, antihypertensive drug treatment should start (if not already initiated) when BP is >140/90 mmHg. It is unclear how low BP should be lowered in patients with heart failure. Outcomes for patients with heart failure have repeatedly been shown to be poor if BP values are low, which suggests (although data interpretation is made difficult by the possibility of reversed causality) that it may be wise to avoid actively lowering BP to <120/70 mmHg. However, some patients may achieve even lower BP levels than this because of the desirability to remain on treatment with guideline-directed heart failure medications, which, if tolerated, should be continued because of their protective effect. <sup>136</sup>

Heart failure guideline-directed medications are recommended for the treatment of hypertension in patients with HFrEF. <sup>136</sup> ACE inhibitors, ARBs, beta-blockers, and MRAs (e.g. spironolactone and epleronone) are all effective in improving clinical outcome in patients with established HFrEF, whereas for diuretics, evidence is limited to symptomatic improvement. If further BP lowering is required, a dihydropyridine CCB may be considered. Sacubutril/valsartan lowers BP, has also been shown to improve outcomes in patients with HFrEF, and is indicated for the treatment of HFrEF as an alternative to ACE inhibitors or ARBs. <sup>507</sup> Non-dihydropiridine CCBs (diltiazem and verapamil), alpha-blockers, and centrally acting agents, such as moxonidine, should not be used.

Antihypertensive treatment is commonly needed in patients with HFpEF; the same BP threshold and target for drug treatment indicated for HFrEF should be used. The optimal treatment strategy for hypertensive patients with HFpEF is not known, but the strategy outlined above for HFrEF patients might also be the one to adopt in HFpEF patients. HFpEF patients commonly have multiple comorbidities that may adversely affect outcomes and complicate management.

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

# Therapeutic strategies in hypertensive patients with heart failure or LVH

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is ≥140/90 mmHg. <sup>c</sup> 136	lla	В
In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a beta-blocker and diuretic and/or MRA if required. 136	1	A
Dihydropyridine CCBs may be added if BP control is not achieved. <sup>d</sup>	Шь	С
In patients with HFpEF, BP treatment threshold and target values should be the same as for HFrEF. 136	lla	В
Because no specific drug has proven its superiority, all major agents can be used.	- 1	С
In all patients with LVH:  It is recommended to treat with an RAS blocker in combination with a CCB or diuretic. 504	1	A
<ul> <li>SBP should be lowered to a range of 120–130 mmHg.<sup>504,506</sup></li> </ul>	lla	В

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVH = left ventricular hypertrophy; MRA = mineralocorticoid receptor antagonist; RAS = renin-angiotensin system; SBP = systolic blood pressure.

# 8.15 Cerebrovascular disease and cognition

Hypertension is a major risk factor for haemorrhagic and ischaemic stroke, and a risk factor for recurrent stroke. BP management during the acute phase of haemorrhagic and ischaemic stroke remains an area of uncertainty. BP is often elevated at presentation with acute stroke, but often declines without intervention. <sup>508</sup>

# 8.15.1 Acute intracerebral haemorrhage

In acute intracerebral haemorrhage, an increased BP is common and is associated with a greater risk of haematoma expansion, increased risk of death, and a worse prognosis for neurological recovery. Results from an RCT suggested that immediate BP lowering (within 6 h) to <140/90 mmHg did not show benefit on the primary outcome of disability or death at 3 months, but might reduce haematoma expansion and improve functional recovery, and was generally safe.  $^{511}$ 

A subsequent RCT, in which SBP was immediately reduced ( $<4.5\ h$ ) from a mean of 200 mmHg to two different target intervals ( $140-170\ vs.\ 110-139\ mmHg$ ), showed that more intensive BP lowering had no benefit on the same primary outcome and was associated with more renal adverse events. Thus, we do not recommend treatment to immediately lower BP in patients with acute intracerebral haemorrhage. One possible caveat to this recommendation is patients with acute intracerebral haemorrhage and very severe hypertension (SBP  $\geq$ 220 mmHg), for whom there are much fewer data. A meta-analysis and secondary outcome data from one RCT have suggested a possible benefit on functional recovery at 3 months, and that acute lowering of SBP to  $<180\ mmHg$  in these patients might be beneficial. Thus, careful lowering of BP via i.v. infusion may be considered in patients with markedly elevated BP (SBP  $\geq$ 220 mmHg).

# 8.15.2 Acute ischaemic stroke

The beneficial effects of BP reduction are even less clear in acute ischaemic stroke. A key consideration is whether the patient will receive thrombolysis, because observational studies have reported an increased risk of intracerebral haemorrhage in patients with a markedly elevated BP who received thrombolysis. 514,515 In patients receiving i.v. thrombolysis, BP should be lowered and maintained at <180/105 mmHg for at least the first 24 h after thrombolysis. The benefit of acute BP lowering in patients with acute ischaemic stroke who do not receive thrombolysis is uncertain. A meta-analysis suggested that BP lowering early after acute ischaemic stroke had a neutral effect on the prevention of death or dependency. 516,517 In such patients with markedly elevated SBP or DBP (i.e. ≥220 or ≥120 mmHg, respectively), clinical judgement should define whether to intervene with drug therapy, in which case a reasonable goal may be to lower BP by 15%, with close monitoring, during the first 24 h after stroke onset. 516,518-520 Patients with acute ischaemic stroke and a BP lower than this in the first 72 h after stroke do not seem to benefit from the introduction or reintroduction of BP-lowering medication. <sup>516,521</sup> For stable patients who remain hypertensive (≥140/90 mmHg) >3 days after an acute ischaemic stroke, initiation or reintroduction of BP-lowering medication should be considered. 522

# 8.15.3 Previous stroke or transient ischaemic attack

RCTs of antihypertensive treatment (placebo controlled) in patients with a previous stroke or TIA, in a stable clinical condition, and with BP >140/90 mmHg, have shown that BP lowering reduces the risk of recurrent stroke. <sup>338,523</sup> No evidence is yet available that recurrent stroke is prevented by initiating therapy when BP is in the high–normal range. We recommend resumption of BP-lowering therapy several days after stroke, or immediately after TIA, for previously treated or untreated patients with hypertension, for prevention of both recurrent stroke and other CV events.

The appropriate BP targets to prevent recurrent stroke are uncertain, but should be considered in the context of a consistent finding in many meta-analyses that stroke is the one major CV event that is reduced at lower achieved BP levels. This is supported by the results from the recent Secondary Prevention of Small Subcortical Strokes 3 study  $^{244,524}$  in patients with a recent lacunar stroke, which suggested an SBP target of <130 mmHg,  $^{525}$  and other studies.  $^{526}$ 

Prevention of stroke is a consistent benefit of antihypertensive therapy and has been observed in all large RCTs using different drug

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

<sup>&</sup>lt;sup>c</sup>A lowest safety BP value is not given as many patients receiving intensive treatment for heart failure may achieve much lower BP levels than recommended BP targets.

<sup>&</sup>lt;sup>d</sup>Non-dihydropyridines are not recommended in HFrEF but may be used in HFpEF.

regimens. However, individual RCTs comparing modern treatment regimens <sup>317,527</sup> and meta-analyses suggest that beta-blockers are less effective at stroke prevention than other classes of antihypertensive agents. <sup>2,528</sup> Although the beta-blocker in these studies was atenolol, there are no data with more modern beta-blockers with regards to stroke prevention in hypertension. Thus, optimal antihypertensive treatment for stroke prevention should not include beta-blockers unless there is a compelling indication for their use, mindful of the fact that the most common recurrent event after stroke is a further stroke rather than myocardial infarction. <sup>529</sup>

### 8.15.4 Cognitive dysfunction and dementia

Several epidemiological and clinical studies have shown that hypertension in midlife predicts cognitive decline and dementia (both Alzheimer's disease and vascular dementia) in older patients. <sup>530–533</sup> However, evidence on the beneficial effects of BP lowering on cognitive decline is scant and conflicting. A meta-analysis <sup>534</sup> of 12 studies investigating the impact of different antihypertensive drugs on dementia and cognitive function concluded that BP lowering reduced the incidence and risk of cognitive impairment and dementia by 9%. One study showed that achieving better BP control over 4 years reduced the progression of cerebral white matter lesions and the decrease in global cognitive performance. <sup>535</sup>

Trials are urgently needed to better define the potential impact of BP lowering on preventing cognitive decline or in delaying dementia when cognitive dysfunction is already present.

# 8.16 Hypertension, atrial fibrillation, and other arrhythmias

Hypertension predisposes to cardiac arrhythmias, including ventricular arrhythmias, but most commonly AF,  $^{536-538}$  which should be considered a manifestation of hypertensive heart disease.  $^{539}$  Even high—normal BP is associated with incident AF,  $^{540,541}$  and hypertension is the most prevalent concomitant condition in AF patients. AF adds to the risk of stroke and heart failure. AF necessitates stroke prevention with oral anticoagulation, with monitoring of the associated risks and prevention of bleeding.  $^{542}$ 

Most patients show a high ventricular rate with AF<sup>542</sup> and, in such patients, beta-blockers or non-dihydropyridine calcium antagonists (e.g. diltiazem and verapamil) are recommended as antihypertensive agents. Non-dihydropyridine CCBs should be avoided in patients with reduced LV systolic function and may precipitate heart failure in some patients. Beta-blockers are often indicated in these patients, and may need to be combined with digoxin to gain rate control.<sup>542</sup>

In RCTs of hypertensive patients with LVH and/or high CV risk, \$543,544\$ RAS blockers have been shown to reduce first occurrence of AF, compared with beta-blockers or CCBs, consistent with similar effects of RAS blockers in patients with heart failure. \$545-547\$ RAS blockers do not prevent recurrence of paroxysmal or persistent AF. \$548-550\$ In patients with heart failure, beta-blockers and MRAs may also prevent AF. The preventive effect of RAS blockers against the development of AF is indirectly supported by a general practice database in the UK, with approximately 5 million patient

# Therapeutic strategies in hypertensive patients with acute stroke and cerebrovascular disease

Recommendations	Class <sup>a</sup>	Levelb
In patients with acute intracerebral haemorrhage:  • Immediate BP lowering is not recommended for patients with SBP <220 mmHg. 509–513	III	А
• In patients with SBP ≥220 mmHg, careful acute BP lowering with i.v. therapy to <180 mmHg should be considered. 509–513	lla	В
In acute ischaemic stroke, routine BP lowering with antihypertensive therapy is not recommended, 516,517 with the exceptions:	Ш	A
<ul> <li>In patients with acute ischaemic stroke who are eligible for i.v. thrombolysis, BP should be carefully lowered and maintained at &lt;180/105 mmHg for at least the first 24 h after thrombolysis.</li> </ul>	lla	В
<ul> <li>In patients with markedly elevated BP who do not receive fibrinolysis, drug therapy may be considered, based on clinical judgement, to reduce BP by 15% during the first 24 h after the stroke onset.</li> </ul>	Шь	С
n hypertensive patients with an acute cerebrovascular event, antihypertensive treatment is recommended:  • Immediately for TIA. 526	1	А
After several days in ischaemic stroke. 526	ı	А
In all hypertensive patients with ischaemic stroke or TIA, an SBP target range of 120–130 mmHg should be considered. <sup>244,524,526</sup>	lla	В
The recommended antihypertensive drug treatment strategy for stroke prevention is a RAS blocker plus a CCB or a thiazide-like diuretic. <sup>338</sup>	1	A

BP = blood pressure; CCB = calcium channel blocker; i.v. = intravenous; RAS = renin-angiotensin system; SBP = systolic blood pressure; TIA = transient ischaemic attack. aClass of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

records, which has reported that ACE inhibitors, ARBs, and betablockers are associated with a lower risk of AF compared with CCBs.<sup>553</sup> Hence, RAS blockers should be considered as part of the antihypertensive treatment strategy in hypertensive patients with a high risk of AF (e.g. LVH), to prevent incident AF.

# 8.16.1 Oral anticoagulants and hypertension

Many patients requiring oral anticoagulants (e.g. with AF) will be hypertensive. Hypertension is not a contraindication to oral anticoagulant use. However, although its role has been unappreciated in most old and more recent RCTs on anticoagulant treatment, 537 hypertension does substantially increase the risk of intracerebral haemorrhage when oral anticoagulants are used, and efforts should be directed towards achieving a BP goal of <130/80 mmHg in patients receiving oral anticoagulants. Detailed information on hypertension and oral anticoagulants has been published recently. 526,536 Anticoagulants should be used to reduce the risk of stroke in most AF patients with hypertension, including those with AF in whom hypertension is the single additional stroke risk factor. 554,555 BP control is important to minimize the risks of AF-related stroke and oral anticoagulant-related bleeding. Until more data are available, BP values in AF patients taking oral anticoagulants should be at least <140 mmHg for SBP and <90 mmHg for DBP. Oral anticoagulants should be used with caution in patients with persistent uncontrolled hypertension (SBP ≥180 mmHg and/or DBP ≥100 mmHg), and urgent efforts to control BP should be made.

# 8.17 Hypertension and vascular disease

# 8.17.1 Carotid atherosclerosis

A small number of studies have reported the effects of the various pharmacological classes of antihypertensive drugs on carotid IMT, and very few on carotid plagues. Reducing BP regresses carotid IMT and may delay the intimal atherosclerotic process. There appear to be differential drug effects on IMT regression, with CCBs having greater efficacy than diuretics and beta-blockers, 146 and ACE inhibitors more than diuretics. 557 However, the relevance of these findings is unclear because most patients receive combinations of treatment and the progression or treatment-induced changes in carotid IMT are poorly predictive of future CV events. 184,558 Patients with carotid plaques are at high risk of atheroembolic stroke and CV events, and BP lowering should be complemented by lifestyle advice and treatment with statins and antiplatelet therapy. A common conundrum faced by clinicians is the hypertensive patient with a tight carotid stenosis, especially when bilateral. No study has addressed this scenario and therefore advice is necessarily pragmatic, and we recommend a more cautious approach to BP lowering, initiating with monotherapy and carefully monitoring for adverse effects.

### 8.17.2 Arteriosclerosis and increased arterial stiffness

Large artery stiffening is a major factor contributing to the rise in SBP and fall in DBP with ageing. Arterial stiffness is usually measured in studies as PWV. Arterial stiffening results from arteriosclerotic structural changes in large conduit arteries, leading to a loss of arterial

### Therapeutic strategies in hypertensive patients with AF

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
In patients with AF, screening for hypertension is recommended. 536	1	С
A beta-blocker or non-dihydropyridine CCB should be considered as part of the treatment of hypertension if rate control is needed. 536	lla	В
Stroke prevention with oral anticoagulation is recommended in patients with AF and hypertension, and a CHA $_2$ DS $_2$ -VASc score of $\ge 2$ in men and $\ge 3$ in women. $^{536,556}$	1	A
Stroke prevention with oral anticoagulants should be considered in AF patients with hypertension, even when hypertension is the single additional risk factor (CHA $_2$ DS $_2$ -VASc score of 1). $^{536,556}$	lla	В
Oral anticoagulants should be used with caution in patients with marked BP elevation (SBP ≥180 mmHg and/or DBP ≥100 mmHg); the aim should be to lower SBP to at least <140 mmHg, and SBP lowering to <130 should be considered. If this is not possible, then patients should make an informed decision that they accept that the stroke protection provided by the anticoagulant will be associated with higher bleeding risk. 536	lla	В

AF = atrial fibrillation; BP = blood pressure; CCB = calcium channel blocker;  $CHA_2DS_2$ -VASc = Congestive heart failure, Hypertension, Age  $\geq$ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); DBP = diastolic blood pressure; SBP = systolic blood pressure  $^{a}Class$  of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

elasticity, and the distending force resulting from the pressure exerted on the arterial wall. Thus, all antihypertensive drugs, by reducing BP, reduce arterial stiffness, as the reduction in BP unloads the stiff components of the arterial wall, leading to a passive decrease in PWV. Pharmacodynamic RCTs<sup>559</sup> and meta-analyses<sup>560,561</sup> suggest that ACE inhibitors and ARBs may reduce PWV beyond the effect of BP lowering on a long-term basis. Whether RAS blockers are more effective than other antihypertensive drugs in this regard has not been demonstrated. Moreover, whether any long-term reduction in aortic stiffness<sup>562</sup> translates into a reduction in CV events beyond the impact of BP lowering alone<sup>563</sup> has not been demonstrated.

# 8.17.3 Lower extremity arterial disease

LEAD is often a manifestation of more widespread atherosclerosis and especially atherosclerotic renal artery disease, <sup>564</sup> and these patients are at very high CV risk. <sup>190</sup> BP control is an important part of the CV risk-reduction strategy in these patients. Beta-blockers have not been shown to worsen the symptoms of claudication in two meta-analyses. <sup>565,566</sup> Thus, beta-blockers remain a treatment option in hypertensive patients with LEAD when there is a specific indication for their use. When critical limb ischaemia is present, BP reduction should be instituted slowly as it may worsen ischaemia. In patients with LEAD, antihypertensive treatment should be complemented by lifestyle changes and especially smoking cessation, as well as statin and antiplatelet therapy. <sup>190</sup>

# Therapeutic strategies in hypertensive patients with LEAD

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	
BP-lowering treatment is recommended to reduce CV risk. <sup>2,190,503</sup>	1	A	
A combination of a RAS blocker, CCB, or diuretic should be considered as initial therapy. <sup>2</sup>	lla	В	SC/ESH 2018
Beta-blockers may also be considered. <sup>566</sup>	IIb	С	90

BP = blood pressure; CCB = calcium channel blocker; CV = cardiovascular; LEAD = lower extremity arterial disease; RAS = renin-angiotensin system.  $^{\rm a}$ Class of recommendation.

# 8.18 Hypertension in valvular disease and aortopathy

### 8.18.1 Coarctation of the aorta

When feasible, treatment of aortic coarctation is predominantly surgical and usually done in childhood. Even after surgical correction, these patients may develop systolic hypertension at a young age and require long-term follow-up. Few patients with aortic coarctation remain undetected until adult life, and by then often have severe hypertension, HMOD (especially LVH and LV dysfunction), and an extensive collateral circulation below the coarctation. Such patients should be evaluated in a specialist centre. The medical therapy for

hypertension in patients with aortic coarctation should follow the treatment algorithm outlined in section 7, as there have been no formal RCTs to define optimal treatment strategies.  $^{567}$ 

# 8.18.2 Prevention of aortic dilation and dissection in highrisk subjects

Chronic hypertension can be associated with modest aortic root dilatation. When more extensive aortic root dilatation is present or the dilatation extends beyond the aortic root, an additional cause for aortopathy should be sought. All hypertensive patients with aortic dilatation, whether associated with Marfan syndrome, bicuspid aortic valve disease, or not, should have their BP controlled  $\leq 130/80$  mmHg.  $^{568}$  In patients with Marfan syndrome, prophylactic use of ACE inhibitors, ARBs, or beta-blockers seems to be able to reduce either the progression of the aortic dilation or the occurrence of complications.  $^{568-570}$  However, there is no evidence for the specific efficacy of these treatments in aortic disease of other aetiologies.

# 8.18.3 Hypertension bicuspid aortic valve-related aortopathy

Bicuspid aortic valve disease occurs in  $\sim$ 1 in 100 people, more often men, and is associated with coexistent aortic coarctation, which should be excluded in patients with bicuspid aortic valve disease. Bicuspid aortic valve disease is associated with an aortopathy, and the risk of development of aortic dilation is higher in patients with bicuspid aortic valve disease than in the normal population<sup>571</sup> and is probably exacerbated by hypertension. Beyond aortic dilation and aneurysm formation, bicuspid aortic valve disease is also a risk factor for dissection and rupture. 572 Thus, BP should be tightly controlled in patients with bicuspid aortic valve disease and targeted < 130/80 mmHg if tolerated. There is popular misconception that BP-lowering treatment has deleterious effects in patients with aortic stenosis and hypertension, when in fact it is well tolerated even in patients with severe aortic stenosis. Moreover, vasodilating drugs (including RAS blockers) also appear to be well tolerated. Thus, treatment of hypertension should be considered in these patients.<sup>573</sup>

# **8.19 Hypertension and sexual dysfunction**

Sexual dysfunction may have an important negative effect on the quality of life of both men and women. Compared with the normotensive population, the prevalence of sexual dysfunction is greater in hypertensive individuals, in whom it presents an important cause of low adherence to or discontinuation of antihypertensive treatment. <sup>574</sup> A large meta-analysis of prospective cohort studies has provided strong evidence that in men, erectile dysfunction (i.e. inadequate penile erection) is a significant independent risk factor for CV events and mortality, 575 which means that it may be viewed as an early marker of vascular damage. 576 Sexual dysfunction may be triggered or aggravated by treatment with thiazide or thiazide-like diuretics, conventional beta-blockers, or centrally acting agents (e.g. clonidine), while ACE inhibitors, ARBs, CCBs, or vasodilating betablockers may have neutral or even beneficial effects. 574,577 Phosphodiesterase-5 inhibitors are effective against erectile dysfunction in patients with hypertension. They should be given only in the absence of nitrate administration, but prescription also appears to be

<sup>&</sup>lt;sup>b</sup>Level of evidence.

safe in patients with multidrug BP-lowering treatment, <sup>578</sup> with some caution if treatment includes alpha-blockers. <sup>577</sup> However, it seems prudent for unstable patients with high CV risk or severe uncontrolled hypertension to defer sexual activity until their condition is stabilized and treatment for erectile dysfunction can be initiated. <sup>575</sup> Overall, studies on the effects of hypertension and antihypertensive therapy on female sexual dysfunction are limited, and the situation is thus less clear than in men, <sup>577,579</sup> although in a recent cross-sectional analysis among middle-aged and older treated hypertensive women in the SPRINT trial, neither BP values nor antihypertensive medication was associated with sexual dysfunction. <sup>579</sup>

It is recommended that information on sexual dysfunction is collected in all hypertensive patients at diagnosis and regularly at the follow-up visits, with special attention to its possible relationship with reluctance to start or adherence to drug treatment. In men reporting sexual dysfunction, the antihypertensive agents more likely to be associated with this effect (e.g. beta-blockers and thiazide diuretics) should be avoided or replaced, unless strictly necessary for the patient's clinical condition.

# 8.20 Hypertension and cancer therapy

Hypertension is the most common CV comorbidity reported in cancer registries, in which an elevated BP is usually found in more than one-third of the patients. This can be due to the high prevalence of hypertension at an age in which cancer is also common. However, it is also due to the pressor effect of two groups of widely used anticancer drugs, the inhibitors of the vascular endothelial growth factor signalling pathway (bevacizumab, sorafenib, sunitinib, and pazopanib) and the proteasome inhibitors (carfilzomib). While the former group of drugs inhibits the production of nitric oxide in the arterial wall, the latter reduces the vasodilator response to acetylcholine, favouring vasoconstriction and vasospasm.

In patients under treatment with the above-mentioned anticancer drugs, a BP increase has been reported in a variable but overall high per cent of patients (≤ 30%). The increase frequently occurs during the first months after starting the anticancer therapy, the temporal association providing evidence for the anticancer drug's pathophysiological role. It follows that office BP should be measured weekly during the initial part of the first cycle of therapy and at least every 2-3 weeks thereafter.<sup>582</sup> After the first cycle is completed and BP values appear to be stable, BP can be measured at the time of the routine clinical evaluations or assessed by HBPM. Patients developing hypertension (≥140/90 mmHg), or showing an increase in DBP ≥20 mmHg compared with pretreatment values, should initiate or optimize antihypertensive therapy, for which RAS blockers and CCBs may be considered the preferred drugs, and a RAS blocker-CCB combination is a frequently needed strategy. CCBs should only be of the dihydropiridine type, because diltiazem and verapamil block the CYP3A4 isoenzyme, which is involved in the metabolic pathway of sorafenib, increasing the drug's levels and

leading to potential toxicity.<sup>583</sup> Although anticancer therapy takes an obvious priority, its temporary discontinuation may be considered when BP values are exceedingly high despite multidrug treatment, in the presence of severe hypertension-generated symptoms, or when there is a CV event requiring an immediate effective BP control.<sup>584</sup>

# 8.21 Perioperative management of hypertension

With the increasing number of patients undergoing surgery, management of hypertension in the perioperative period (a term that includes the intraoperative phase) has emerged as an important issue in clinical practice. 585 ESC Guidelines have been issued for the assessment of CV variables, risk, and disease management of patients undergoing non-cardiac surgery. 586 While a BP elevation is per se not a strong risk factor for CV complications in non-cardiac surgery, overall CV risk assessment, including the search for HMOD, is important in treated and untreated hypertensive patients, and mandatory when a BP elevation is newly detected. 537,586 Postponing necessary surgery is usually not warranted in patients with grade 1 or 2 hypertension, whereas in those with an SBP ≥180 mmHg and/or DBP ≥110 mmHg, deferring the intervention until BP is reduced or controlled is advisable, except for emergency situations. What seems to be also important is to avoid large perioperative BP fluctuations. 537,586 This approach is supported by the findings from a recent RCT that has shown that in patients undergoing abdominal surgery, an individualized intraoperative treatment strategy, which kept BP values within a 10% difference from the preoperative office SBP, resulted in reduced risk of postoperative organ dysfunction. 587 There is no clear evidence in favour or against one vs. another antihypertensive treatment mode in patients undergoing non-cardiac surgery, and thus the general drug treatment algorithms apply to these patients as well.<sup>588,589</sup> However, the perioperative use of beta- blockers has been the object of controversy for many years, and the concern has recently been revived by meta-analyses showing some increase in the risk of hypotension, stroke, and mortality in patients on perioperative beta-blockers vs. placebo. 586,588,589 Continuation of beta-blockers is nevertheless recommended in hypertensive patients on chronic beta-blocker treatment<sup>586</sup> in whom their abrupt discontinuation may lead to BP or heart rate rebounds. 537 This may also occur with the abrupt discontinuation of central agents such as clonidine. More recently, the guestion has been raised whether RAS blockers should be discontinued before surgery to reduce the risk of intraoperative hypotension. 586,590 Preoperative discontinuation of these drugs has also been supported by a recent international prospective cohort study, in a heterogenous group of patients, in which withholding ACE inhibitors or ARBs 24 h before non-cardiac surgery was associated with a significant reduction in CV events and mortality 30 days after the intervention.<sup>591</sup>

# Perioperative management of hypertension

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that newly diagnosed hypertensive patients who are scheduled for elective surgery should be preoperatively screened for HMOD and CV risk.	1	C
It is recommended to avoid large perioperative BP fluctuations during the perioperative period. <sup>587</sup>	1	С
Non-cardiac surgery may not be deferred in patients with grade 1 or 2 hypertension (SBP <180 mmHg; DBP <110 mmHg).	IIb	U
Perioperative continuation of beta-blockers is recommended in hypertensive patients on chronic treatment with these drugs. 592,593	1	В
Abrupt discontinuation of beta-blockers or centrally acting agents (e.g. clonidine) is potentially harmful and is not recommended. 589,594	ш	В
Transient preoperative discontinuation of RAS blockers should be considered in patients with hypertension undergoing non-cardiac surgery.	lla	С

BP = blood pressure; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; RAS = renin-angiotensin system; SBP = systolic blood pressure.

# 9 Managing concomitant cardiovascular disease risk

# 9.1 Statins and lipid-lowering drugs

Patients with hypertension, and more so those with type 2 diabetes or metabolic syndrome, often have atherogenic dyslipidaemia characterized by elevated triglycerides and LDL cholesterol (LDL-C), and low HDL cholesterol (HDL-C). The benefit of adding a statin to antihypertensive treatment was well established in the ASCOT-Lipid Lowering Arm study and further studies, as summarized in previous European Guidelines. The beneficial effect of statin administration to patients without previous CV events [targeting an LDL-C value of <3.0 mmol/L (115 mg/dL)] has been strengthened by the findings from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) and HOPE-3 studies, 343,598 showing that lowering LDL-C in patients with baseline values <3.4 mmol/L (130 mg/dL) reduced the incidence of CV events by between 44 and 24%. This justifies the use of statins in hypertensive patients who have moderate—high CV risk. 599

As detailed in the recent ESC/EAS Guidelines, <sup>599</sup> when overt CVD is present and the CV risk is very high, statins should be administered to achieve LDL-C levels of <1.8 mmol/L (70 mg/dL) or a reduction of ≥50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL). <sup>600–602</sup> In patients at high CV risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL) or a reduction of ≥50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended. <sup>602</sup> Beneficial effects of statin therapy have also been shown in patients with a previous stroke with LDL-C targets <2.6 mmol/L (100 mg/dL). <sup>525</sup> Whether they also benefit from a target of <1.8 mmol/L (70 mg/dL) is open to future research. The summary of the available evidence suggests that many patients with hypertension would benefit from statin therapy.

# **9.2** Antiplatelet therapy and anticoagulant therapy

The most common complications of hypertension are related to thrombosis. 603 Hypertension predisposes to a prothrombotic state, 603 and also predisposes to LEAD, heart failure, or AF, which are common conditions associated with thromboembolism, whether systemic or venous.

Antiplatelet and anticoagulant therapy use in patients with hypertension was addressed in a Cochrane systematic review, <sup>604</sup> which included four randomized trials with a combined total of 44 012 patients. The authors concluded that overall acetylsalicylic acid (aspirin) did not reduce stroke or CV events compared with placebo in primary prevention patients with elevated BP and no previous CVD. <sup>604</sup> For secondary prevention, antiplatelet therapy in patients with elevated BP was reported as causing an absolute reduction in vascular events of 4.1% compared with placebo. <sup>604</sup>

Benefit has not been demonstrated for anticoagulation therapy, alone or in combination with aspirin, in patients with hypertension in the absence of other indications requiring anticoagulants, such as AF or venous thromboembolism.  $^{604}$  In anticoagulated patients, uncontrolled hypertension is one of the independent risk factors for intracranial haemorrhage and major bleeding.  $^{605}$  In such patients, attention to modifiable bleeding risk factors should be made during all patient contacts. Bleeding risk assessment with clinical risk scores such as the HAS-BLED [Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Older (>65), Drugs/alcohol concomitantly (1 point each)] score, includes uncontrolled hypertension (defined as SBP >160 mmHg) as one of the risk factors for bleeding;  $^{606}$  these should be used to 'flag up' patients at particularly high risk (e.g. HAS-BLED  $\geq$ 3) for more regular review and follow-up.  $^{607}$ 

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

In summary, aspirin is not recommended for primary prevention in hypertensive patients without CVD.<sup>35</sup> For secondary prevention, the benefit of antiplatelet therapy in patients with hypertension may be greater than the harm.<sup>35,604</sup> Ticlopidine, clopidogrel, and newer antiplatelet agents such as prasugrel and ticagrelor have not been sufficiently evaluated in patients with high BP.

# Treatment of CV risk factors associated with hypertension

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes. <sup>33</sup>	1	В
For patients at very high CV risk, statins are recommended to achieve LDL-C levels of <1.8 mmol/L (70 mg/dL), or a reduction of ≥50% if the baseline LDL-C is 1.8–3.5 mmol/L (70–135 mg/dL).	ı	В
For patients at high CV risk, statins are recommended to achieve an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of ≥50% if the baseline LDL-C is 2.6–5.2 mmol/L (100–200 mg/dL). 599,602	ı	В
For patients at low–moderate CV risk, statins should be considered to achieve an LDL-C value of <3.0 mmol/L (115 mg/dL). 598	lla	С
Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients. 35,604	ı	A
Aspirin is not recommended for primary prevention in hypertensive patients without CVD. 35,604	ш	A

CV = cardiovascular; CVD = cardiovascular disease; LDL-C = LDL cholesterol; SCORE = Systematic COronary Risk Evaluation.

# 9.3. Glucose-lowering drugs and blood pressure

The impact of new glucose-lowering drugs on BP and the reduction in CV and renal risk, beyond their effect of glucose control, have

received attention after the publication of the US Food and Drug Administration recommendations for evaluating CV risk in new therapies to treat type 2 diabetes. New generations of antidiabetes drugs, i.e. dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 agonists, slightly reduce BP, and also body weight with glucagon-like peptide 1 agonists. Two glucagon-like peptide 1 agonists (liraglutide and semaglutide) reduced CV and total mortality, but not heart failure, in patients with type 2 diabetes. More data are required with respect to the capacity of glucagon-like peptide 1 agonists and dipeptidyl peptidase 4 inhibitors to prevent heart failure.

Inhibitors of sodium-glucose co-transporter-2 are the only glucose-lowering drug class to reduce BP beyond the projected impact of weight reduction on BP. Empaglifozine<sup>475</sup> and canagliflozin<sup>476</sup> have demonstrated a reduction in heart failure and total and CV mortality, and a protective effect on renal function. Several mechanisms may account for these effects, and increased sodium excretion and improvements in tubuloglomerular balance reducing hyperfiltration are suggested mechanisms for the observed CV and renal protection, respectively.

# 10 Patient follow-up

# 10.1 Follow-up of hypertensive patients

After the initiation of antihypertensive drug therapy, it is important to review the patient at least once within the first 2 months to evaluate the effects on BP and assess possible side effects until BP is under control. The frequency of review will depend on the severity of hypertension, the urgency to achieve BP control, and the patient's comorbidities. SPC therapy should reduce BP within 1-2 weeks and may continue to reduce BP over the next 2 months. Once the BP target is reached, a visit interval of a few months is reasonable and evidence has been obtained that no difference exists in BP control between 3 and 6 month intervals.<sup>610</sup> Depending on the local organization of health resources, many of the later visits may be performed by non-physician health workers such as nurses.<sup>611</sup> For stable patients, HBPM and electronic communication with the physician may also provide an acceptable alternative to reduce the frequency of visits. 60,612,613 It is nevertheless advisable to assess risk factors and asymptomatic organ damage at least every 2 years.

# 10.2 Follow-up of subjects with high-normal blood pressure and white-coat hypertension

Patients with high—normal BP or white-coat hypertension frequently have additional risk factors, including HMOD, and have a higher risk of developing sustained hypertension 427,614–618 (see section 4). Thus, even when untreated, they should be scheduled for regular follow-up (at least annual visits) to measure office and out-of-office BP, as well as to check the CV risk profile. At annual visits, recommendations on

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

lifestyle changes, which represent the appropriate treatment in many of these patients, should be reinforced.

## **10.3 Elevated blood pressure at control visits**

The finding of an elevated BP should always lead physicians to search for the cause(s), particularly the most common ones such as poor adherence to the prescribed treatment regimen, persistence of a white-coat effect, and occasional or more regular consumption of salt, drugs, or substances that raise BP or oppose the antihypertensive effect of treatment (e.g. alcohol or non-steroidal anti-inflammatory drugs). This may require tactful but stringent questioning of the patient (and his/her relatives) to identify interfering factors, as well as repeated measurements of BP in the following weeks to ensure that BP has returned to controlled values. If ineffective treatment is regarded as the reason for inadequate BP control, the treatment regimen should be uptitrated in a timely fashion (see section 7); this avoids clinical inertia, a major contributor to poor BP control worldwide. 311

# 10.4 Improvement in blood pressure control in hypertension: drug adherence

There is growing evidence that poor adherence to treatment—in addition to physician inertia (i.e. lack of therapeutic action when the patient's BP is uncontrolled)—is the most important cause of poor BP control. Non-adherence to antihypertensive therapy correlates with higher risk of CV events. 312,622

Early discontinuation of treatment and suboptimal daily use of the prescribed regimens are the most common facets of poor adherence. After 6 months, more than one-third, and after 1 year, about one-half of patients may stop their initial treatment. Studies based on the detection of antihypertensive medications in blood or urine have shown that low adherence to the prescribed medications can affect  $\leq 50\%$  of patients with apparently resistant hypertension, and that poor adherence is strongly and inversely correlated with the number of pills prescribed. Early recognition of a lack of adherence might reduce the number of costly investigations and procedures (including interventional treatment), and avoid the prescription of unnecessary drugs.  $^{625}$ 

A major emphasis of these Guidelines has been to simplify the treatment strategy to try and improve adherence to treatment and BP control, by prescribing a single pill to most patients with hypertension. This is a response to the fact that despite the clear-cut benefits of BP treatment in trials, most treated patients do not achieve recommended BP targets in real life. The lower BP targets recommended in these Guidelines will mean that BP control rates will be even worse unless action is taken to ensure that patients are more likely to adhere to logical combinations of treatment.

Several methods are available to detect poor adherence, but most are indirect, poorly reliable, and provide little information on the most important issue: dosing history. Today, the most accurate methods that can be recommended, despite their limitations, are the detection of prescribed drugs in blood or urine samples. Directly observed treatment, followed by BP measurement over subsequent hours via HBPM or ABPM, can also be very useful to determine if BP really is poorly controlled despite witnessed consumption of medication in patients with apparent resistant hypertension. In contrast, questionnaires frequently overestimate drug adherence. The assessment of adherence should be improved with the development of cheaper and more reliable methods of detection that are easily applicable in daily practice. 354,626

Barriers to optimal adherence may be linked with physician attitudes, patient beliefs and behaviour, the complexity and tolerability of drug therapies, the healthcare system, and several other factors. Therefore, the assessment of adherence should always be conducted in a no-blame approach, and should favour an open discussion to identify the specific barriers limiting the patient's ability to follow the therapeutic recommendations. Individualized solutions should be found. Patients should be encouraged to take responsibility for their own CV health.

Patient adherence to therapy can be improved by several interventions. The most useful interventions are those linking drug intake with habits, <sup>347</sup> those giving adherence feedback to patients, self-monitoring of BP<sup>64</sup> using pill boxes and other special packaging, and motivational interviewing. Increasing the integration among health-care providers with the involvement of pharmacists and nurses increases drug adherence. Using multiple components has a greater effect on adherence, as the effect size of each intervention is generally modest. Recent data suggest that adherence to treatment may also be improved with the use of telemetry for transmission of recorded home values, maintaining contact between patients and physicians, and studies are ongoing. <sup>627</sup>

Prescription of an appropriate therapeutic regimen is crucial.<sup>389</sup> This might be achieved through: (i) possible drug-related adverse events, (ii) using long-acting drugs that require once daily dosage,<sup>628,629</sup> (iii) avoiding complex dosing schedules, (iv) using SPCs whenever possible, and (v) taking into consideration the effect of treatment on a patient's budget.

Compared with the large number of trials for individual drugs and treatments, there are only a limited number of rigorous trials on adherence interventions. Thus, the level of evidence indicating that a sustained improvement in medication adherence can be achieved within the resources available today in clinical practice is low. This is essentially due to the short duration of most studies, their heterogeneity, and their questionable designs. Whether available interventions ameliorate treatment outcomes remains to be demonstrated in adequate trials.

A list of the interventions associated with improved patient adherence to treatment is shown in *Table 33*.

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### Table 33 Interventions that may improve drug adherence in hypertension

### Physician level

Provide information on the risks of hypertension and the benefits of treatment, as well as agreeing a treatment strategy to achieve and maintain BP control using lifestyle measures and a single-pill-based treatment strategy when possible (information material, programmed learning, and computer-aided counselling)

Empowerment of the patient

Feedback on behavioural and clinical improvements

Assessment and resolution of individual barriers to adherence

Collaboration with other healthcare providers, especially nurses and pharmacists

#### Patient level

Self-monitoring of BP (including telemonitoring)

Group sessions

Instruction combined with motivational strategies

Self-management with simple patient-guided systems

Use of reminders

Obtain family, social, or nurse support

Provision of drugs at worksite

#### Drug treatment level

Simplification of the drug regimen favouring the use of SPC therapy

Reminder packaging

#### Health system level

Supporting the development of monitoring systems (telephone follow-up, home visits, and telemonitoring of home BP)

Financially supporting the collaboration between healthcare providers (e.g. pharmacists and nurses)

Reimbursement of SPC pills

Development of national databases, including prescription data, available for physicians and pharmacists

Accessibility to drugs

 $\label{eq:BP} BP = blood\ pressure; SPC = single-pill\ combination.$ 

## 10.5 Continued search for asymptomatic hypertension-mediated organ damage

The importance and need to detect HMOD at initial assessment to help risk stratify the patient, and to review the progression or regression of HMOD during follow-up, have been described in section 4. The presence of HMOD demonstrates that BP is elevated and that the patient would benefit from treatment. The regression of asymptomatic organ damage occurring during treatment can often indicate an improved prognosis (see section 5).

## 10.6 Can antihypertensive medications be reduced or stopped?

In some patients in whom treatment is accompanied by effective BP control for an extended period, it may be possible to reduce the number and/or dosage of drugs. This may particularly be the case if BP control is accompanied by healthy lifestyle changes such as weight loss, exercise habit, and a low-fat and low-salt diet, which remove environmental pressor influences. A reduction of medications should be made gradually, and the patient should be checked frequently

because reappearance of hypertension can occur quickly, within weeks, or may take many months. Patients with prior HMOD or previous accelerated hypertension should not have their treatment withdrawn.

### 11 Gaps in the evidence

### Gaps in the evidence and need for further studies

What is the optimal population screening programme for detecting hypertension?

What is the optimal method to measure BP in patients with AF?

What is the incremental benefit for CV risk prediction of the addition of out-of-office BP (HBPM and ABPM) to office BP measurement?

What is the incremental benefit, over the SCORE system, of measures of HMOD in reclassifying the CV risk of patients with hypertension?

What are the appropriate BP thresholds and targets for drug treatment in younger hypertensive patients?

What are the optimal BP treatment targets according to HBPM and ABPM?

What are the outcome benefits associated with antihypertensive treatment in patients with resistant hypertension?

What are the benefits of BP treatment for patients with BP in the high–normal range?

What baseline level of CV risk predicts treatment benefit?

More data on the benefits of BP treatment in the very elderly and the influence of frailty

Outcome-based comparison between office BP- and out-of-office BP-guided treatment

Outcome-based comparison between treatments guided by BP control and by HMOD reductions, especially in younger patients

More outcome studies of the optimal SBP treatment target for patients at different levels of baseline CV risk and with different comorbidities, including diabetes and CKD

More outcome studies of the optimal DBP treatment target

Impact of single-pill vs. multidrug treatment strategies on adherence to treatment, BP control, and clinical outcomes

Outcome-based comparison between treatment strategies based on initial monotherapy vs. initial combination therapy

What is the optimal salt intake to reduce CV and mortality risk?

What are the long-term outcome benefits resulting from the recommended lifestyle changes?

Outcome-based comparison between treatments based on thiazide vs. thiazide-like diuretics

Incremental value of central vs. peripheral BP in risk estimation and risk reduction by treatment

Outcome-based comparison of BP treatment with classical vs. vasodilator beta-blockers

Optimal BP treatment targets in specific clinical conditions (e.g. diabetes, CKD, and post-stroke)

Protective effect of antihypertensive treatment in patients with cognitive dysfunction or dementia

Role of antihypertensive treatment in white-coat hypertension

Role of antihypertensive treatment in masked hypertension

Optimal treatment of hypertension in different ethnic groups

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### 12 Key messages

(1) BP, epidemiology, and risk. Globally, over 1 billion people have hypertension. As populations age and adopt more sedentary lifestyles, the worldwide prevalence of hypertension will continue to rise towards 1.5 billion by 2025. Elevated BP is the leading global contributor to premature death, accounting for almost 10 million deaths in 2015, 4.9 million due to ischaemic heart disease and 3.5 million due to stroke. Hypertension is also a major risk factor for heart failure, AF, CKD, PAD, and cognitive decline.

- (2) Definition of hypertension. The classification of BP and the definition of hypertension is unchanged from previous European Guidelines, and is defined as an office SBP ≥140 and/or DBP ≥90 mmHg, which is equivalent to a 24 h ABPM average of ≥130/80 mmHg, or a HBPM average >135/85 mmHg.
- (3) Screening and diagnosis of hypertension. Hypertension is usually asymptomatic (hence the term 'silent killer'). Because of its high prevalence, screening programmes should be established to ensure that BP is measured in all adults at least every 5 years, and more frequently in people with a high–normal BP. When hypertension is suspected because of an elevated screening BP, the diagnosis of hypertension should be confirmed either by repeated office BP measurements over a number of visits or by out-of-office BP measurement using 24 h ABPM or HBPM.
- (4) The importance of cardiovascular risk assessment and detection of HMOD. Other CV risk factors such as dyslipidaemia and metabolic syndrome frequently cluster with hypertension. Thus, unless the patient is already at high or very high risk due to established CVD, formal CV risk assessment is recommended using the SCORE system. However, it is important to recognise that the presence of HMOD, especially LVH, CKD, or advanced retinopathy, further increases the risk of CV morbidity and mortality, and should be screened for as part of risk assessment in hypertensive patients because the SCORE system alone may underestimate their risk.
- (5) Think: could this patient have secondary hypertension? For most people with hypertension, no underlying cause will be detected. Secondary (and potentially remediable) causes of hypertension are more likely to be present in people with young onset of hypertension (<40 years), people with severe or treatment-resistant hypertension, or people who suddenly develop significant hypertension in midlife on a background of previously normal BP. Such patients should be referred for specialist evaluation.</p>
- (6) Treatment of hypertension: importance of lifestyle interventions. The treatment of hypertension involves lifestyle interventions and drug therapy. Many patients with hypertension will require drug therapy, but lifestyle interventions are important because they can delay the need for drug treatment or complement the BP-lowering effect of drug treatment. Moreover, lifestyle interventions such as sodium restriction, alcohol moderation, healthy eating, regular exercise, weight control, and smoking cessation all have health benefits beyond their impact on BP.
- (7) When to consider drug treatment of hypertension. The treatment thresholds for hypertension are now less conservative than they were in previous Guidelines. We now recommend that patients with low-moderate-risk grade 1 hypertension (office BP 140–159/90–99), even if they do not have HMOD, should now

- receive drug treatment if their BP is not controlled after a period of lifestyle intervention alone. For higher-risk patients with grade 1 hypertension, including those with HMOD, or patients with higher grades of hypertension (e.g. grade 2 hypertension, ≥160/100 mmHg), we recommend initiating drug treatment alongside lifestyle interventions. These recommendations apply to all adults aged <80 years.
- (8) Special considerations in frail and older patients. It is increasingly recognised that biological rather than chronological age, as well as consideration of frailty and independence, are important determinants of the tolerability of and likely benefit from BP-lowering medications. It is important to note that even in the very old (i.e. >80 years), BP-lowering therapy reduces mortality, stroke, and heart failure. Thus, these patients should not be denied treatment or have treatment withdrawn simply on the basis of age. For people >80 years who have not yet received treatment for their BP, treatment is recommended when their office SBP is ≥160 mmHg, provided that the treatment is well tolerated.
- (9) How low should SBP be lowered? This has been a hotly debated topic. A key discussion point is the balance of potential benefits vs. potential harm or adverse effects. This is especially important whenever BP targets are lowered, as there is a greater potential for harm to exceed benefit. Thus, in these Guidelines, we recommend a target range. The evidence strongly suggests that lowering office SBP to <140 mmHg is beneficial for all patient groups, including independent older patients. There is also evidence to support targeting SBP to 130 mmHg for most patients, if tolerated. Even lower SBP levels (<130 mmHg) will be tolerated and potentially beneficial for some patients, especially to further reduce the risk of stroke. SBP should not be targeted to <120 mmHg because the balance of benefit vs. harm becomes concerning at these levels of treated SBP.</p>
- BP targets in old and very old patients. As discussed above, independence, frailty, and comorbidities will all influence treatment decisions, especially in older (≥65 years) and very old (>80 years) patients. The desired SBP target range for all patients aged >65 years is 130–139 mmHg. This is lower than in previous Guidelines and may not be achievable in all older patients, but any BP lowering towards this target is likely to be beneficial provided that the treatment is well tolerated.
- (11) **BP** targets in patients with diabetes and/or CKD. The BP treatment targets for patients with diabetes or kidney disease have been a moving target in previous Guidelines because of seemingly contradictory results from major outcome trials and meta-analyses. For diabetes, targeting the SBP to <140 mmHg and towards 130 mmHg, as recommended for all other patient groups, is beneficial on major outcomes. Moreover, targeting SBP to <130 mmHg, for those who will tolerate it, may further reduce the risk of stroke but not other major outcomes. SBP should not be <120 mmHg. For patients with CKD, the evidence suggests that the target BP range should be 130–139 mmHg.
- (12) **How low should DBP be lowered?** The optimal DBP target has been less well defined, but a DBP target of <80 mmHg is recommended. Some patients with stiff arteries and isolated systolic hypertension will already have DBP levels below this target. These are high-risk patients and the low DBP should not discourage

treatment of their elevated SBP to the recommended target, provided that treatment is well tolerated.

- (13) The need to do better on BP control. A key message in these Guidelines is the need to do better at improving BP control rates. Despite the overwhelming evidence of treatment benefit, on average, <50% of patients with treated hypertension achieve an SBP target of <140 mmHg. Physician inertia (inadequate uptitration of treatment, especially from monotherapy) and poor patient adherence to treatment (especially when based on multiple pills) are now recognised as the major factors contributing to poor BP control.
- (14) Start treatment in most patients with two drugs, not one. Monotherapy is usually inadequate therapy for most people with hypertension; this will be especially true now that the BP treatment targets for many patients are lower than in previous Guidelines. These Guidelines have set out to normalize the concept that initial therapy for the majority of patients with hypertension should be with a combination of two drugs, not a single drug. The only exception would be in a limited number of patients with a lower baseline BP close to their recommended target, who might achieve that target with a single drug, or in some frailer old or very old patients in whom more gentle reduction of BP may be desirable. Evidence suggests that this approach will improve the speed, efficiency, and consistency of initial BP lowering and BP control, and is well tolerated by patients.
- (15) A single-pill strategy to treat hypertension. Poor adherence to longer-term BP-lowering medication is now recognised as a major factor contributing to poor BP control rates. Research has shown a direct correlation between the number of BP-lowering pills and poor adherence to medications. Moreover, SPC therapy has been shown to improve adherence to treatment. SPC therapy is now the preferred strategy for initial two-drug combination treatment of hypertension and for three-drug combination therapy when required. This will control the BP of most patients with a single pill and could transform BP control rates.
- (16) A simplified drug treatment algorithm. We have simplified the treatment strategy so that patients with uncomplicated hypertension and many patients with a variety of comorbidities (e.g. HMOD, diabetes, PAD, or cerebrovascular disease) receive similar

- medication. We recommend a combination of an ACE inhibitor or ARB with a CCB or thiazide/thiazide-like diuretic as initial therapy for most patients. For those requiring three drugs, we recommend a combination of an ACE inhibitor or ARB with a CCB and a thiazide/thiazide-like diuretic. We recommend that beta-blockers be used when there is a specific indication for their use (e.g. angina, post-myocardial infarction, HFrEF, or when heart rate control is required).
- (17) Hypertension in women and in pregnancy. In women with hypertension who are planning pregnancy, ACE inhibitors or ARBs and diuretics should be avoided, and the preferred medications to lower BP, if required, include alpha-methyl dopa, labetalol, or CCBs. The same drugs are suitable if BP lowering is required in pregnant women. ACE inhibitors or ARBs should not be used in pregnant women.
- (18) Is there a role for device-based therapy for the treatment of hypertension? A number of device-based interventions have been developed and studied for the treatment of hypertension. To date, the results from these studies have not provided sufficient evidence to recommend their routine use. Consequently, the use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.
- (19) Managing cardiovascular disease risk in hypertensive patients beyond BP: statins. For hypertensive patients at moderate CVD risk or higher, or those with established CVD, BP lowering alone will not optimally reduce their risk. These patients would also benefit from statin therapy, which further reduces the risk of a myocardial infarction by approximately one-third and stroke by approximately one-quarter, even when BP is controlled. Similar benefits have been seen in hypertensive patients at the border between low and moderate-risk. Thus, many more hypertensive patients would benefit from statin therapy than are currently receiving this treatment.
- (20) Managing cardiovascular disease risk in hypertensive patients beyond BP: antiplatelet therapy. Antiplatelet therapy, especially low-dose aspirin, is recommended for secondary prevention in hypertensive patients, but is not recommended for primary prevention (i.e. in patients without CVD).

### 13 'What to do' and 'what not to do' messages from the Guidelines

ecommendations	Class <sup>a</sup>	Levelb
classification of BP		
is recommended that BP be classified as optimal, normal, or high–normal, or grades 1–3 hypertension, according to office P.	1	С
creening for hypertension		
creening programmes for hypertension are recommended. All adults (≥18 years) should have their office BP measured and ecorded in their medical file, and be aware of their BP.	1	В
piagnosis of hypertension		
is recommended to base the diagnosis of hypertension on:  Repeated office BP measurements on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). At each visit, three BP measurements should be recorded, 1–2 min apart, and additional measurements performed if the first two readings differ by >10 mmHg. The patient's BP is the average of the last two BP readings.	1	С
PR Out-of-office BP measurement with ABPM and/or HBPM, provided that these measurements are logistically and econor cally feasible.	ni- <b>I</b>	С
Office BP thresholds for the initiation of drug treatment for hypertension		
rompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of C\sk, simultaneously with the initiation of lifestyle changes.	1	Α
patients with grade 1 hypertension:  Lifestyle interventions are recommended to determine if this will normalize BP.	1	В
In patients with grade 1 hypertension at low-moderate-risk and without evidence of HMOD, BP-lowering drug treatment recommended if the patient remains hypertensive after a period of lifestyle intervention. <sup>c</sup>		A
In patients with grade 1 hypertension at high risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions.	)- I	A
fit older patients with hypertension (even if aged >80 years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is ≥160 mmHg.	1	А
P-lowering drug treatment and lifestyle intervention are recommended in fit older patients (>65 years but not >80 years) then SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.	1	A
patients with high–normal BP (130–139/85–89 mmHg), lifestyle changes are recommended.	1	Α
vithdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥80 years, is not recomended, provided that treatment is well tolerated.	Ш	A
Office BP treatment targets		
is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients, and provided nat the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.	1	А
patients <65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120–129 imHg in most patients. <sup>d</sup>	1	А
older patients (aged ≥65 years) receiving BP-lowering drugs, it is recommended that SBP should be targeted to a BP range of 30–139 mmHg.	of I	А

Salt restriction to <5 g per day is recommended.	1	A
It is recommended to restrict alcohol consumption to <14 units per week for men and <8 units per week for women.	ı	Α
Increased consumption of vegetables, fresh fruits, fish, nuts, unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended.	- 1	А
Body weight control is indicated to avoid obesity (BMI >30 kg/m², or waist circumference >102 cm in men and >88 cm in women) and aim for healthy BMI (about 20–25 kg/m²) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk.	-	A
Regular aerobic exercise (e.g. ≥30 min of moderate dynamic exercise on 5–7 days per week) is recommended.	ı	Α
Smoking cessation and supportive care and referral to smoking cessation programmes are recommended.	ı	В
It is recommended to avoid binge drinking.	Ш	A
Treatment of hypertension: drug treatment		
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes	ı	A
can be used.It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations (e.g. angina, post-myocardial infarction, heart failure, or heart rate control).	_	A
It is recommended to initiate antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg). 342,346,351	- 1	В
It is recommended that if BP is not controlled <sup>e</sup> with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and thiazide/thiazide-like diuretics, preferably as an SPC.	- 1	А
It is recommended that if BP is not controlled <sup>e</sup> with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.	_	В
The combination of two RAS blockers is not recommended.	Ш	A
Treatment of hypertension: device-based therapies		
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.	ш	В
Management of CVD risk in hypertensive patients		
CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes.	ı	В
For patients at high or very high CV risk, statins are recommended.	ı	В
Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients.	ı	Α
Aspirin is not recommended for primary prevention in hypertensive patients without CVD.	ш	A
Routine genetic testing for hypertensive patients is not recommended.	Ш	С

ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; CCB = calcium channel blocker; CV = cardiovascular; CVD = cardiovascular disease; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; RAS = renin-angiotensin system; RCT = randomized controlled trial; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation; SPC = single-pill combination.

<sup>&</sup>lt;sup>a</sup>Class of recommendation.

<sup>&</sup>lt;sup>b</sup>Level of evidence.

In patients with grade 1 hypertension and low-moderate-risk, drug treatment may be preceded by a prolonged period of lifestyle intervention to determine if this will normalize BP. The duration of the lifestyle intervention alone will depend on the level of BP within the grade 1 range (i.e. the likelihood of achieving BP control with lifestyle intervention alone) and the opportunities for significant lifestyle change in individual patients.

 $<sup>^{\</sup>rm d} Less$  evidence is available for this target in low-moderate-risk patients.

<sup>&</sup>lt;sup>e</sup>Adherence to medication should be checked.

### 14 Appendix

ESC Committee for Practice Guidelines (CPG): Stephan Windecker (Chairperson) (Switzerland), Victor Aboyans (France), Stefan Agewall (Norway), Emanuele Barbato (Italy), Héctor Bueno (Spain), Antonio Coca (Spain), Jean-Philippe Collet (France), Ioan Mircea Coman (Romania), Veronica Dean (France), Victoria Delgado (The Netherlands), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Gerhard Hindricks (Germany), Bernard Iung (France), Peter Jüni (Canada), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Patrizio Lancellotti (Belgium), Christophe Leclercq (France), Theresa A. McDonagh (UK), Massimo Francesco Piepoli (Italy), Piotr Ponikowski (Poland), Dimitrios J. Richter (Greece), Marco Roffi (Switzerland), Evgeny Shlyakhto (Russia), Iain A. Simpson (UK), Miguel Sousa-Uva (Portugal), Jose Luis Zamorano (Spain).

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