2013 ESH/ESC Guidelines for the management of arterial hypertension

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

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Abbreviations and acronyms: ABCD, Appropriate Blood pressure Control in Diabetes; ABI, ankle-brachial index; ABPM, ambulatory blood pressure monitoring; ACCESS, Acute Candesartan Cilexetil Therapy in Stroke Survival; ACCOMPLISH, Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACE, angiotensin-converting enzyme; ACTIVE I, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; AHEAD, Action for HEAlth in Diabetes; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart ATtack; ALTITUDE, ALiskiren Trial In Type 2 Diabetes Using Cardio-renal Endpoints; ANTIPAF, ANgioTensin II Antagonist In Paroxysmal Atrial Fibrillation; APOLLO, A Randomized Controlled Trial of Aliskiren in the Prevention of Major Cardiovascular Events in Elderly People; ARB, angiotensin receptor blocker; ARIC, Atherosclerosis Risk In Communities; ARR, aldosterone renin ratio; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; ASTRAL, Angioplasty and STenting for Renal Artery Lesions; A-V, atrioventricular; BB, beta-blocker; BMI, body mass index; BP, blood pressure; BSA, body surface area; CA, calcium antagonist; CABG, coronary artery bypass graft; CAPPP, CAPtopril Prevention Project; CAPRAF, CAndesartan in the Prevention of Relapsing Atrial Fibrillation; CHD, coronary heart disease; CHHIPS, Controlling Hypertension and Hypertension Immediately Post-Stroke; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease—EPIdemiology collaboration; CONVINCE, Controlled ONset Verapamil INvestigation of CV Endpoints; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; D, diuretic; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; DCCT, Diabetes Control and Complications Study; DIRECT, DIabetic REtinopathy Candesartan Trials; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase 4; EAS, European Atherosclerosis Society; EASD, European Association for the Study of

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The affiliations of the Task Force members are listed in Appendix 2. The disclosure forms of the authors and reviewers are available on the respective Society websites: http://eshonline.org and www.escardio.org/guidelines

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Diabetes; ECG, electrocardiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ELSA, European Lacidipine Study on Atherosclerosis; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ESRD, end-stage renal disease; EXPLOR, Amlodipine-Valsartan Combination Decreases Central Systolic Blood Pressure more Effectively than the Amlodipine-Atenolol Combination; FDA, U.S. Food and Drug Administration; FEVER, Felodipine EVent Reduction study; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation; HbA1c, glycated haemoglobin; HBPM, home blood pressure monitoring; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment; HRT, hormone replacement therapy; HT, hypertension; HYVET, HYpertension in the Very Elderly Trial; IMT, intima-media thickness; INTERHEART, Effect of Potentially Modifiable Risk Factors associated with Myocardial Infarction in 52 Countries; INVEST, INternational VErapamil SR/T Trandolapril; I-PRESERVE, Irbesartan in Heart Failure with Preserved Systolic Function; ISH, Isolated systolic hypertension; JNC, Joint National Committee; JUPITER, Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; LAVi, left atrial volume index; LIFE, Losartan Intervention For Endpoint Reduction in Hypertensives; LV, left ventricle/left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass; MDRD, Modification of Diet in Renal Disease; MRFIT, Multiple Risk Factor Intervention Trial; MRI, magnetic resonance imaging; NORDIL, The Nordic Diltiazem Intervention study; OC, oral contraceptive; OD, organ damage; ONTARGET, ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PAD, peripheral artery disease; PATHS, Prevention And Treatment of Hypertension Study; PCI, percutaneous coronary intervention; PPAR, peroxisome proliferator-activated receptor; PREVEND, Prevention of REnal and Vascular ENdstage Disease; PROFESS, Prevention Regimen for Effectively Avoiding Secondary Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; PWV, pulse wave velocity; QALY, Quality adjusted life years; RAA, renin-angiotensin-aldosterone; RAS, renin-angiotensin system; RCT, randomized controlled trials; RF, risk factor; ROADMAP, Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention; SBP, systolic blood pressure; SCAST, Angiotensin-Receptor Blocker Candesartan for Treatment of Acute STroke; SCOPE, Study on COgnition and Prognosis in the Elderly; SCORE, Systematic COronary Risk Evaluation; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trials in Old Patients with Hypertension; STOP-2, The second Swedish Trial in Old Patients with Hypertension; SYSTCHINA, SYSTolic Hypertension in the Elderly: Chinese trial; SYSTEUR, SYSTolic Hypertension in Europe; TIA, transient ischaemic attack; TOHP, Trials Of Hypertension Prevention; TRANSCEND, Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans' Affairs Diabetes Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; WHO, World Health Organization

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1. INTRODUCTION

1.1 Principles

The 2013 guidelines on hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) follow the guidelines jointly issued by the two societies in 2003 and 2007 [1,2]. Publication of a new document 6 years after the previous one was felt to be timely because, over this period, important studies have been conducted and many new results have been published on both the diagnosis and treatment of individuals with an elevated blood pressure (BP), making refinements, modifications and expansion of the previous recommendations necessary.

The 2013 ESH/ESC guidelines continue to adhere to some fundamental principles that inspired the 2003 and 2007 guidelines, namely (i) to base recommendations on properly conducted studies identified from an extensive review of the literature, (ii) to consider, as the highest priority, data from randomized, controlled trials (RCTs) and their meta-analyses, but not to disregard—particularly when dealing with diagnostic aspects—the results of observational and other studies of appropriate scientific calibre, and (iii) to grade the level of scientific evidence and the strength of recommendations on major diagnostic and treatment issues as in European guidelines on other diseases, according to ESC recommendations (Tables 1 and 2). While it was not done in the 2003 and 2007 guidelines, providing the recommendation class and the level of evidence is now regarded as important for providing interested readers with a standard approach, by which to compare the state of knowledge across different fields of medicine. It was also thought that this could more effectively alert physicians on recommendations that are based on the opinions of the experts rather than on evidence. This is not uncommon in medicine because, for a great part of daily medical practice, no good science is available and recommendations must therefore stem from common sense and personal clinical experience, both of which can be fallible. When appropriately recognized, this can avoid guidelines being perceived as prescriptive and favour the performance of studies where opinion prevails and evidence is lacking. A fourth principle, in line with its educational purpose, is to provide a large number of tables and a set of concise recommendations that could be easily and rapidly consulted by physicians in their routine practice.

The European members of the Task Force in charge of the 2013 guidelines on hypertension have been appointed by the ESH and ESC, based on their recognized expertise and absence of major conflicts of interest [their declaration of interest forms can be found on the ESC website (www.escardio.org/guidelines) and ESH website (www.eshonline.org)]. Each member was assigned a specific writing task, which was reviewed by three co-ordinators

TABLE 1. 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

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TABLE 2. 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.

and then by two chairmen, one appointed by ESH and another by ESC. The text was finalized over approximately 18 months, during which the Task Force members met collectively several times and corresponded intensively with one another between meetings. Before publication, the document was also assessed twice by 42 European reviewers, half selected by ESH and half by ESC. It can thus be confidently stated that the recommendations issued by the 2013 ESH/ESC guidelines on hypertension largely reflect the state of the art on hypertension, as viewed by scientists and physicians in Europe. Expenses for meetings and the remaining work have been shared by ESH and ESC.

1.2 New aspects

Because of new evidence on several diagnostic and therapeutic aspects of hypertension, the present guidelines differ in many respects from the previous ones [2]. Some of the most important differences are listed below:

1. Epidemiological data on hypertension and BP control in Europe.
2. Strengthening of the prognostic value of home blood pressure monitoring (HBPM) and of its role for diagnosis and management of hypertension, next to ambulatory blood pressure monitoring (ABPM).
3. Update of the prognostic significance of night-time BP, white-coat hypertension and masked hypertension.
4. Re-emphasis on integration of BP, cardiovascular (CV) risk factors, asymptomatic organ damage (OD) and clinical complications for total CV risk assessment.
5. Update of the prognostic significance of asymptomatic OD, including heart, blood vessels, kidney, eye and brain.
6. Reconsideration of the risk of overweight and target body mass index (BMI) in hypertension.
7. Hypertension in young people.
8. Initiation of antihypertensive treatment. More evidence-based criteria and no drug treatment of high normal BP.
9. Target BP for treatment. More evidence-based criteria and unified target systolic blood pressure (SBP) (<140 mmHg) in both higher and lower CV risk patients.
10. Liberal approach to initial monotherapy, without any all-ranking purpose.
11. Revised schema for priorital two-drug combinations.
12. New therapeutic algorithms for achieving target BP.
13. Extended section on therapeutic strategies in special conditions.
14. Revised recommendations on treatment of hypertension in the elderly.
15. Drug treatment of octogenarians.
16. Special attention to resistant hypertension and new treatment approaches.
17. Increased attention to OD-guided therapy.
18. New approaches to chronic management of hypertensive disease.

2. EPIDEMIOLOGICAL ASPECTS

2.1 Relationship of blood pressure to cardiovascular and renal damage

The relationship between BP values and CV and renal morbid-and fatal events has been addressed in a large number of observational studies [3]. The results, reported in detail in the 2003 and 2007 ESH/ESC guidelines [1,2], can be summarized as follows:

1. Office BP bears an independent continuous relationship with the incidence of several CV events [stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease (PAD)] as well as of end-stage renal disease (ESRD) [3–5]. This is true at all ages and in all ethnic groups [6,7].
2. The relationship with BP extends from high BP levels to relatively low values of 110–115 mmHg for SBP and 70–75 mmHg for diastolic BP (DBP). SBP appears to be a better predictor of events than DBP after the age of 50 years [8,9], and in elderly individuals pulse pressure (the difference between SBP and DBP values) has been reported to have a possible additional prognostic role [10]. This is indicated also by the particularly high CV risk exhibited by patients with an elevated SBP and a normal or low DBP [isolated systolic hypertension (ISH)] [11].
3. A continuous relationship with events is also exhibited by out-of-office BP values, such as those obtained by ABPM and HBPM (see Section 3.1.2).
4. The relationship between BP and CV morbidity and mortality is modified by the concomitance of other CV risk factors. Metabolic risk factors are more common when BP is high than when it is low [12,13].

2.2 Definition and classification of hypertension

The continuous relationship between BP and CV and renal events makes the distinction between normotension and hypertension difficult when based on cut-off BP values. This is even more so because, in the general population,

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TABLE 3. Definitions and classification of office blood pressure levels (mmHg)[a]

Category	Systolic		Diastolic
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	≥140	and	<90

[a]The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.

SBP and DBP values have a unimodal distribution [14]. In practice, however, cut-off BP values are universally used, both to simplify the diagnostic approach and to facilitate the decision about treatment. The recommended classification is unchanged from the 2003 and 2007 ESH/ESC guidelines (Table 3). Hypertension is defined as values >140 mmHg SBP and/or >90 mmHg DBP, based on the evidence from RCTs that in patients with these BP values treatment-induced BP reductions are beneficial (see Sections 4.1 and 4.2). The same classification is used in young, middle-aged and elderly subjects, whereas different criteria, based on percentiles, are adopted in children and teenagers for whom data from interventional trials are not available. Details on BP classification in boys and girls according to their age and height can be found in the ESH's report on the diagnosis, evaluation and treatment of high BP in children and adolescents [15].

2.3 Prevalence of hypertension

Limited comparable data are available on the prevalence of hypertension and the temporal trends of BP values in different European countries [16]. Overall the prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing. There also appear to be noticeable differences in the average BP levels across countries, with no systematic trends towards BP changes in the past decade [17–37].

Owing to the difficulty of obtaining comparable results among countries and overtime, the use of a surrogate of hypertension status has been suggested [38]. Stroke mortality is a good candidate, because hypertension is by far the most important cause of this event. A close relationship between prevalence of hypertension and mortality for stroke has been reported [39]. The incidence and trends of stroke mortality in Europe have been analysed by use of World Health Organization (WHO) statistics. Western European countries exhibit a downward trend, in contrast to eastern European countries, which show a clear-cut increase in death rates from stroke [40].

2.4 Hypertension and total cardiovascular risk

For a long time, hypertension guidelines focused on BP values as the only- or main variables determining the need for—and the type of—treatment. In 1994, the ESC, ESH and European Atherosclerosis Society (EAS) developed joint recommendations on prevention of coronary heart disease (CHD) in clinical practice [41], and emphasized that prevention of CHD should be related to quantification of total (or global) CV risk. This approach is now generally accepted and had already been integrated into the 2003 and 2007 ESH/ESC guidelines for the management of arterial hypertension [1,2]. The concept is based on the fact that only a small fraction of the hypertensive population has an elevation of BP alone, with the majority exhibiting additional CV risk factors. Furthermore, when concomitantly present, BP and other CV risk factors may potentiate each other, leading to a total CV risk that is greater than the sum of its individual components. Finally, in high-risk individuals, antihypertensive treatment strategies (initiation and intensity of treatment, use of drug combinations, etc.: see Sections 4,5,6 and 7), as well as other treatments, may be different from those to be implemented in lower-risk individuals. There is evidence that, in high-risk individuals, BP control is more difficult and more frequently requires the combination of antihypertensive drugs with other therapies, such as aggressive lipid-lowering treatments. The therapeutic approach should consider total CV risk in addition to BP levels in order to maximize cost-effectiveness of the management of hypertension.

2.4.1 Assessment of total cardiovascular risk

Estimation of total CV risk is easy in particular subgroups of patients, such as those with antecedents of established cardiovascular disease (CVD), diabetes, CHD or with severely elevated single risk factors. In all of these conditions, the total CV risk is high or very high, calling for intensive CV risk-reducing measures. However, a large number of patients with hypertension do not belong to any of the above categories and the identification of those at low, moderate, high or very high risk requires the use of models to estimate total CV risk, so as to be able to adjust the therapeutic approach accordingly.

Several computerized methods have been developed for estimating total CV risk [41–48]. Their values and limitations have been reviewed recently [49]. The Systematic COronary Risk Evaluation (SCORE) model has been developed based on large European cohort studies. The model estimates the risk of dying from CV (not just coronary) disease over 10 years based on age, gender, smoking habits, total cholesterol and SBP [43]. The SCORE model allows calibration of the charts for individual countries, which has been done for numerous European countries. At the international level, two sets of charts are provided: one for high-risk and one for low-risk countries. The electronic, interactive version of SCORE, known as Heart Score (available through www.heartscore.org), is adapted to also allow

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adjustment for the impact of high-density lipoprotein cholesterol on total CV risk.

The charts and their electronic versions can assist in risk assessment and management but must be interpreted in the light of the physician's knowledge and experience, especially with regard to local conditions. Furthermore, the implication that total CV risk estimation is associated with improved clinical outcomes when compared with other strategies has not been adequately tested.

Risk may be higher than indicated in the charts in:

1. Sedentary subjects and those with central obesity; the increased relative risk associated with overweight is greater in younger subjects than in older subjects.
2. Socially deprived individuals and those from ethnic minorities.
3. Subjects with elevated fasting glucose and/or an abnormal glucose tolerance test, who do not meet the diagnostic criteria for diabetes.
4. Individuals with increased triglycerides, fibrinogen, apolipoprotein B, lipoprotein(a) levels and high-sensitivity C-reactive protein.
5. Individuals with a family history of premature CVD (before the age of 55 years in men and 65 years in women).

In SCORE, total CV risk is expressed as the absolute risk of dying from CVD within 10 years. Because of its heavy dependence on age, in young patients, absolute total CV risk can be low even in the presence of high BP with additional risk factors. If insufficiently treated, however, this condition may lead to a partly irreversible high-risk condition years later. In younger subjects, treatment decisions should better be guided by quantification of relative risk or by estimating heart and vascular age. A relative-risk chart is available in the Joint European Societies'Guidelines on CVD Prevention in Clinical Practice [50], which is helpful when advising young persons.

Further emphasis has been given to identification of OD, since hypertension-related asymptomatic alterations in several organs indicate progression in the CVD continuum, which markedly increases the risk beyond that caused by the simple presence of risk factors. A separate section (Section 3.7) is devoted to searching for asymptomatic OD [51–53], where evidence for the additional risk of each subclinical alteration is discussed.

For more than a decade, international guidelines for the management of hypertension (the 1999 and 2003 WHO/International Society of Hypertension Guidelines and the 2003 and 2007 ESH/ESC Guidelines) [1,2,54,55] have stratified CV risk in different categories, based on BP category, CV risk factors, asymptomatic OD and presence of diabetes, symptomatic CVD or chronic kidney disease (CKD), as also done by the 2012 ESC prevention guidelines [50]. The classification in low, moderate, high and very high risk is retained in the current guidelines and refers to the 10-year risk of CV mortality as defined by the 2012 ESC prevention guidelines (Fig. 1) [50]. The factors on which the stratification is based are summarized in Table 4.

2.4.2 Limitations

All currently available models for CV risk assessment have limitations that must be appreciated. The significance of OD in determining calculation of overall risk is dependent on how carefully the damage is assessed, based on available facilities. Conceptual limitations should also be mentioned. One should never forget that the rationale of estimating total CV risk is to govern the best use of limited resources to prevent CVD; that is, to grade preventive measures in relation to the increased risk. Yet, stratification of absolute risk is often used by private or public healthcare providers to establish a barrier, below which treatment is discouraged. It should be kept in mind that any threshold used to define high total CV risk is arbitrary, as well as the use of a cut-off value leading to intensive interventions above this threshold and no action at all below. Finally, there is a

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

FIGURE 1 Stratification of total CV risk in categories of low, moderate, high and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKD stage or symptomatic CVD. Subjects with a high normal office but a raised out-of-office BP (masked hypertension) have a CV risk in the hypertension range. Subjects with a high office BP but normal out-of-office BP (white-coat hypertension), particularly if there is no diabetes, OD, CVD or CKD, have lower risk than sustained hypertension for the same office BP.

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TABLE 4. Factors—other than office BP—influencing prognosis; used for stratification of total CV risk in Fig. 1

Risk factors
Male sex
Age (men ≥55 years; women ≥65 years)
Smoking
Dyslipidaemia
Total cholesterol >4.9 mmol/L (190 mg/dL), and/or
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or
Triglycerides >1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity [BMI ≥30 kg/m^2 (height^2)]
Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)
Family history of premature CVD (men aged <55 years; women aged <65 years)
Asymptomatic organ damage
Pulse pressure (in the elderly) ≥60 mmHg
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or
Echocardiographic LVH [LVM index: men >115 g/m^2; women >95 g/m^2 (BSA)][a]
Carotid wall thickening (IMT >0.9 mm) or plaque
Carotid–femoral PWV >10 m/s
Ankle-brachial index <0.9
CKD with eGFR 30–60 ml/min/1.73 m^2 (BSA)
Microalbuminuria (30–300 mg/24 h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)
Diabetes mellitus
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or
HbA_{1c} >7% (53 mmol/mol), and/or
Post-load plasma glucose >11.0 mmol/L (198 mg/dL)
Established CV or renal disease
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral artery disease
CKD with eGFR <30 mL/min/1.73m^2 (BSA); proteinuria (>300 mg/24 h).
Advanced retinopathy: haemorrhages or exudates, papilloedema

BMI, body mass index; BP, blood pressure; BSA, body surface area; CABG, coronary artery bypass graft; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IMT, intima-media thickness; LVH, left ventricular hypertrophy; LVM, left ventricular mass; PCI, percutaneous coronary intervention; PWV, pulse wave velocity.
[a]Risk maximal for concentric LVH: increased LVM index with a wall thickness/radius ratio of 0.42.

strong effect of age on total CV risk models. It is so strong that younger adults (particularly women) are unlikely to reach high-risk levels even when they have more than one major risk factor and a clear increase in relative risk. By contrast, many elderly men (e.g. >70 years) reach a high total risk level whilst being at very little increased risk relative to their peers. The consequences are that most resources are concentrated in older subjects, whose potential lifespan is relatively short despite intervention, and little attention is given to young subjects at high relative risk despite the fact that, in the absence of intervention, their long-term exposure to an increased risk may lead to a high and partly irreversible risk situation in middle age, with potential shortening of their otherwise longer life expectancy.

2.4.3 Summary of recommendations on total cardiovascular risk assessment

Total cardiovascular risk assessment

Recommendations	Class[a]	Level[b]	Ref.[c]
In asymptomatic subjects with hypertension but free of CVD, CKD, and diabetes, total CV risk stratification using the SCORE model is recommended as a minimal requirement.	I	B	43
As there is evidence that OD predicts CV death independently of SCORE, a search for OD should be considered, particularly in individuals at moderate risk.	IIa	B	51, 53
It is recommended that decisions on treatment strategies depend on the initial level of total CV risk.	I	B	41, 42, 50

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; OD, organ damage; SCORE, Systematic COronary Risk Evaluation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

3. DIAGNOSTIC EVALUATION

The initial evaluation of a patient with hypertension should (i) confirm the diagnosis of hypertension, (ii) detect causes of secondary hypertension, and (iii) assess CV risk, OD and concomitant clinical conditions. This calls for BP measurement, medical history including family history, physical examination, laboratory investigations and further diagnostic tests. Some of the investigations are needed in all patients; others only in specific patient groups.

3.1 Bood pressure measurement

3.1.1. Office or clinic blood pressure

At present, BP can no longer be estimated using a mercury sphygmomanometer in many—although not all—European countries. Auscultatory or oscillometric semiautomatic sphygmomanometers are used instead. These

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devices should be validated according to standardized protocols and their accuracy should be checked periodically through calibration in a technical laboratory [56]. Measurement of BP at the upper arm is preferred and cuff and bladder dimensions should be adapted to the arm circumference. In the event of a significant (>10 mmHg) and consistent SBP difference between arms, which has been shown to carry an increased CV risk [57], the arm with the higher BP values should be used. A between-arms difference is meaningful if demonstrated by simultaneous arm measurement; if one gets a difference between arms with sequential measurement, it could be due to BP variability. In elderly subjects, diabetic patients and in other conditions in which orthostatic hypotension may be frequent or suspected, it is recommended that BP be measured 1 min and 3 min after assumption of the standing position. Orthostatic hypotension—defined as a reduction in SBP of >20 mmHg or in DBP of >10 mmHg within 3 min of standing—has been shown to carry a worse prognosis for mortality and CV events [58,59]. If feasible, automated recording of multiple BP readings in the office with the patient seated in an isolated room, though providing less information overall, might be considered as a means to improve reproducibility and make office BP values closer to those provided by daytime ABPM or HBPM [60,61].

BP measurements should always be associated with measurement of heart rate, because resting heart rate values independently predict CV morbid or fatal events in several conditions, including hypertension [62,63]. Instructions for correct office BP measurements are summarized in Table 5.

TABLE 5. Office blood pressure measurement

When measuring BP in the office, care should be taken:
• To allow the patients to sit for 3–5 minutes before beginning BP measurements.
• To take at least two BP measurements, in the sitting position, spaced 1–2 min apart, and additional measurements if the first two are quite different. Consider the average BP if deemed appropriate.
• To take repeated measurements of BP to improve accuracy in patients with arrhythmias, such as atrial fibrillation.
• To use a standard bladder (12–13 cm wide and 35 cm long), but have a larger and a smaller bladder available for large (arm circumference >32 cm) and thin arms, respectively.
• To have the cuff at the heart level, whatever the position of the patient.
• When adopting the auscultatory method, use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic BP, respectively.
• To measure BP in both arms at first visit to detect possible differences. In this instance, take the arm with the higher value as the reference.
• To measure at first visit BP 1 and 3 min after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which orthostatic hypotension may be frequent or suspected.
• To measure, in case of conventional BP measurement, heart rate by pulse palpation (at least 30 s) after the second measurement in the sitting position.

BP, blood pressure.

3.1.2 Out-of-office blood pressure

The major advantage of out-of-office BP monitoring is that it provides a large number of BP measurements away from the medical environment, which represents a more reliable assessment of actual BP than office BP. Out-of-office BP is commonly assessed by ABPM or HBPM, usually by self-measurement. A few general principles and remarks hold for the two types of monitoring, in addition to recommendations for office BP measurement [64–67]:

1. The procedure should be adequately explained to the patient, with verbal and written instructions; in addition, self-measurement of BP requires appropriate training under medical supervision.
2. Interpretation of the results should take into account that the reproducibility of out-of-office BP measurements is reasonably good for 24-h, day and night BP averages but less for shorter periods within the 24 hs and for more complex and derived indices [68]
3. ABPM and HBPM provide somewhat different information on the subject's BP status and risk and the two methods should thus be regarded as complementary, rather than competitive or alternative. The correspondence between measurements with ABPM and HBPM is fair to moderate.
4. Office BP is usually higher than ambulatory and home BP and the difference increases as office BP increases. Cut-off values for the definition of hypertension for home and ambulatory BP, according to the ESH Working Group on BP Monitoring, are reported in Table 6 [64–67].
5. Devices should have been evaluated and validated according to international standardized protocols and should be properly maintained and regularly calibrated; at least every 6 months. The validation status can be obtained on dedicated websites.

3.1.2.1. Ambulatory blood pressure monitoring

3.1.2.1.1. Methodological aspects

A number of methodological aspects have been addressed by the ESH Working Group on Blood Pressure Monitoring [64,65]. ABPM is performed with the patient wearing a portable BP measuring device, usually on the nondominant arm, for a 24–25 h period, so that it gives information on BP during daily activities and at night during sleep. At the time of fitting of the portable device, the difference between the initial values and those from BP measurement by the operator should not be greater than 5 mmHg. In the event of a larger difference, the ABPM cuff should be removed and fitted again. The patient is instructed to engage in normal activities but to refrain from strenuous exercise and, at the time of cuff inflation, to stop moving and talking and keep the arm still with the cuff at heart level. The patient is asked to provide information in a diary on symptoms and events that may influence BP, in addition to the times of drug ingestion, meals and going to- and

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TABLE 6. Definitions of hypertension by office and out-of-office blood pressure levels

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

BP, blood pressure.

rising from bed. In clinical practice, measurements are often made at 15 min intervals during the day and every 30 min overnight; excessive intervals between BP readings should be avoided because they reduce the accuracy of 24-h BP estimates [69]. It may be recommended that measurements be made at the same frequency during the day and night—for example every 20 min throughout. The measurements are downloaded to a computer and a range of analyses can be performed. At least 70% of BPs during daytime and night-time periods should be satisfactory, or else the monitoring should be repeated. The detection of artifactual readings and the handling of outlying values have been subject to debate but, if there are sufficient measurements, editing is not considered necessary and only grossly incorrect readings should be deleted. It is noteworthy that readings may not be accurate when the cardiac rhythm is markedly irregular [70].

3.1.2.1.2 Daytime, night-time and 24-h blood pressure

In addition to the visual plot, average daytime, night-time and 24-h BP are the most commonly used variables in clinical practice. Average daytime and night-time BP can be calculated from the diary on the basis of the times of getting up and going to bed. An alternative method is to use short, fixed time periods, in which the rising and retiring periods—which differ from patient to patient—are eliminated. It has, for example, been shown that average BPs from 10 am to 8 pm and from midnight to 6 am correspond well with the actual waking and sleeping BPs [71], but other short, fixed time periods have been proposed, such as from 9 am to 9 pm and from 1 am to 6 am. In the event of different measurement intervals during the day and the night, and to account for missing values, it is recommended that average 24-h BP be weighted for the intervals between successive readings or to calculate the mean of the 24 hourly averages to avoid overestimation of average 24-h BP [72].

The night-to-day BP ratio represents the ratio between average night-time and daytime BP. BP normally decreases during the night—defined as 'dipping'. Although the degree of night-time dipping has a normal distribution in a population setting, it is generally agreed that the finding of a nocturnal BP fall of >10% of daytime values (night-day BP ratio <0.9) will be accepted as an arbitrary cut-off to define subjects as 'dippers'. Recently, more dipping categories have been proposed: absence of dipping, i.e. nocturnal BP increase (ratio >1.0); mild dipping (0.9 <ratio <1.0); dipping (0.8 < ratio <0.9); and extreme dipping (ratio <0.8). One should bear in mind that the reproducibility of the dipping pattern is limited [73,74]. Possible reasons for absence of dipping are sleep disturbance, obstructive sleep apnoea, obesity, high salt intake in salt-sensitive subjects, orthostatic hypotension, autonomic dysfunction, chronic kidney disease (CKD), diabetic neuropathy and old age.

3.1.2.1.3 Additional analyses

A number of additional indices may be derived from ABPM recordings [75–81]. They include: BP variability [75], morning BP surge [76,77,81], blood pressure load [78], and the ambulatory arterial stiffness index [79,80]. However, their added predictive value is not yet clear and they should thus be regarded as experimental, with no routine clinical use. Several of these indices are discussed in detail in ESH position papers and guidelines [64,65], including information on facilities recommended for ABPM software in clinical practice, which include the need for a standardized clinical report, an interpretative report, a trend report to compare recordings obtained overtime and a research report, offering a series of additional parameters such as those listed above.

3.1.2.1.4 Prognostic significance of ambulatory BP

Several studies have shown that hypertensive patients' left ventricular hypertrophy (LVH), increased carotid intima-media thickness (IMT) and other markers of OD correlate with ambulatory BP more closely than with office BP [82,83]. Furthermore, 24-h average BP has been consistently shown to have a stronger relationship with morbid or fatal events than office BP [84–87]. There are studies in which accurately measured office BP had a predictive value similar to ambulatory BP [87]. Evidence from meta-analyses of published observational studies and pooled individual data [88–90], however, has shown that ambulatory BP in general is a more sensitive risk predictor of clinical CV outcomes, such as coronary morbid or fatal events and stroke, than office BP. The superiority of ambulatory BP has been shown in the general population, in young and old, in men and women, in untreated and treated hypertensive patients, in patients at high risk and in patients with CV or renal disease [89–93]. Studies that accounted for daytime and night-time BP in the same statistical model found that night-time BP is a stronger predictor than daytime BP [90,94]. The night-day ratio is a significant predictor of clinical CV outcomes but adds little prognostic information over and above 24-h BP [94,95]. With regard to the dipping pattern, the most consistent finding is that the incidence of CV events is higher in patients with a lesser drop in nocturnal BP than in those with greater drop [89,91,92,95,96], although the limited reproducibility of this phenomenon limits the reliability of the results for small between-group differences in nocturnal hypotension [89,91,92,95]. Extreme dippers may have an increased risk for stroke [97]. However, data on the increased CV risk in extreme dippers are inconsistent and thus the clinical significance of this phenomenon is uncertain [89,95].

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3.1.2.2 Home blood pressure monitoring

3.1.2.2.1 Methodological aspects

The ESH Working Group on Blood Pressure Monitoring has proposed a number of recommendations for HBPM [66,67]. The technique usually involves self-measurement of BP but, in some patients, the support of a trained health-provider or family member may be needed. Devices worn on the wrist are currently not recommended but their use might be justified in obese subjects with an extremely large arm circumference. For diagnostic evaluation, BP should be measured daily on at least 3–4 days and preferably on 7 consecutive days in the mornings as well as in the evenings. BP is measured in a quiet room, with the patient in the seated position, back and arm supported, after 5 min of rest and with two measurements per occasion taken 1–2 min apart: the results are reported in a standardized logbook immediately after each measurement. However, BP values reported by the patient may not always be reliable, which can be overcome by storage in a memory-equipped device. Home BP is the average of these readings, with exclusion of the first monitoring day. Use of telemonitoring and smartphone applications for HBPM may be of further advantage [98,99]. Interpretation of the results should always be under the close guidance of the physician.

When compared with office BP, HBPM yields multiple measurements over several days, or even longer periods, taken in the individual's usual environment. Compared with ambulatory BP, it provides measurements over extended periods and day-to-day BP variability, is cheaper [100], more widely available and more easily repeatable. However, unlike ABPM, it does not provide BP data during routine, day-to-day activities and during sleep, or the quantification of short-term BP variability [101].

3.1.2.2.2 Prognostic significance of home BP

Home BP is more closely related to hypertension-induced OD than office BP, particularly LVH [82,83], and recent meta-analyses of the few prospective studies in the general population, in primary care and in hypertensive patients, indicate that the prediction of CV morbidity and mortality is significantly better with home BP than with office BP [102,103]. Studies in which both ABPM and HBPM were performed show that home BP is at least as well correlated with OD as is the ambulatory BP [82,83], and that the prognostic significance of home BP is similar to that of ambulatory BP after adjustment for age and gender [104,105].

3.1.3 White-coat (or isolated office) hypertension and masked (or isolated ambulatory) hypertension

Office BP is usually higher than BP measured out of the office, which has been ascribed to the alerting response, anxiety and/or a conditional response to the unusual situation [106], and in which regression to the mean may play a role. Although several factors involved in office or out-of-office BP modulation may be involved [107], the difference between the two is usually referred to—although somewhat improperly—as the 'white-coat effect' [107,108], whereas 'white-coat-' or 'isolated office-' or 'isolated clinic hypertension' refers to the condition in which BP is elevated in the office at repeated visits and normal out of the office, either on ABPM or HBPM. Conversely, BP may be normal in the office and abnormally high out of the medical environment, which is termed 'masked-' or 'isolated ambulatory hypertension'. The terms 'true-' or 'consistent normotension' and 'sustained hypertension' are used when both types of BP measurement are, respectively, normal or abnormal. Whereas the cut-off value for office BP is the conventional 140/90 mmHg, most studies in white-coat or masked hypertension have used a cut-off value of 135/85 mmHg for out-of-office daytime or home BP and 130/80 mmHg for 24-h BP. Notably, there is only moderate agreement between the definition of white-coat or masked hypertension diagnosed by ABPM or HBPM [101]. It is recommended that the terms 'white-coat hypertension' and 'masked hypertension' be reserved to define untreated individuals.

3.1.3.1 White-coat hypertension

Based on four population studies, the overall prevalence of white-coat hypertension averaged 13% (range 9–16%) and it amounted to about 32% (range 25–46%) among hypertensive subjects in these surveys [109]. Factors related to increased prevalence of white-coat hypertension are: age, female sex and nonsmoking. Prevalence is lower in the case of target OD or when office BP is based on repeated measurements or when measured by a nurse or another healthcare provider [110,111]. The prevalence is also related to the level of office BP: for example, the percentage of white-coat hypertension amounts to about 55% in grade 1 hypertension and to only about 10% in grade 3 hypertension [110]. OD is less prevalent in white-coat hypertension than in sustained hypertension and prospective studies have consistently shown this to be the case also for CV events [105,109,112,113]. Whether subjects with white-coat hypertension can be equalled to true normotensive individuals is an issue still under debate because, in some studies, the long-term CV risk of this condition was found to be intermediate between sustained hypertension and true normotension [105], whereas in meta-analyses it was not significantly different from true normotension when adjusted for age, gender and other covariates [109,112,113]. The possibility exists that, because white-coat hypertensive patients are frequently treated, the reduction of clinic BP leads to a reduced incidence of CV events [112]. Other factors to consider are that, compared with true normotensive subjects, in white-coat hypertensive patients, (i) out-of-office BP is higher [105,109], (ii) asymptomatic OD such as LVH may be more frequent [114], and (iii) this is the case also for metabolic risk factors and long-term risk of new-onset diabetes and progression to sustained hypertension [115,116]. It is recommended that the diagnosis of white-coat hypertension be confirmed within 3–6 months and these patients be investigated and followed-up closely, including repeated out-of-office BP measurements (see Section 6.1).

3.1.3.2 Masked hypertension

The prevalence of masked hypertension averages about 13% (range 10–17%) in population-based studies [109]. Several factors may raise out-of-office BP relative to office

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BP, such as younger age, male gender, smoking, alcohol consumption, physical activity, exercise-induced hypertension, anxiety, job stress, obesity, diabetes, CKD and family history of hypertension and the prevalence is higher when office BP is in the high normal range [117]. Masked hypertension is frequently associated with other risk factors, asymptomatic OD and increased risk of diabetes and sustained hypertension [114–119]. Meta-analyses of prospective studies indicate that the incidence of CV events is about two times higher than in true normotension and is similar to the incidence in sustained hypertension. [109,112,117]. The fact that masked hypertension is largely undetected and untreated may have contributed to this finding. In diabetic patients masked hypertension is associated with an increased risk of nephropathy, especially when the BP elevation occurs mainly during the night [120,121].

3.1.4 Clinical indications for out-of-office blood pressure

It is now generally accepted that out-of-office BP is an important adjunct to conventional office BP measurement, but the latter currently remains the 'gold standard' for screening, diagnosis and management of hypertension. The time-honoured value of office BP, however, has to be balanced against its important limitations, which have led to the increasingly frequent suggestion that out-of-office BP measurements play an important role in hypertension management. Although there are important differences between ABPM and HBPM, the choice between the two methods will in the first place depend on availability, ease, cost of use and, if appropriate, patient preference. For initial assessment of the patient, HBPM may be more suitable in primary care and ABPM in specialist care. However, it is advisable to confirm borderline or abnormal findings on HBPM with ABPM [122], which is currently considered the reference for out-of-office BP, with the additional advantage of providing night-time BP values. Furthermore, most—if not all—patients should be familiarized with self-measurement of BP in order to optimize follow-up, for which HBPM is more suitable than ABPM. However, (self-measured) HBPM may not be feasible because of cognitive impairment or physical limitations, or may be contra-indicated because of anxiety or obsessive patient behaviour, in which case ABPM may be more suitable. Conditions considered as clinical indications for out-of-office BP measurement for diagnostic purposes are listed in Table 7.

TABLE 7. Clinical indications for out-of-office blood pressure measurement for diagnostic purposes

Clinical indications for HBPM or ABPM
• Suspicion of white-coat hypertension
- Grade I hypertension in the office
- High office BP in individuals without asymptomatic organ damage and at low total CV risk
• Suspicion of masked hypertension
- High normal BP in the office
- Normal office BP in individuals with asymptomatic organ damage or at high total CV risk
• Identification of white-coat effect in hypertensive patients
• Considerable variability of office BP over the same or different visits
• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension
• Elevated office BP or suspected pre-eclampsia in pregnant women
• Identification of true and false resistant hypertension
Specific indications for ABPM
• Marked discordance between office BP and home BP
• Assessment of dipping status
• Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or diabetes
• Assessment of BP variability

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; HBPM, home blood pressure monitoring.

3.1.5 Blood pressure during exercise and laboratory stress

BP increases during dynamic and static exercise, whereby the increase is more pronounced for systolic than for diastolic BP [123]. Exercise testing usually involves dynamic exercise, either on a bicycle ergometer or a treadmill. Notably, only SBP can be measured reliably with non-invasive methods. There is currently no consensus on the normal BP response during dynamic exercise testing. A SBP of >210 mmHg for men and >190 mmHgfor women has been termed 'exercise hypertension' in a number of studies, but other definitions of an exaggerated BP response to exercise have also been used [124,125]. Furthermore, the increase of SBP at fixed submaximal exercise is related to preexercise BP, age, arterial stiffness and abdominal obesity and is somewhat greater in women than in men and less in fit than in unfit individuals [123–127]. Most—but not all—studies have shown that an excessive rise of BP during exercise predicts the development of hypertension in normotensive subjects, independently of BP at rest [123,124,128]. However, exercise testing to predict future hypertension is not recommended because of a number of limitations, such as lack of standardization of methodology and definitions. Furthermore, there is no unanimity on the association of exercise BP with OD, such as LVH, after adjustment for resting BP and other covariates, as well in normotensives as in hypertensive patients [123,124]. Also the results on the prognostic significance of exercise BP are not consistent [125], which may be due to the fact that the two haemodynamic components of BP change in opposite directions during dynamic exercise: systemic vascular resistance decreases whereas cardiac output increases. It is likely that the decisive prognostic factor is a blunted reduction of systemic vascular resistance during exercise, compatible with structural pathophysiological changes in arteries and arterioles [123,129]. Whether or not the impaired arterial dilatation is translated into an excessive rise of BP may at least partly depend on cardiac output. In normotensive subjects and in mild hypertensive patients with adequate increase of cardiac output, an exaggerated BP response predicts a poorer long-term outcome [125,130]. In the case of normal resting BP, exercise-induced hypertension can be considered an indication for ABPM because of its association with masked

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hypertension [131]. On the other hand, when hypertension is associated with cardiac dysfunction and blunted exercise-induced increase of cardiac output, the prognostic significance of exercise BP may be lost [129]. Finally, a higher BP during exercise may even carry a better prognosis, such as in 75-year-old individuals [132], in patients with suspected cardiac disease [133], or with heart failure [134], in whom a higher exercise BP implies relatively preserved systolic cardiac function [125]. In conclusion, the overall results question the clinical utility of BP measurements during exercise testing for diagnostic and prognostic purposes in patients with hypertension. However, exercise testing is useful as a general prognostic indicator using exercise capacity and electrocardiogram (ECG) data and an abnormal BP response may warrant ABPM.

A number of mental stress tests have been applied to evoke stress and increase BP via a problem of mathematical, technical, or decisional nature [123]. However, these laboratory stress tests in general do not reflect real-life stress and are not well standardized, have limited reproducibility, and correlations between BP responses to the various stressors are limited. In addition, results on the independent relationships of the BP response to mental stressors with future hypertension are not unanimous and, if significant, the additional explained variance is usually small [123,135]. A recent meta-analysis suggested that greater responsiveness to acute mental stress has an adverse effect on future CV risk status—a composite of elevated BP, hypertension, left ventricular mass (LVM),subclinical atherosclerosis and clinical cardiac events [136]. The overall results suggest that BP measurements during mental stress tests are currently not clinically useful.

3.1.6 Central blood pressure

The measurement of central BP in hypertensive patients raises increasing interest because of both its predictive value for CV events and the differential effect of antihypertensive drugs, compared with brachial BP. The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave [137]. It should be analysed at the central level, i.e. in the ascending aorta, since it represents the true load imposed on heart, brain, kidney and large arteries. The phenomenon of wave reflection can be quantified through the augmentation index—defined as the difference between the second and first systolic peaks, expressed as a percentage of the pulse pressure, preferably adjusted for heart rate. Owing to the variable superimposition of incoming and reflected pressure waves along the arterial tree, aortic systolic and pulse pressures may be different from the conventionally measured brachial pressure. In recent years several methods, including applanation tonometry and transfer function, have been developed to estimate central systolic BP or pulse pressure from brachial pressure wave. They have been critically reviewed in an expert consensus document [138].

Early epidemiological studies in the 2000s showed that central augmentation index and pulse pressure, directly measured by carotid tonometry, were independent predictors of all-cause and CV mortality in patients with ESRD [139]. A recent meta-analysis confirmed these findings in several populations [140]. However, the additive predictive value of central BP beyond brachial BP was either marginal or not statistically significant in most studies [140].

Thus the current guidelines, like previous ones [2,141], consider that, although the measurement of central BP and augmentation index is of great interest for mechanistic analyses in pathophysiology, pharmacology and therapeutics, more investigation is needed before recommending their routine clinical use. The only exception may be ISH in the young: in some of these individuals increased SBP at the brachial level may be due to high amplification of the central pressure wave, while central BP is normal [142].

3.2 Medical history

The medical history should address the time of the first diagnosis of arterial hypertension, current and past BP measurements and current and past antihypertensive medications. Particular attention should be paid to indications of secondary causes of hypertension. Women should be questioned about pregnancy-related hypertension. Hypertension translates into an increased risk of renal and CV complications (CHD; heart failure; stroke; PAD; CV death), especially when concomitant diseases are present. Therefore, a careful history of CVDs should be taken in all patients, to allow assessment of global CV risk, including concomitant diseases such as diabetes, clinical signs or a history of heart failure, CHD or PAD, valvular heart disease, palpitations, syncopal episodes, neurological disorders with an emphasis on stroke and transient ischaemic attack (TIA). A history of CKD should include the type and duration of kidney disease. Nicotine abuse and evidence for dyslipidaemia should be sought. A family history of premature hypertension and/or premature CVD is an important first indicator of familial (genetic) predisposition to hypertension and CVD and may trigger clinically indicated genetic tests. Details on family and medical history are summarized in Table 8.

3.3 Physical examination

Physical examination aims to establish or verify the diagnosis of hypertension, establish current BP, screen for secondary causes of hypertension and refine global CV risk estimation. BP should be measured as summarized in Section 3.1.1 and should be repeated to confirm the diagnosis of hypertension. On at least one occasion, BP needs to be measured at both arms and differences between the two arms in SBP >20 mmHg and/or in DBP >10 mmHg—if confirmed—should trigger further investigations of vascular abnormalities. All patients should undergo auscultation of the carotid arteries, heart and renal arteries. Murmurs should suggest further investigation (carotid ultrasound, echocardiography, renal vascular ultrasound, depending on the location of the murmur). Height, weight, and waist circumference should be measured with the patient standing, and BMI calculated. Pulse palpation and cardiac auscultation may reveal arrhythmias. In all patients, heart rate should be measured while the patient is at rest. An increased heart rate indicates

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TABLE 8. Personal and family medical history

1. Duration and previous level of high BP, including measurements at home.
2. Secondary hypertension
a) Family history of CKD (polycystic kidney).
b) History of renal disease, urinary tract infection, haematuria, analgesic abuse (parenchymal renal disease).
c) Drug/substance intake, e.g. oral contraceptives, liquorice, carbenoxolone, vasoconstrictive nasal drops, cocaine, amphetamines, gluco- and mineralocorticosteroids, non-steroidal anti-inflammatory drugs, erythropoietin, cyclosporine.
d) Repetitive episodes of sweating, headache, anxiety, palpitations (pheochromocytoma).
e) Episodes of muscle weakness and tetany (hyperaldosteronism).
f) Symptoms suggestive of thyroid disease.
3. Risk factors
a) Family and personal history of hypertension and CVD
b) Family and personal history of dyslipidaemia.
c) Family and personal history of diabetes mellitus (medications, blood-glucose levels, polyuria).
d) Smoking habits.
e) Dietary habits.
f) Recent weight changes; obesity.
g) Amount of physical exercise.
h) Snoring; sleep apnoea (information also from partner).
i) Low birth-weight.
4. History and symptoms of organ damage and cardiovascular disease.
a) Brain and eyes: headache, vertigo, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization.
b) Heart: chest pain, shortness of breath, swollen ankles, myocardial infarction, revascularization, syncope, history of palpitations, arrhythmias, especially atrial fibrillation.
c) Kidney: thirst, polyuria, nocturia, haematuria.
d) Peripheral arteries: cold extremities, intermittent claudication, pain-free walking distance, peripheral revascularization.
e) History of snoring/chronic lung disease/sleep apnoea.
f) Cognitive dysfunction.
5. Hypertension management
a) Current antihypertensive medication.
b) Past antihypertensive medication.
c) Evidence of adherence or lack of adherence to therapy.
d) Efficacy and adverse effects of drugs.

BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; TIA, transient ischaemic attack.

an increased risk of heart disease. An irregular pulse should raise the suspicion of atrial fibrillation, including silent atrial fibrillation. Details on physical examination are summarized in Table 9.

TABLE 9. Physical examination for secondary hypertension, organ damage and obesity

Signs suggesting secondary hypertension
• Features of Cushing syndrome.
• Skin stigmata of neurofibromatosis (pheochromocytoma).
• Palpation of enlarged kidneys (polycystic kidney).
• Auscultation of abdominal murmurs (renovascular hypertension).
• Auscultation of precordial or chest murmurs (aortic coarctation; aortic disease; upper extremity artery disease).
• Diminished and delayed femoral pulses and reduced femoral blood pressure compared to simultaneous arm BP (aortic coarctation; aortic disease; lower extremity artery disease).
• Left–right arm BP difference (aortic coarctation; subclavian artery stenosis).
Signs of organ damage
• Brain: motor or sensory defects.
• Retina: fundoscopic abnormalities.
• Heart: heart rate, 3rd or 4th heart sound, heart murmurs, arrhythmias, location of apical impulse, pulmonary rales, peripheral oedema.
• Peripheral arteries: absence, reduction, or asymmetry of pulses, cold extremities, ischaemic skin lesions.
• Carotid arteries: systolic murmurs.
Evidence of obesity
• Weight and height.
• Calculate BMI: body weight/height^2 (kg/m^2).
• Waist circumference measured in the standing position, at a level midway between the lower border of the costal margin (the lowest rib) and uppermost border of the iliac crest.

BP, blood pressure; BMI, body mass index.

3.4 Summary of recommendations on blood pressure MANAGEMENT, history, and physical examination

See 'Blood pressure MANAGEMENT, history, and physical examination' on page 1295.

3.5 Laboratory investigations

Laboratory investigations are directed at providing evidence for the presence of additional risk factors, searching for secondary hypertension and looking for the absence or presence of OD. Investigations should progress from the most simple to the more complicated ones. Details on laboratory investigations are summarized in Table 10.

3.6 Genetics

A positive family history is a frequent feature in hypertensive patients [143,144], with the heritability estimated to vary between 35% and 50% in the majority of studies [145], and heritability has been confirmed for ambulatory BP [146]. 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 [147]. Essential hypertension is a highly heterogeneous disorder with a

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Blood pressure MANAGEMENT, history, and physical examination

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to obtain a comprehensive medical history and physical examination in all patients with hypertension to verify the diagnosis, detect causes of secondary hypertension, record CV risk factors, and to identify OD and other CVDs.	I	C	-
Obtaining a family history is recommended to investigate familial predisposition to hypertension and CVDs.	I	B	143, 144
Office BP is recommended for screening and diagnosis of hypertension.	I	B	3
It is recommended that the diagnosis of hypertension be based on at least two BP measurements per visit and on at least two visits.	I	C	-
It is recommended that all hypertensive patients undergo palpation of the pulse at rest to determine heart rate and to search for arrhythmias, especially atrial fibrillation.	I	B	62, 63
Out-of-office BP should be considered to confirm the diagnosis of hypertension, identify the type of hypertension, detect hypotensive episodes, and maximize prediction of CV risk.	IIa	B	89, 90, 103, 105, 109, 113, 117
For out-of-office BP measurements, ABPM or HBPM may be considered depending on indication, availability, ease, cost of use and, if appropriate, patient preference.	IIb	C	-

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; HBPM, home blood pressure monitoring; OD, organ damage.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

TABLE 10. Laboratory investigations

Routine tests
• Haemoglobin and/or haematocrit.
• Fasting plasma glucose.
• Serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol.
• Fasting serum triglycerides.
• Serum potassium and sodium.
• Serum uric acid.
• Serum creatinine (with estimation of GFR).
• Urine analysis: microscopic examination; urinary protein by dipstick test; test for microalbuminuria.
• 12-lead ECG.
Additional tests, based on history, physical examination, and findings from routine laboratory tests
• Haemoglobin A_{1c} (if fasting plasma glucose is >5.6 mmol/L (102 mg/dL) or previous diagnosis of diabetes).
• Quantitative proteinuria (if dipstick test is positive); urinary potassium and sodium concentration and their ratio.
• Home and 24-h ambulatory BP monitoring.
• Echocardiogram.
• Holter monitoring in case of arrhythmias.
• Carotid ultrasound.
• Peripheral artery/abdominal ultrasound.
• Pulse wave velocity.
• Ankle-brachial index.
• Fundoscopy.
Extended evaluation (mostly domain of the specialist)
• Further search for cerebral, cardiac, renal, and vascular damage, mandatory in resistant and complicated hypertension.
• Search for secondary hypertension when suggested by history, physical examination, or routine and additional tests.

BP, blood pressure; ECG, electrocardiogram; GFR, glomerular filtration rate.

multifactorial aetiology. Several genome-wide association studies and their meta-analyses point to a total of 29 single nucleotide polymorphisms, which are associated with systolic and/or diastolic BP [148]. These findings might become useful contributors to risk scores for OD.

3.7 Searching for asymptomatic organ damage

Owing to the importance of asymptomatic OD as an intermediate stage in the continuum of vascular disease, and as a determinant of overall CV risk, signs of organ involvement should be sought carefully by appropriate techniques if indicated (Table 10). It should be pointed out that a large body of evidence is now available on the crucial role of asymptomatic OD in determining the CV risk of individuals with and without high BP. The observation that any of four markers of OD (microalbuminuria, increased pulse wave velocity [PWV], LVH and carotid plaques) can predict CV mortality independently of SCORE stratification is a relevant argument in favour of using assessment of OD in daily clinical practice [51–53], although more data from larger studies in different populations would be desirable. It is also noteworthy that the risk increases as the number of damaged organs increases [51].

3.7.1 Heart

3.7.1.1 Electrocardiography

A 12-lead electrocardiogram (ECG) should be part of the routine assessment of all hypertensive patients. Its sensitivity in detecting LVH is low but, nonetheless, LVH detected by the Sokolow-Lyon index (SV1 + RV5 >3.5 mV), the modified Sokolow-Lyon index (largest S-wave + largest R-wave >3.5 mV), RaVL >1.1 mV, or Cornell voltage QRS duration product (>244 mV∗ms) has been found in observational studies and clinical trials to be an independent predictor of CV events [149]. Accordingly, the ECG is valuable, at least in patients over 55 years of age [150,151]. Electrocardiography can also be used to detect patterns of ventricular overload or 'strain', which indicates more severe risk [149,150,152], ischaemia, conduction abnormalities, left atrial dilatation and arrhythmias, including atrial fibrillation. Twenty-four-hour Holter

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electrocardiography is indicated when arrhythmias and possible ischaemic episodes are suspected. Atrial fibrillation is a very frequent and common cause of CV complications [153,154], especially stroke, in hypertensive patients [153]. Early detection of atrial fibrillation would facilitate the prevention of strokes by initiating appropriate anticoagulant therapy if indicated.

3.7.1.2 Echocardiography

Although not immune from technical limitations, echocardiography is more sensitive than electrocardiography in diagnosing LVH and is useful to refine CV and renal risk [155–157]. It may therefore help in a more precise stratification of overall risk and in determining therapy [158]. Proper evaluation of the LV in hypertensive patients includes linear measurements of interventricular septal and posterior wall thickness and internal end-diastolic diameter. While left ventricular mass (LVM) measurements indexed for body size identify LVH, relative wall thickness or the wall-to-radius ratio (2 x posterior wall thickness/end-diastolic diameter) categorizes geometry (concentric or eccentric). Calculation of LVM is currently performed according to the American Society of Echocardiography formula [159]. Although the relation between LVM and CV risk is continuous, thresholds of 95 g/m^2 for women and 115 g/m^2 (BSA) for men are widely used for estimates of clear-cut LVH [159]. Indexation of LVM for height, in which height to the allometric power of 1.7 or 2.7 has been used [160,161], can be considered in overweight and obese patients in order to scale LVM to body size and avoid under-diagnosis of LVH [159]. It has recently been shown that the optimal method is to scale allometrically by body height to the exponent 1.7 (g/m$^{1.7}$) and that different cut-offs for men and women should be used [160]. Scaling LVM by height exponent 2.7 could overestimate LVH in small subjects and underestimate in tall ones [160]. Concentric LVH (relative wall thickness >0.42 with increased LVM), eccentric LVH (relative wall thickness <0.42 with increased LVM) and concentric remodelling (relative wall thickness >0.42 with normal LVM) all predict an increased incidence of CVD, but concentric LVH is the strongest predictor of increased risk [162–164].

Hypertension is associated with alterations of LV relaxation and filling, globally defined as diastolic dysfunction. Hypertension-induced diastolic dysfunction is associated with concentric geometry and can per se induce symptoms/signs of heart failure, even when ejection fraction (EF) is still normal (heart failure with preserved EF) [165]. The Doppler transmitral inflow pattern can quantify filling abnormalities and predict subsequent heart failure and all-cause mortality [166,167], but is not sufficient to completely stratify the hypertensive clinical status and prognosis [166,167]. According to recent echocardiographical recommendations [168], it should therefore be combined with pulsed Tissue Doppler of the mitral annulus. Reduction of the Tissue Doppler-derived early diastolic velocity (e′) is typical of hypertensive heart disease and, often, the septal e′ is reduced more than the lateral e′. Diagnosis and grading of diastolic dysfunction is based on e′ (average of septal and lateral mitral annulus) and additional measurements including the ratio between transmitral E and e′ (E/e′ ratio) and left atrial size [168]. This grading is an important predictor of all-cause mortality in a large epidemiological study [169]. The values of e′ velocity and of E/e′ ratio are highly dependent on age and somewhat less on gender [170]. The E/e′ ratio is able to detect an increase of LV filling pressures. The prognostic value of e′ velocity is recognized in the hypertensive setting [171], and E/e′ ratio >13 [168] is associated with increased cardiac risk, independent of LVM and relative wall thickness in hypertensive patients [171]. Determination of left atrial dilatation can provide additional information and is a prerequisite for the diagnosis of diastolic dysfunction. Left atrial size is best assessed by its indexed volume or LAVi [159]. LAVi >34 mL/m^2 has been shown to be an independent predictor of death, heart failure, atrial fibrillation and ischaemic stroke [172].

Normal ranges and cut-off values for hypertensive heart disease for key echocardiographic parameters are summarized in Table 11. The most used scaling for evaluating LVH in hypertension is to divide LVM by body surface area (BSA), so that the effects on LVM of body size and obesity are largely eliminated. Despite largely derived from control study populations with the obvious possibility for bias, these parameters recommended by the American Society of Echocardiography and the European Association of Echocardiography are used in the majority of laboratories for echocardiography. Data from large general populations in different ethnicities will be available soon.

To assess subclinical systolic dysfunction, speckle tracking echocardiography can quantify longitudinal contractile function (longitudinal strain) and help to unmask early subclinical systolic dysfunction of newly diagnosed hypertensive patients without LVH [173,174]. However, assessment of LV systolic function in hypertensive heart disease does not add prognostic information to LVM, at least in the context of a normal EF.

In clinical practice, echocardiography should be considered in hypertensive patients in different clinical contexts and with different purposes: in hypertensive patients at moderate total CV risk, it may refine the risk evaluation by detecting LVH undetected by ECG; in hypertensive patients with ECG evidence of LVH it may more precisely assess the hypertrophy quantitatively and define its geometry and

TABLE 11. Cut-off values for parameters used in the assessment of LV remodelling and diastolic function in patients with hypertension. Based on Lang *et al.* [159] and Nagueh *et al.* [168]

Parameter	Abnormal if
LV mass index (g/m²)	>95 (women) >115 (men)
Relative wall thickness (RWT)	>0.42
Diastolic function: Septal e' velocity (cm/sec) Lateral e' velocity (cm/sec) LA volume index (mL/m²)	 <8 <10 ≥34
LV Filling pressures : E/e' (averaged) ratio	 ≥13

LA, left atrium; LV, left ventricle; RWT, relative wall thickness.

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risk; in hypertensive patients with cardiac symptoms, it may help to diagnose underlying disease. It is obvious that echocardiography, including assessment of ascending aorta and vascular screening, may be of significant diagnostic value in most patients with hypertension and should ideally be recommended in all hypertensive patients at the initial evaluation. However, a wider or more restricted use will depend on availability and cost.

3.7.1.3 Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) should be considered for assessment of LV size and mass when echocardiography is technically not feasible and when imaging of delayed enhancement would have therapeutic consequences [175,176].

3.7.1.4 Myocardial ischaemia

Specific procedures are reserved for diagnosis of myocardial ischaemia in hypertensive patients with LVH [177]. This is particularly challenging because hypertension lowers the specificity of exercise electrocardiography and perfusion scintigraphy [178]. An exercise test, demonstrating a normal aerobic capacity and without significant ECG changes, has an acceptable negative predictive value in patients without strong symptoms indicative of obstructive CHD. When the exercise ECG is positive or uninterpretable/ambiguous, an imaging test of inducible ischaemia, such as stress cardiac MRI, perfusion scintigraphy, or stress echocardiography is warranted for a reliable identification of myocardial ischaemia [178–180]. Stress-induced wall motion abnormalities are highly specific for angiographically assessed epicardial coronary artery stenosis, whereas myocardial perfusion abnormalities are frequently found with angiographically normal coronary arteries associated with LVH and/or coronary microvascular disease [177]. The use of dual echocardiographic imaging of regional wall motion and transthoracic, Doppler-derived coronary flow reserve on the left anterior descending artery has recently been suggested to distinguish obstructive CHD (reduced coronary reserve plus inducible wall motion abnormalities) from isolated coronary microcirculatory damage (reduced coronary reserve without wall motion abnormalities) [180]. A coronary flow reserve <1.91 has been shown to have an independent prognostic value in hypertension [181,182].

3.7.2 Blood vessels

3.7.2.1 Carotid arteries

Ultrasound examination of the carotid arteries with measurement of intima media thickness (IMT) and/or the presence of plaques has been shown to predict the occurrence of both stroke and myocardial infarction, independently of traditional CV risk factors [51,183–186]. 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 vascular hypertrophy). The relationship between carotid IMT and CV events is a continuous one and determining a threshold for high CV risk is rather arbitrary. Although a carotid IMT >0.9 mm has been taken as a conservative estimate of existing abnormalities in the 2007 Guidelines [2], the threshold value for high CV risk was higher in the elderly patients of the Cardiovascular Health Study and in the middle-aged patients of the European Lacidipine Study on Atherosclerosis (ELSA) study (1.06 and 1.16 mm, respectively) [184,186]. Presence of a plaque can be identified by an IMT >1.5 mm or by a focal increase in thickness of 0.5 mm or 50% of the surrounding carotid IMT value [187]. Although plaque has a strong independent predictive value for CV events [51,183–185,188], presence of a plaque and increased carotid IMT added little to each other for predicting CV events and re-classifying patients into another risk category in the Atherosclerosis Risk In Communities (ARIC) study [185]. A recent systematic review concluded that the added predictive value of additional carotid screening may be primarily found in asymptomatic individuals at intermediate CV risk [189].

3.7.2.2 Pulse wave velocity

Large artery stiffening and the wave-reflection phenomenon have been identified as being the most important pathophysiological determinants of ISH and pulse pressure increase with ageing [190]. Carotid-femoral PWV is the 'gold standard' for measuring aortic stiffness [138]. Although the relationship between aortic stiffness and events is continuous, a threshold of >12 m/s has been suggested by the 2007 ESH/ESC Guidelines as a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients [2]. A recent expert consensus statement adjusted this threshold value to 10 m/s [191], by using the direct carotid-to-femoral distance and taking into account the 20% shorter true anatomical distance travelled by the pressure wave (i.e. 0.8×12 m/s or 10 m/s). Aortic stiffness has independent predictive value for fatal and nonfatal CV events in hypertensive patients [192,193]. The additive value of PWV above and beyond traditional risk factors, including SCORE and Framingham risk score, has been quantified in a number of studies [51,52,194,195]. In addition, a substantial proportion of patients at intermediate risk could be reclassified into a higher or lower CV risk, when arterial stiffness is measured [51,195,196].

3.7.2.3 Ankle-brachial index

Ankle-brachial index (ABI) can be measured either with automated devices, or with a continuous-wave Doppler unit and a BP sphygmomanometer. A low ABI (i.e. <0.9) signals PAD and, in general, advanced atherosclerosis [197], has predictive value for CV events [198], and was associated with approximately twice the 10-year CV mortality and major coronary event rate, compared with the overall rate in each Framingham category [198]. Furthermore, even asymptomatic PAD, as detected by a low ABI, has prospectively been found to be associated in men with an incidence of CV morbid and fatal events approaching 20% in 10 years [198,199]. However, ABI is more useful for detecting PAD in individuals with a high likelihood of PAD.

3.7.2.4 Other methods

Although measurements of carotid IMT, aortic stiffness or ABI are reasonable for detecting hypertensive patients at high CV risk, several other methods, used in the research

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setting for detecting vascular OD, cannot be supported for clinical use. An increase in the wall-lumen ratio of small arteries can be measured in subcutaneous tissues obtained through gluteal biopsies. These measurements can demonstrate early alterations in diabetes and hypertension and have a predictive value for CV morbidity and mortality [199–202], but the invasiveness of the method makes this approach unsuitable for general use. Increase in coronary calcium, as quantified by high-resolution cardiac computed tomography, has also been prospectively validated as a predictor of CVD and is highly effective in re-stratifying asymptomatic adults into either a moderate or a high CVD risk group [203,204], but the limited availability and high cost of the necessary instrumentations present serious problems. Endothelial dysfunction predicts outcome in patients with a variety of CVDs [205], although data on hypertension are still rather scant [206]. Furthermore, the techniques available for investigating endothelial responsiveness to various stimuli are laborious, time consuming and often invasive.

3.7.3 Kidney

The diagnosis of hypertension-induced renal damage is based on the finding of a reduced renal function and/or the detection of elevated urinary excretion of albumin [207]. Once detected, CKD is classified according to eGFR, calculated by the abbreviated 'modification of diet in renal disease' (MDRD) formula [208], the Cockcroft-Gault formula or, more recently, through the Chronic Kidney Disease EPIdemiology Collaboration (CKD-EPI) formula [209], which require age, gender, ethnicity and serum creatinine. When eGFR is below 60 mL/min/1.73 m^2, three different stages of CKD are recognized: stage 3 with values between 30–60 mL/min/1.73 m^2; and stages 4 and 5 with values below 30 and 15 mL/min/1.73 m^2, respectively [210]. These formulae help to detect mild impairment of renal function when serum creatinine values are still within the normal range [211]. A reduction in renal function and an increase in CV risk can be inferred from the finding of increased serum levels of cystatin C [212]. A slight increase (up to 20%) in serum creatinine may sometimes occur when antihypertensive therapy—particularly by renin-angiotensin system (RAS) blockers—is instituted or intensified but this should not be taken as a sign of progressive renal deterioration. Hyperuricaemia is frequently seen in untreated hypertensive patients (particularly in preeclampsia) and has been shown to correlate with a reduced renal blood flow and nephrosclerosis [213].

While an elevated serum creatinine concentration or a low eGFR point to diminished renal function, the finding of an increased rate of urinary albumin or protein excretion points, in general, to a derangement in glomerular filtration barrier. Microalbuminuria has been shown to predict the development of overt diabetic nephropathy in both type 1 and type 2 diabetic patients [214], while the presence of overt proteinuria generally indicates the existence of established renal parenchymatous disease [215]. In both diabetic and non-diabetic hypertensive patients, microalbuminuria, even below the threshold values usually considered [216], has been shown to predict CV events [217–225], and continuous relationships between CV, as well as non-CV mortality and urinary albumin/creatinine ratios >3.9 mg/g in men and >7.5 mg/g in women, have been reported in several studies [224,226]. Both in the general population and in diabetic patients, the concomitance of an increased urinary protein excretion and a reduced eGFR indicates a greater risk of CV and renal events than either abnormality alone, making these risk factors independent and cumulative [227,228]. An arbitrary threshold for the definition of microalbuminuria has been established as 30 mg/g of creatinine [228].

In conclusion, the finding of an impaired renal function in a hypertensive patient, expressed as any of the abnormalities mentioned above, constitutes a very potent and frequent predictor of future CV events and death [218,229–233]. Therefore it is recommended, in all hypertensive patients, that eGFR be estimated and that a test for microalbuminuria be made on a spot urine sample.

3.7.4 Fundoscopy

The traditional classification system of hypertensive retinopathy by fundoscopy is based on the pioneering work by Keith, Wagener and Barker in 1939 and its prognostic significance has been documented in hypertensive patients [234]. Grade III (retinal haemorrhages, microaneurysms, hard exudates, cotton wool spots) and grade IV retinopathy (grade III signs and papilloedema and/or macular oedema) are indicative of severe hypertensive retinopathy, with a high predictive value for mortality [234,235]. Grade I (arteriolar narrowing either focal or general in nature) and grade II (arteriovenous nicking) point to early stage of hypertensive retinopathy and the predictive value of CV mortality is controversially reported and, overall, less stringent [236,237]. Most of these analyses have been done by retinal photography with interpretation by ophthalmologists, which is more sensitive than direct ophthalmoscopy/fundoscopy by general physicians [238]. Criticism with respect to the reproducibility of grade I and grade II retinopathy has been raised, since even experienced investigators displayed high inter-observer and intra-observer variability (in contrast to advanced hypertensive retinopathy) [239,240].

The relationship of retinal vessel calibre to future stroke events has been analysed in a systematic review and individual participant meta-analysis: wider retinal venular calibre predicted stroke, whereas the calibre of retinal arterioles was not associated with stroke [241]. Retinal arteriolar and venular narrowing, similarly to capillary rarefaction in other vascular beds [242,243], may be an early structural abnormality of hypertension but its additive value to identify patients at risk for other types of OD needs to be defined [243–244]. The arteriovenous ratio of retinal arterioles and venules predicted incident stroke and CV morbidity, but criticism that concomitant changes of the venule diameters may affect this ratio and the methodology (digitized photographs, need of core reading centre) prohibited its widespread clinical use [245–248]. New technologies to assess the wall-lumen ratio of retinal arterioles that directly measure the vascular remodelling in early and later stages of hypertensive disease are currently being investigated [249].

3.7.5 Brain

Hypertension, beyond its well known effect on the occurrence of clinical stroke, is also associated with the risk of

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asymptomatic brain damage noticed on cerebral MRI, in particular in elderly individuals [250,251]. The most common types of brain lesions are white matter hyperintensities, which can be seen in almost all elderly individuals with hypertension [250] - although with variable severity - and silent infarcts, the large majority of which are small and deep (lacunar infarctions) and the frequency of which varies between 10% and 30% [252]. Another type of lesion, more recently identified, are microbleeds, seen in about 5% of individuals. White matter hyperintensities and silent infarcts are associated with an increased risk of stroke, cognitive decline and dementia [250,252–254]. In hypertensive patients without overt CVD, MRI showed that silent cerebrovascular lesions are even more prevalent (44%) than cardiac (21%) and renal (26%) subclinical damage and do frequently occur in the absence of other signs of organ damage [255]. Availability and cost considerations do not allow the widespread use of MRI in the evaluation of elderly hypertensives, but white matter hyperintensity and silent brain infarcts should be sought in all hypertensive patients with neural disturbance and, in particular, memory loss [255–257]. As cognitive disturbances in the elderly are, at least in part, hypertension related [258,259], suitable cognitive evaluation tests may be used in the clinical assessment of the elderly hypertensive patient.

3.7.6 Clinical value and limitations

Table 12 summarizes the CV predictive value, availability, reproducibility and cost-effectiveness of procedures for detection of OD. The recommended strategies for the search for OD are summarized in the Table.

3.7.7 Summary of recommendations on the search for asymptomatic organ damage, cardiovascular disease, and chronic kidney disease

See 'Search for asymptomatic organ damage, cardiovascular disease, and chronic kidney disease' on page 1301.

3.8 Searching for secondary forms of hypertension

A specific, potentially reversible cause of BP elevation can be identified in a relatively small proportion of adult patients with hypertension. However, because of the overall high prevalence of hypertension, secondary forms can affect millions of patients worldwide. If appropriately diagnosed and treated, patients with a secondary form of hypertension might be cured, or at least show an improvement in BP control and a reduction of CV risk. Consequently, as a wise precaution, all patients should undergo simple screening for secondary forms of hypertension. This screening can be based on clinical history, physical examination and routine laboratory investigations (Tables 8–10). Furthermore, a secondary form of hypertension can be indicated by a severe elevation in BP, sudden onset or worsening of hypertension, poor BP response to drug therapy and OD disproportionate to the duration of hypertension. If the basal work-up leads to the suspicion that the patient is suffering from a secondary form of hypertension, specific diagnostic procedures may become necessary, as outlined in Table 13. Diagnostics of secondary forms of hypertension, especially in cases with asuspicion of endocrine hypertension, should preferably be performed in referral centres.

4 TREATMENT APPROACH

4.1 Evidence favouring therapeutic reduction of high blood pressure

Evidence favouring the administration of BP-lowering drugs to reduce the risk of major clinical CV outcomes (fatal and nonfatal stroke, myocardial infarction, heart failure and other CV deaths) in hypertensive individuals results from a number of RCTs—mostly placebo-controlled—carried out between 1965 and 1995. Their meta-analysis [260] was referred to in the 2003 edition of ESH/ESC Guidelines

TABLE 12. Predictive value, availability, reproducibility and cost–effectiveness of some markers of organ damage

Marker	Cardiovascular predictive value	Availability	Reproducibility	Cost-effectiveness
Electrocardiography	+++	++++	++++	++++
Echocardiography, plus Doppler	++++	+++	+++	+++
Estimated glomerular filtration rate	+++	++++	++++	++++
Microalbuminuria	+++	++++	++	++++
Carotid intima–media thickness and plaque	+++	+++	+++	+++
Arterial stiffness (pulse wave velocity)	+++	++	+++	+++
Ankle–brachial index	+++	+++	+++	+++
Fundoscopy	+++	++++	++	+++
Additional measurements				
Coronary calcium score	++	+	+++	+
Endothelial dysfunction	++	+	+	+
Cerebral lacunae/white matter lesions	++	+	+++	+
Cardiac magnetic resonance	++	+	+++	++

Scores are from + to ++ + +.

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TABLE 13. Clinical indications and diagnostics of secondary hypertension

	Clinical indications		Diagnostics		
Common causes	Clinical history	Physical examination	Laboratory investigations	First-line test(s)	Additional/ confirmatory test(s)
Renal parenchymal disease	History of urinary tract infection or obstruction, haematuria, analgesic abuse; family history of polycystic kidney disease.	Abdominal masses (in case of polycystic kidney disease).	Presence of protein, erythrocytes, or leucocytes in the urine, decreased GFR.	Renal ultrasound	Detailed work-up for kidney disease.
Renal artery stenosis	Fibromuscular dysplasia: early onset hypertension (especially in women). Atherosclerotic stenosis: hypertension of abrupt onset, worsening or Increasingly difficult to treat; flash pulmonary oedema.	Abdominal bruit	Difference of >1.5 cm in length between the two kidneys (renal ultrasound), rapid deterioration in renal function (spontaneous or in response to RAA blockers).	Renal Duplex Doppler ultrasonography	Magnetic resonance angiography, spiral computed tomography, intra-arterial digital subtraction angiography.
Primary aldosteronism	Muscle weakness; family history of early onset hypertension and cerebrovascular events at age <40 years.	Arrhythmias (in case of severe hypokalaemia).	Hypokalaemia (spontaneous or diuretic-induced); incidental discovery of adrenal masses.	Aldosterone–renin ratio under standardized conditions (correction of hypokalaemia and withdrawal of drugs affecting RAA system).	Confirmatory tests (oral sodium loading, saline infusion, fludrocortisone suppression, or captopril test); adrenal CT scan; adrenal vein sampling.
Uncommon causes					
Pheochromocytoma	Paroxysmal hypertension or a crisis superimposed to sustained hypertension; headache, sweating, palpitations and pallor; positive family history of pheochromocytoma.	Skin stigmata of neurofibromatosis (café-au-lait spots, neurofibromas).	Incidental discovery of adrenal (or in some cases, extra-adrenal) masses.	Measurement of urinary fractionated metanephrines or plasma-free metanephrines.	CT or MRI of the abdomen and pelvis; 123 I-labelled meta-iodobenzyl-guanidine scanning; genetic screening for pathogenic mutations.
Cushing's syndrome	Rapid weight gain, polyuria, polydipsia, psychological disturbances	Typical body habitus (central obesity, moon-face, buffalo hump, red striae, hirsutism).	Hyperglycaemia	24-h urinary cortisol excretion	Dexamethasone-suppression tests

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

[1]. Supportive evidence also comes from finding that a BP-induced regression of OD, such as LVH and urinary protein excretion, may be accompanied by a reduction of fatal and nonfatal outcomes [261,262], although this evidence is obviously indirect, being derived from post-hoc correlative analyses of randomized data.

Randomized trials based on hard clinical CV outcomes do, however, also have limitations, which have been considered in previous ESH/ESC Guidelines [2]: (i) to limit the number of patients needed, trials commonly enrol high-risk patients (old age, concomitant or previous disease) and for practical reasons, the duration of controlled trials is necessarily short (in best cases between 3 and 6 years, with an average time to an endpoint of only half of this)—so that recommendations for life-long intervention are based on considerable extrapolation from data obtained over periods much shorter than the life expectancy of most patients. Support for the belief that the benefits measured during the first few years will continue over a much longer term comes from observational studies of a few decades duration [263].

The recommendations that now follow are based on available evidence from randomized trials and focus on important issues for medical practice: (i) when drug therapy should be initiated, (ii) the target BP to be achieved by treatment in hypertensive patients at different CV risk levels, and therapeutic strategies and choice of drugs in hypertensive patients with different clinical characteristics.

4.2 When to initiate antihypertensive drug treatment

4.2.1 Recommendations of previous Guidelines

The 2007 ESH/ESC Guidelines [2], like many other scientific guidelines [54,55,264], recommended the use of antihypertensive drugs in patients with grade 1 hypertension even in the absence of other risk factors or OD, provided that nonpharmacological treatment had proved unsuccessful. This recommendation also specifically included the elderly hypertensive patient. The 2007 Guidelines [2], furthermore, recommended a lower threshold for antihypertensive drug intervention in patients with diabetes, previous CVD or

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Search for asymptomatic organ damage, cardiovascular disease, and chronic kidney disease

Recommendations	Class[a]	Level[b]	Ref.[c]
Heart			
An ECG is recommended in all hypertensive patients to detect LVH, left atrial dilatation, arrhythmias, or concomitant heart disease.	I	B	149, 150, 151, 154
In all patients with a history or physical examination suggestive of major arrhythmias, long-term ECG monitoring, and, in case of suspected exercise-induced arrhythmias, a stress ECG test should be considered.	IIa	C	-
An echocardiogram should be considered to refine CV risk, and confirm ECG diagnosis of LVH, left atrial dilatation or suspected concomitant heart disease, when these are suspected.	IIa	B	156, 158, 160, 163, 164
Whenever history suggests myocardial ischaemia, a stress ECG test is recommended, and, if positive or ambiguous, an imaging stress test (stress echocardiography, stress cardiac magnetic resonance or nuclear scintigraphy) is recommended.	I	C	–
Arteries			
Ultrasound scanning of carotid arteries should be considered to detect vascular hypertrophy or asymptomatic atherosclerosis, particularly in the elderly.	IIa	B	51, 183–185, 188
Carotid–femoral PWV should be considered to detect large artery stiffening.	IIa	B	51, 138, 192–195
Ankle–brachial index should be considered to detect PAD.	IIa	B	198, 199
Kidney			
Measurement of serum creatinine and estimation of GFR is recommended in all hypertensive patients.[d]	I	B	228, 231, 233
Assessment of urinary protein is recommended in all hypertensive patients by dipstick.	I	B	203, 210
Assessment of microalbuminuria is recommended in spot urine and related to urinary creatinine excretion.	I	B	222, 223, 225, 228
Fundoscopy			
Examination of the retina should be considered in difficult to control or resistant hypertensive patients to detect haemorrhages, exudates, and papilloedema, which are associated with increased CV risk.	IIa	C	-
Examination of the retina is not recommended in mild-to-moderate hypertensive patients without diabetes, except in young patients.	III	C	-
Brain			
In hypertensive patients with cognitive decline, brain magnetic resonance imaging or computed tomography may be considered for detecting silent brain infarctions, lacunar infarctions, microbleeds, and white matter lesions.	IIb	C	-

CV, cardiovascular; ECG, electrocardiogram; GFR, glomerural filtration rate; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; PAD, peripheral artery disease; PWV, pulse wave velocity.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.
[d]The MDRD formula is currently recommended but new methods such as the CKD-EPI method aim to improve the accuracy of the measurement.

CKD and suggested treatment of these patients, even when BP was in the high normal range (130–139/85–89 mmHg). These recommendations were re-appraised in a 2009 ESH Task Force document [141] on the basis of an extensive review of the evidence [265]. The following now summarizes the conclusions for the current Guidelines.

4.2.2 Grade 2 and 3 hypertension and high-risk grade 1 hypertension

RCTs providing incontrovertible evidence in favour of antihypertensive therapy [260], as referred to in Section 4.1, were carried out primarily in patients with SBP >160 mmHg or DBP >100 mmHg, who would now be classified as grade 2 and 3 hypertensives—but also included some patients with grade 1 high-risk hypertension. Despite some difficulty in applying new classifications to old trials, the evidence favouring drug therapy in patients with marked BP elevation or in hypertensive patients at high total CV risk appears overwhelming. BP represents a considerable component of overall risk in these patients and so merits prompt intervention.

4.2.3 Low-to-moderate risk, grade 1 hypertension

The evidence favouring drug treatment in these individuals is scant because no trial has specifically addressed this condition. Some of the earlier trials on 'mild' hypertension used a different grading of hypertension (based on DBP only) [266–268] or included patients at high risk [268]. The more recent Felodipine EVent Reduction (FEVER) study switched patients from preexisting therapies to randomized treatments and, therefore, could not precisely define baseline hypertension grade; it also included complicated and uncomplicated hypertensives [269]. Further analyses of FEVER have recently confirmed a significant benefit attached to more-intensive lowering of BP after exclusion of all patients with previous CVD or diabetes, and in

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patients with randomization SBP below the median (153 mmHg) [270]. Because, at randomization, all patients were on a 12.5 mg daily dose of hydrochlorothiazide only, it is likely that these individuals—if untreated—would be within or very close to the SBP range defining grade 1 hypertension. Overall, a number of trials have shown significant reductions of stroke in patients at low-to-moderate CV risk (8–16% major CV events in 10 years) with baseline BP values close to, even if not exactly within, the range of grade 1 hypertension. [266,267,270]. Also a recent Cochrane Collaboration meta-analysis (2012-CD006742) limited to patients strictly responding to grade 1 low risk criteria finds a trend towards reduction of stroke with active therapy, but the very small number of patients retained (half of those in 266, 267) makes attainment of statistical significance problematic.

Recent guidelines have also underlined the paucity of data for treating grade 1 hypertension [271], recommending treatment only after confirming hypertension by ABPM and restricting treatment to grade 1 hypertensive patients with signs of OD or at high total CV risk. The advantage of systematically excluding white-coat hypertensives from the possible benefit of treatment is unproven. Further arguments in favour of treating even low-moderate risk grade 1 hypertensives are that: (i) waiting increases total risk, and high risk is often not entirely reversible by treatment [272], (ii) a large number of safe antihypertensive drugs are now available and treatment can be personalized in such away as to enhance its efficacy and tolerability, and (iii) many antihypertensive agents are out of patent and are therefore cheap, with a good cost-benefit ratio.

4.2.4 Isolated systolic hypertension in youth

A number of young healthy males have elevated values of brachial SBP (>140 mmHg) and normal values of brachial DBP (<90 mmHg). As mentioned in section 3.1, these subjects sometimes have normal central BP. No evidence is available that they benefit from antihypertensive treatment; on the contrary there are prospective data that the condition does not necessarily proceed to systolic/diastolic hypertension [142]. On the basis of current evidence, these young individuals can only receive recommendations on lifestyle, but because available evidence is scanty and controversial they should be followed closely.

4.2.5 Grade 1 hypertension in the elderly

Although the 2007 ESH/ESC and other guidelines recommended treating grade 1 hypertensives independently of age [2,273], it has been recognized that all the trials showing the benefits of antihypertensive treatment in the elderly have been conducted in patients with SBP >160 mmHg (grades 2 and 3) [141,265].

4.2.6 High normal blood pressure

The 2007 ESH/ESC Guidelines suggested initiation of antihypertensive drug treatment when BP is in the high normal range (130–139/8589 mmHg) in high- and very high-risk patients because of diabetes or concomitant CV or renal disease [2]. The 2009 re-appraisal document pointed out that evidence in favour of this early intervention was, at best, scanty [141,265]. For diabetes, the evidence is limited to: (i) the small 'normotensive' Appropriate Blood Pressure in Diabetes (ABCD) trial, in which the definition of normotension was unusual (<160 mmHg SBP) and benefit of treatment was seen only in one of several secondary CV events [274], and (ii) subgroup analyses of two trials [275,276], in which results in 'normotensives' (many of whom were under treatment) were reported not to be significantly different from those in 'hypertensives' (homogeneity test). Furthermore, in two studies in prediabetic or metabolic syndrome patients with a baseline BP in the high normal range, administration of ramipril or valsartan was not associated with any significant improvement in morbid and fatal CV events, compared with placebo [277,278].

Of two trials showing CV event reduction by lowering of BP in patients with a previous stroke, one included only 16% normotensives [279], while, in a sub-analysis of the other, significant benefits were restricted to patients with baseline SBP >140 mmHg (most already under baseline antihypertensive therapy) [280]. A review of placebo-controlled trials of antihypertensive therapy in coronary patients showed dissimilar results in different studies [265]. In most of these trials, randomized drugs were added on a background of antihypertensive drugs, therefore it is inappropriate to classify these patients as normotensive [265]. This consideration also applies to recent large meta-analyses showing the benefits of BP-lowering therapy also in individuals with baseline SBP above and below 140 mmHg, since the great majority of the individuals had been involved in trials in which antihypertensive agents were present at baseline [281–284]. It is true that two studies have shown that a few years' administration of antihypertensive agents to individuals with high normal BP can delay transition to hypertension [285,286], but how far the benefit of this early intervention lasts—and whether it can also delay events and be cost-effective—remains to be proven.

4.2.7 Summary of recommendations on initiation of antihypertensive drug treatment

Recommendations on initiation of antihypertensive drug treatment are summarized in Fig. 2 and below.

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Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

FIGURE 2 Initiation of lifestyle changes and antihypertensive drug treatment. Targets of treatment are also indicated. Colours are as in Figure 1. Consult Section 6.6 for evidence that, in patients with diabetes, the optimal DBP target is between 80 and 85 mmHg. In the high normal BP range, drug treatment should be considered in the presence of a raised out-of-office BP (masked hypertension). Consult section 4.2.4 for lack of evidence in favour of drug treatment in young individuals with isolated systolic hypertension.

Initiation of antihypertensive drug treatment

Recommendations	Class[a]	Level[b]	Ref.[c]
Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes.	I	A	260, 265, 284
Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range.	I	B	260, 284
Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low to 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.	IIa	B	266, 267
In elderly hypertensive patients drug treatment is recommended when SBP is ≥160 mmHg.	I	A	141, 265
Antihypertensive drug treatment may also 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.	IIb	C	-
Unless the necessary evidence is obtained it is not recommended to initiate antihypertensive drug therapy at high normal BP.	III	A	265
Lack of evidence does also not allow recommending to initiate antihypertensive drug therapy in young individuals with isolated elevation of brachial SBP, but these individuals should be followed closely with lifestyle recommendations.	III	A	142

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; OD, organ damage; SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

4.3 Blood pressure treatment targets

4.3.1 Recommendations of previous Guidelines

The 2007 ESH/ESC Guidelines [2], in common with other guidelines, recommended two distinct BP targets, namely <140/90 in low-moderate risk hypertensives and <130/80 mmHg in high-risk hypertensives (with diabetes, cerebrovascular, CV, or renal disease). More recently, the European Guidelines on CVD Prevention recommended a target of <140/80 mmHgfor patients with diabetes [50]. A

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careful review of the available evidence [265], however, leads to a re-appraisal of some of these recommendations [141], as detailed below.

4.3.2 Low-to-moderate risk hypertensive patients

In three trials [266,268,269], reducing SBP below 140 mmHg compared with a control group at >140 mmHg was associated with a significant reduction in adverse CV outcomes. Although, in two of these trials [268,269], CV risk in the less-intensively treated group was in the high-risk range (>20% CV morbidity and mortality in 10 years), a recent sub-analysis of FEVER has shown, over ten years, CV outcome reduction through lowering SBP to 137 rather than 142 mmHg in patients free of CVD and diabetes with CV risk of about 11% and 17% [270].

4.3.3 Hypertension in the elderly

In the large number of randomized trials of antihypertensive treatment in the elderly (including one in hypertensive patients aged 80 years or more) [287] all showing reduction in CV events through lowering of BP, the average achieved SBP never attained values <140 mmHg [265]. Conversely, two recent Japanese trials of more- vs. less-intensive BP lowering were unable to observe benefits by lowering average SBP to 136 and 137 mmHg rather than 145 and 142 mmHg [288,289]. On the other hand, a subgroup analysis of elderly patients in the FEVER study showed reduction of CV events by lowering SBP just below 140 mmHg (compared with 145 mmHg) [270].

4.3.4 High-risk patients

The re-appraisal of ESH/ESC Guidelines carried out in 2009 [141] has adopted the results of an extensive review of RCT evidence [265], showing that the recommendation of previous Guidelines [2], to lower BP to <130/80 mmHg in patients with diabetes or a history of CV or renal disease, is not supported by RCT evidence.

4.3.4.1 Diabetes mellitus

Lowering BP was found to be associated with important reductions in CV events: (i) in patients with diabetes included in a number of trials [270,275,290–292], (ii) in two trials entirely devoted to these patients [276,293], and (iii) in a recent meta-analysis [294]. In two trials [290,293], the beneficial effect was seen from DBP reductions to between 80–85 mmHg, whereas in no trial was SBP ever reduced below 130 mmHg. The only trial in patients with diabetes that achieved SBP values just lower than 130 mmHg in the more intensively treated group, was the 'normotensive'ABCD study, a very small study in which CV events (only a secondary endpoint) were not consistently reduced [274]. Although being somewhat underpowered, the much larger Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was unable to find a significant reduction in incidence of major CV events in patients with diabetes whose SBP was lowered to an average of 119 mmHg, compared with patients whose SBP remained at an average of 133 mmHg [295].

4.3.4.2 Previous cardiovascular events

In two studies of patients who had experienced previous cerebrovascular events [279,296], more aggressive lowering of BP, although associated with significant reductions in stroke and CV events, did not achieve average SBP values lower than 130 mmHg: a third, much larger, study was unable to find outcome differences between groups achieving SBP of 136 vs. 140 mmHg [297]. Among several trials in patients who had previous coronary events, SBP values lower than 130 mmHg were achieved by more intensive treatment in five trials, but with inconsistent results (a significant reduction of CV events in one [298], a significant reduction by one antihypertensive agent, but not by another, in a second trial [299], and no significant reduction in hard CV outcomes in three other studies) [300–302].

4.3.4.3 Renal disease

In patients with CKD—with or without diabetes—there are two treatment objectives: (i) prevention of CV events (the most frequent complication of CKD) and (ii) prevention or retardation of further renal deterioration or failure. Unfortunately, evidence concerning the BP target to be achieved in these patients is scanty and confused by the uncertainty about the respective roles of reduction of BP and specific effects of RAS blockers [303]. In three trials in CKD patients, almost exclusively without diabetes [304–306], patients randomized to a lower target BP (125–130 mmHg) had no significant differences in ESRD or death from patients randomized to a higher target (<140 mmHg). Only in a prolonged observational follow-up of two of these trials was there a trend towards lower incidence of events, which was more evident in patients with proteinuria [307,308]. The two large trials in patients with diabetic nephropathy are not informative on the supposed benefit of a SBP target below 130 mmHg [309,310], since the average SBPs achieved in the groups with more intensive treatment were 140 and 143 mmHg. Only a recent co-operative study has reported a reduction in renal events (GFR reduction and ESRD) in children randomized to a BP target below—rather than above—the 50th percentile [311], but these values in children can hardly be compared with adult values. Furthermore it should be considered that, in ACCORD, although eGFR at baseline was in the normal range, more intensive lowering of BP (119/67 vs. 134/73 mmHg) was associated with a near-doubling of cases with eGFR <30 ml/min/1.73 m^2 [295]. Finally, recent meta-analyses of trials investigating different BP targets in patients with CKD failed to demonstrate definite benefits from achieving lower BP goals in terms of CV or renal clinical events [312,313].

4.3.5 The 'lower the better' vs. the J-shaped curve hypothesis

The concept that 'the lower the SBP and DBP achieved the better the outcome' rests on the direct relationship between BP and incident outcomes, down to at least 115 mmHg SBP and 75 mmHg DBP, described in a large meta-analysis of 1 million individuals free of CVD at baseline and subsequently followed for about 14 years [3]—not the usual situation for hypertension trials. The concept assumes that the BP/outcome relationship down to the lowest BP values is also seen when the BP differences are induced by drug therapy and that the relationship in patients with CVD can be superimposed on that described in individuals free of CV complications. In the absence of trials that have specifically

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investigated low SBP ranges (see above), the only available data in favour of the 'lower the better' concept are those of a meta-analysis of randomized trials, showing that reduction of SBP to a mean of 126 mmHg, compared with 131 mmHg, had the same proportional benefits as reduction to a mean of 140 mmHg, compared with 145 mmHg [281]. Of course, this was a post-hoc analysis, in which randomization was lost because the splitting of the patients into the BP categories was not considered at the randomization stage. Demonstration of the 'lower the better' hypothesis is also made difficult by the fact that the curve relating BP and adverse CV events may flatten at low BP values, and therefore demonstration of benefits requires much larger and longer studies than those yet available. This is consistent with the semi-logarithmic nature of the relationship shown in observational studies [3], but it may also raise the question of whether a small benefit is worth large effort.

An alternative to the 'lower the better' concept is the hypothesis of a J-shaped relationship, according to which the benefits of reducing SBP or DBP to markedly low values are smaller than for reductions to more moderate values. This hypothesis continues to be widely popular for several reasons: (i) common sense indicates that a threshold BP must exist, below which survival is impaired, (ii) physiology has shown that there is a low (as well as a high) BP threshold for organ blood-flow autoregulation and this threshold can be elevated when there is vascular disease, and (iii) there is a persistent hang-over from an old belief viewing high BP as a compensatory mechanism for preserving organ function (the 'essential' nature of hypertension) [314]. Correct investigation of the J-curve requires randomized comparison of three BP targets, only attempted in the Hypertension Optimal Treatment (HOT) study but in low-risk hypertensives and using DBP targets [290]. Owing to the lack of direct evidence, recourse has been made to the indirect observational approach of relating outcomes to achieved BP. A number of trials have been so analysed and their results recently reviewed [314]. Some of the trial analyses have concluded that no J-curve exists [280,290,315], while others have concluded in favour of its existence [316–319], although in some trials it was also seen in placebo-treated patients [320,321]. Furthermore, two recent trials investigating more- or less-intensive low-density lipoprotein cholesterol lowering by statins also found a J-curve relating BP to adverse CV events, although protocols did not include BP-lowering interventions [322,323]. The approach used to investigate the J-curve raises important hypotheses, yet has obvious limitations: (i) it changes a randomized study into an observational one, (ii) the numbers of patients and events in the lowest BP groups are usually very small, (iii) patients in the lowest BP groups are often at increased baseline risk and, despite statistical adjustments, reverse-causality cannot be excluded; and (iv) the 'nadir' SBP and DBP values (the values at which risk starts to increase) are extremely different from trial to trial, even when baseline CV risk is similar [314]. Some trial analyses have also raised the point that a J-curve may exist for coronary events but not for strokes—but this is not a consistent finding in various trials [317,318,324–326]. Whether or not the underlying high risk to patients is more important than the excessive BP reduction should be considered. The limitations of the current approach for investigating the J-curve obviously also apply to their meta-analyses [327]. Yet the J-curve hypothesis is an important issue: it has a pathophysiological rationale and deserves to be investigated in a correctly designed trial.

4.3.6 Evidence on target blood pressure from organ damage studies

It would be of some interest to receive guidance about target BP from OD studies, but unfortunately this information must be judged with great caution. Indeed, trials using OD as an endpoint often do not have sufficient statistical power to safely measure effects on CV outcome and the data they provide on fatal and nonfatal CV events are subject to the effects of chance. For example, a study of 1100 nondiabetic hypertensive patients, followed for 2 years, showed that the incidence of electrocardiographic LVH is reduced by tighter (about 132/77 mmHg) vs. less-tight BP control (about 136/79 mmHg) and reported a parallel reduction in CV events (although there were only about 40 hard outcome events) [328]. On the other hand, the recent Randomized Olmesartan And Diabetes Micro-Albuminuria Prevention (ROADMAP) study [329] in diabetic patients showed a significant reduction of new-onset microalbuminuria in more intensively treated patients (olmesartan vs. placebo), but the more intensively treated group also had a higher incidence of CV outcomes [329]. Because of the small number of CV events in the two trials, it is likely that both their reduction and their increase are due to chance effects. Furthermore, when analyses of OD and event effects are made in large trials, dissociation of the two types of effects has been reported: in the Losartan Intervention For Endpoint Reduction in Hypertensives (LIFE) study, LVH regression was linearly related to the treatment-induced BP changes (the lower the better) [330], whereas, in the same trial, achieved BP and morbid and fatal CV events were related in a J-shaped manner [319]. In ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), the lowest BP achieved by the ramipril-telmisartan combination was associated with reduced proteinuria, but with a greater risk of acute renal failure and a similar CV risk [331]. The clinical significance of treatment-induced changes in OD is further discussed in Section 8.4.

4.3.7 Clinic vs. home and ambulatory blood pressure targets

No direct evidence from randomized outcome studies is yet available about BP targets when home or ambulatory BP measurements are used [332], although some evidence is available that differences with office BP may not be too pronounced when office BP is effectively reduced [333]. Out-of-office measurements should always be evaluated together with measurements at the clinic. Notably, however, the adjustment of antihypertensive therapy on the basis of a similar target ambulatory or home BP led to less-intensive drug treatment, without a significant difference in OD [334–336]. The lower cost of medications in the out-of-office BP groups was partially offset by other costs in the home BP groups [335,336].

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4.3.8 Summary of recommendations on blood pressure targets in hypertensive patients

Recommendations on BP targets are summarized in Fig. 2 and below.

Blood pressure goals in hypertensive patients

Recommendations	Class[a]	Level[b]	Ref.[c]
A SBP goal <140 mmHg:			
a) is recommended in patients at low–moderate CV risk;	I	B	266, 269, 270
b) is recommended in patients with diabetes;	I	A	270, 275, 276
c) should be considered in patients with previous stroke or TIA;	IIa	B	296, 297
d) should be considered in patients with CHD;	IIa	B	141, 265
e) should be considered in patients with diabetic or non-diabetic CKD.	IIa	B	312, 313
In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.	I	A	265
In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability.	IIb	C	-
In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions.	I	B	287
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated.	I	A	269, 290, 293

CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

5. TREATMENT STRATEGIES

5.1 Lifestyle changes

Appropriate lifestyle changes are the cornerstone for the prevention of hypertension. They are also important for its treatment, although they should never delay the initiation of drug therapy in patients at a high level of risk. Clinical studies show that the BP-lowering effects of targeted lifestyle modifications can be equivalent to drug monotherapy [337], although the major drawback is the low level of adherence over time—which requires special action to be overcome. Appropriate lifestyle changes may safely and effectively delay or prevent hypertension in non-hypertensive subjects, delay or prevent medical therapy in grade 1 hypertensive patients and contribute to BP reduction in hypertensive individuals already on medical therapy, allowing reduction of the number and doses of antihypertensive agents [338]. Beside the BP-lowering effect, lifestyle changes contribute to the control of other CV risk factors and clinical conditions [50].

The recommended lifestyle measures that have been shown to be capable of reducing BP are: (i) salt restriction, (ii) moderation of alcohol consumption, (iii) high consumption of vegetables and fruits and low-fat and other types of diet, (iv) weight reduction and maintenance and (v) regular physical exercise [339]. In addition, insistence on cessation of smoking is mandatory in order to improve CV risk, and because cigarette smoking has an acute pressor effect that may raise daytime ambulatory BP [340–342].

5.1.1 Salt restriction

There is evidence for a causal relationship between salt intake and BP and excessive salt consumption may contribute to resistant hypertension. Mechanisms linking salt intake and BP elevation include an increase in extracellular volume—but also in peripheral vascular resistance, due in part to sympathetic activation [343]. The usual salt intake is between 9 and 12 g/day in many countries and it has been shown that reduction to about 5 g/day has a modest (1–2 mmHg) SBP-lowering effect in normotensive individuals and a somewhat more pronounced effect (4–5 mmHg) in hypertensive individuals [339,344,345]. A daily intake of 5–6 g of salt is thus recommended for the general population. The effect of sodium restriction is greater in black people, older people and in individuals with diabetes, metabolic syndrome or CKD, and salt restriction may reduce the number and doses of antihypertensive drugs [345,346]. The effect of reduced dietary salt on CVD events remains unclear [347–350], although the long-term follow-up of the Trials of Hypertension Prevention (TOHP) trial showed a reduced salt intake to be associated with lower risk of CV events [351]. Overall there is no evidence that reducing sodium from high- to moderate intakes causes harm [352].

At the individual level, effective salt reduction is by no means easy to achieve. Advice should be given to avoid added salt and high-salt food. A reduction in population-wide salt intake remains a public health priority but requires a combined effort by the food industry, governments and the public in general, since 80% of salt consumption involves 'hidden salt'. It has been calculated that salt reduction in the manufacturing processes of bread, processed meat and cheese, margarine and cereals will result in an increase in quality-adjusted life-years [353].

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5.1.2 Moderation of alcohol consumption

The relationship between alcohol consumption, BP levels and the prevalence of hypertension is linear. Regular alcohol use raises BP in treated hypertensive subjects [354]. While moderate consumption may do no harm, the move from moderate to excessive drinking is associated both with raised BP and with an increased risk of stroke. The Prevention And Treatment of Hypertension Study (PATHS) investigated the effects of alcohol reduction on BP. The intervention group had a 1.2/0.7 mmHg greater reduction in BP than the control group at the end of the 6-month period [355]. No studies have been designed to assess the impact of alcohol reduction on CV endpoints. Hypertensive men who drink alcohol should be advised to limit their consumption to no more than 20–30 g, and hypertensive women to no more than 10–20 g, of ethanol per day. Total alcohol consumption should not exceed 140 g per week for men and 80 g per week for women.

5.1.3 Other dietary changes

Hypertensive patients should be advised to eat vegetables, low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources, reduced in saturated fat and cholesterol. Fresh fruits are also recommended—although with caution in overweight patients because their sometimes high carbohydrate content may promote weight gain [339,356]. The Mediterranean type of diet, especially, has attracted interest in recent years. A number of studies and meta-analyses have reported on the CV protective effect of the Mediterranean diet [357,358]. Patients with hypertension should be advised to eat fish at least twice a week and 300–400 g/day of fruit and vegetables. Soy milk appeared to lower BP when compared with skimmed cows' milk [359]. Diet adjustment should be accompanied by other lifestyle changes. In patients with elevated BP, compared with the Dietary Approaches to Stop Hypertension (DASH) diet alone, the combination of the DASH diet with exercise and weight loss resulted in greater reductions in BP and LVM [360]. With regard to coffee consumption, a recent systematic review found that most of the available studies (10 RCTs and 5 cohort studies) were of insufficient quality to allow a firm recommendation to be given for or against coffee consumption as related to hypertension [361].

5.1.4 Weight reduction

Hypertension is closely correlated with excess body weight [362], and weight reduction is followed by a decrease in BP. In a meta-analysis, the mean SBP and DBP reductions associated with an average weight loss of 5.1 kg were 4.4 and 3.6 mmHg, respectively [363]. Weight reduction is recommended in overweight and obese hypertensive patients for control of risk factors, but weight stabilisation may be a reasonable target for many of them. In patients with established CVD manifestations, observational data indicate a worse prognosis following weight loss. This seems to be true also in the elderly. Maintenance of a healthy body weight (BMI of about 25 kg/m^2) and waist circumference (<102 cm for men and <88 cm for women) is recommended for nonhypertensive individuals to prevent hypertension and for hypertensive patients to reduce BP. It is noteworthy, however, that the optimal BMI is unclear, based on two large meta-analyses of prospective observational population-based outcome studies. The Prospective Studies Collaboration concluded that mortality was lowest at a BMI of about 22.5–25 kg/m^2 [364], whereas a more recent meta-analysis concluded that mortality was lowest in overweight subjects [365]. 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 and regular exercise. Weight-loss programmes are not so successful and influences on BP may be overestimated. Furthermore, short-term results are often not maintained in the long term. In a systematic review of diabetic patients [366], the mean weight loss after 1–5 years was 1.7 kg. In 'prediabetic' patients, combined dietary and physical activity interventions gave a 2.8 kg extra weight reduction after 1 year and a further 2.6 kg reduction after 2 years: while not impressive, this is sufficient to have a protective effect against the incidence of diabetes [367]. In established type 2 diabetes mellitus (DM), intentional weight loss—according to the Action for HEalth in Diabetes (AHEAD) study—did not reduce CV events, so that a general control of risk factors is probably more important than weight loss per se. Weight loss can also be promoted by antiobesity drugs, such as orlistat and, to a greater degree, by bariatic surgery, which appears to decrease CV risk in severely obese patients [368]. Details are available in a recent document by the ESH and the European Association for the Study of Obesity [368].

5.1.5 Regular physical exercise

Epidemiological studies suggest that regular aerobic physical activity may be beneficial for both prevention and treatment of hypertension and to lower CV risk and mortality. A meta-analysis of randomized controlled trials has shown that aerobic endurance training reduces resting SBP and DBP by 3.0/2.4 mmHg overall and even by 6.9/4.9 mmHg in hypertensive participants [369]. Even regular physical activity of lower intensity and duration has been shown to be associated with about a 20% decrease in mortality in cohort studies [370,371], and this is also the case for measured physical fitness [372]. Hypertensive patients should be advised to participate in at least 30 min of moderate-intensity dynamic aerobic exercise (walking, jogging, cycling or swimming) on 5–7 days per week [373]. Aerobic interval training has also been shown to reduce BP [374]. The impact on BP values of other forms of exercise, such as isometric resistance training (muscular force development without movement) and dynamic resistance exercise (force development associated with movement) has been reviewed recently [375,376]. Dynamic resistance training was followed by significant BP reduction, as well as improvements in other metabolic parameters, and performance of resistance exercises on 2–3 days per week can be advised. Isometric exercises are not recommended, since data from only a few studies are available.

5.1.6 Smoking cessation

Smoking is a major risk factor for atherosclerotic CVD. Although the rate of smoking is declining in most European

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countries (in which a legalized smoking ban is effective) it is still common in many regions and age groups, partly due to education-related inequalities in cessation of smoking [377]. There is evidence also on the ill-health effects of passive smoking [378]. Smoking causes an acute increase in BP and heart rate, persisting for more than 15 min after smoking one cigarette [340], as a consequence of stimulation of the sympathetic nervous system at the central level and at the nerve endings [379]. A parallel change in plasma catecholamines and BP, plus an impairment of the baroreflex, have been described that are related to smoking [379–381]. Studies using ABPM have shown that both normotensive and untreated hypertensive smokers present higher daily BP values than nonsmokers [341,342,382]. No chronic effect of smoking has been reported for office BP [383], which is not lowered by giving up smoking. Beside the impact on BP values, smoking is a powerful CV risk factor and quitting smoking is probably the single most effective lifestyle measure for the prevention of CVDs including stroke, myocardial infarction and peripheral vascular disease [384–386]. Therefore tobacco use status should be established at each patient visit and hypertensive smokers should be counselled regarding giving up smoking.

Even in motivated patients, programmes to stop smoking are successful (at 1 year) in only 20–30% [387]. Where necessary, smoking cessation medications, such as nicotine replacement therapy, bupropion, or varenicline, should be considered. A meta-analysis of 36 trials comparing longterm cessation rates using bupropion vs. control yielded a relative success rate of 1.69 (1.53–1.85) [388], whereas evidence of any additional effect of adding bupropion to nicotine replacement therapy was inadequate [389]. The partial nicotine-receptor agonist varenicline has shown a modest benefit over nicotine replacement therapy and bupropion [388], but the U.S. Food & Drug Administration (FDA) has recently issued a warning regarding the safety profile of varenicline (http://www.fda.gov/Drugs/DrugSafety/ucm330367.htm). Although these drugs have been shown to be effective in clinical trials, they are underused due to adverse effects, contra-indications, low acceptance, high costand lack of reimbursement in many countries. Relapse prevention is a cornerstone in fighting nicotine addiction but the field is inadequately studied and existing evidence is disappointing [388]. There is insufficient evidence to support the use of any specific behavioural intervention; some positive results can be expected from interventions focussing on identifying and resolving temptation situations, as well as from strategies steering patients towards changes in behaviours, such as motivational interviews. Extended treatment with varenicline may prevent relapse but studies of extended treatment with nicotine replacement are not available [390].

5.1.7 Summary of recommendations on adoption of lifestyle changes

The following lifestyle change measures are recommended in all patients with hypertension to reduce BP and/or the number of CV risk factors.

Adoption of lifestyle changes

Recommendations	Class[a]	Level[b,d]	Level[b,e]	Ref.[c]
Salt restriction to 5–6 g per day is recommended.	I	A	B	339, 344–346, 351
Moderation of alcohol consumption to no more than 20–30 g of ethanol per day in men and to no more than 10–20 g of ethanol per day in women is recommended.	I	A	B	339, 354, 355
Increased consumption of vegetables, fruits, and low-fat dairy products is recommended.	I	A	B	339, 356–358
Reduction of weight to BMI of 25 kg/m^2 and of waist circumference to <102 cm in men and <88 cm in women is recommended, unless contraindicated.	I	A	B	339, 363–365
Regular exercise, i.e. at least 30 min of moderate dynamic exercise on 5 to 7 days per week is recommended.	I	A	B	339, 369, 373, 376
It is recommended to give all smokers advice to quit smoking and to offer assistance.	I	A	B	384–386

BMI, body mass index.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.
[d]Based on the effect on BP and/or CV risk profile.
[e]Based on outcome studies.

5.2 Pharmacological therapy

5.2.1 Choice of antihypertensive drugs

In the 2003 and 2007 versions [1,2]. the ESH/ESC Guidelines reviewed the large number of randomized trials of antihypertensive therapy and concluded that the main benefits of antihypertensive treatment are due to lowering of BP per se and are largely independent of the drugs employed. Although meta-analyses occasionally appear, claiming superiority of one class of agents over another for some outcomes [391–393], this largely depends on the selection bias of trials and the largest meta-analyses available do not show clinically relevant differences between drug classes [284,394,395]. Therefore the current Guidelines reconfirm

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that diuretics (including thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. However, some therapeutic issues that have recently been raised are discussed below.

5.2.1.1 Beta-blockers

The reasons why, at variance from some guidelines, beta-blockers were maintained as a possible choice for antihypertensive treatment were summarized in the 2007 ESH/ESC Guidelines and further discussed in the 2009 reappraisal document [2,141]. Although acknowledging that the quality of the evidence was low, a Cochrane meta-analysis (substantially reproducing a 2006 meta-analysis by the same group) [396,397] has reported that beta-blockers may be inferior to some—but not all—other drug classes for some outcomes. Specifically, they appear to be worse than calcium antagonists (but not diuretics and RAS blockers) for total mortality and CV events, worse than calcium antagonists and RAS blockers for stroke and equal to calcium antagonists, RAS blockers and diuretics for CHD. On the other hand, the large meta-analysis by Law *et al*. has shown beta-blocker-initiated therapy to be (i) equally as effective as the other major classes of antihypertensive agents in preventing coronary outcomes and (ii) highly effective in preventing CV events in patients with a recent myocardial infarction and those with heart failure [284]. A similar incidence of CV outcomes with beta-blockers and/or diuretics or their combinations compared with other drug classes has also been reported in the meta-analysis of the BP-lowering treatment trialists' collaboration [394].

A slightly lower effectiveness of beta-blockers in preventing stroke [284] has been attributed to a lesser ability to reduce central SBP and pulse pressure [398,399]. However, a lower effectiveness in stroke prevention is also shared by ACE inhibitors [284], although these compounds have been reported to reduce central BP better than beta-blockers [398]. Beta-blockers also appear (i) to have more side-effects (although the difference with other drugs is less pronounced in double blind studies) [400] and (ii) to be somewhat less effective than RAS blockers and calcium antagonists in regressing or delaying OD, such as LVH, carotid IMT, aortic stiffness and small artery remodelling [141]. Also, beta-blockers tend to increase body weight [401] and, particularly when used in combination with diuretics, to facilitate new-onset diabetes in predisposed patients [402]. This phenomenon may have been overemphasized by the fact that all trial analyses have been limited to patients free of diabetes or with glucose <7.0 mmol/L, ignoring the fact that a noticeable number of patients with a diagnosis of diabetes at baseline do not have this diagnosis reconfirmed at study end, which obviously reduces the weight of treatment-induced diabetes and raises doubts about the precision of the definition of diabetes used in the above analyses [403]. Some of the limitations of traditional beta-blockers do not appear to be shared by some of the vasodilating beta-blockers, such as celiprolol, carvedilol and nebivolol—more widely used today—which reduce central pulse pressure and aortic stiffness better than atenolol or metoprolol [404–406] and affect insulin sensitivity less than metoprolol [407,408]. Nebivolol has recently been shown not to worsen glucose tolerance compared with placebo and when added to hydrochlorothiazide [409]. Both carvedilol and nebivolol have been favourably tested in RCTs, although in heart failure rather than arterial hypertension [410]. Finally, beta-blockers have recently been reported not to increase, but even reduce, the risk of exacerbations and to reduce mortality in patients with chronic obstructive lung disease [411].

5.2.1.2 Diuretics

Diuretics have remained the cornerstone of antihypertensive treatment since at least the first Joint National Committee (JNC) report in 1977 [412] and the first WHO report in 1978 [413], and still, in 2003, they were classified as the only first-choice drug by which to start treatment, in both the JNC-7 [264] and the WHO/International Society of Hypertension Guidelines [55,264]. The wide use of thiazide diuretics should take into account the observation in the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [414] that their association with an ACE inhibitor was less effective in reducing CV events than the association of the same ACE inhibitor with a calcium antagonist. The interesting findings of ACCOMPLISH will be discussed in Section 5.2.2 but need replication, because no other randomized study has shown a significant superiority of a calcium antagonist over a diuretic. Therefore, the evidence provided by ACCOMPLISH does not appear to bear sufficient weight to exclude diuretics from first-line choice.

It has also been argued that diuretics such as chlorthalidone or indapamide should be used in preference to conventional thiazide diuretics, such as hydrochlorothiazide [271]. The statement that 'There is limited evidence confirming benefit of initial therapy on clinical outcomes with low doses of hydrochlorothiazide' [271] is not supported by a more extensive review of available evidence [332,415]. Meta-analyses claiming that hydrochlorothiazide has a lesser ability to reduce ambulatory BP than other agents, or reduces outcomes less than chlorthalidone [416,417], are confined to a limited number of trials and do not include head-to-head comparisons of different diuretics (no large randomized study is available). In the Multiple Risk Factor Intervention Trial (MRFIT), chlorthalidone and hydrochlorothiazide were not compared by randomized assignment and, overall, chlorthalidone was used at higher doses than hydrochlorothiazide [418]. Therefore no recommendation can be given to favour a particular diuretic agent.

Spironolactone has been found to have beneficial effects in heart failure [419] and, although never tested in RCTs on hypertension, can be used as a third- or fourth-line drug (see Section 6.14) and helps in effectively treating undetected cases of primary aldosteronism. Eplerenone has also shown a protective effect in heart failure and can be used as an alternative to spironolactone [420].

5.2.1.3 Calcium antagonists

Calcium antagonists have been cleared from the suspicion of causing a relative excess of coronary events by the same

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authors who had raised the question. Some meta-analyses suggest that these agents may be slightly more effective in preventing stroke [284,394,421], although it is not clear whether this can be ascribed to a specific protective effect on the brain circulation or to a slightly better or more uniform BP control with this class of drugs [141]. The question of whether calcium antagonists may be less effective than diuretics, beta-blockers and ACE inhibitors in preventing incipient heart failure is still an open one. In the largest available meta-analysis [284], calcium antagonists reduced new-onset heart failure by about 20% compared with placebo but, when compared with diuretics, beta-blockers and ACE inhibitors were inferior by about 20% (which means a 19% rather than 24% reduction). The lower effectiveness of calcium antagonists on the onset of heart failure may also be a consequence of the design of the trials pointing to this conclusion, which required prevention or withdrawal of agents essential in heart failure therapy such as diuretics, beta-blockers and ACE inhibitors in patients randomized to calcium antagonists [422]. In fact, in all trials in which the design permitted or prescribed the simultaneous use of diuretics, beta-blockers or ACE inhibitors [269,299,301, 423], calcium antagonists were not inferior to comparative therapies in preventing heart failure. Calcium antagonists have shown a greater effectiveness than beta-blockers in slowing down progression of carotid atherosclerosis and in reducing LV hypertrophy in several controlled studies (see sections 6.11.4 and 6.12.1).

5.2.1.4 Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Both classes are among those most widely used in antihypertensive therapy. Some meta-analyses have suggested that ACE inhibitors may be somewhat inferior to other classes in preventing stroke [284,395,421] and that angiotensin receptor blockers may be inferior to ACE inhibitors in preventing myocardial infarction [424] or all-cause mortality [393]. The hypothesis raised by these meta-analyses has been undermined by the results of the large ONTARGET, directly comparing outcomes under treatment with the ACE inhibitor ramipril and the angiotensin receptor blocker telmisartan (section 5.2.2.2). ONTARGET has shown telmisartan not to be statistically inferior to ramipril as far as incidence of major cardiac outcomes, stroke and all-cause death is concerned. ONTARGET has also disproved the hypothesis that the peroxisome proliferator-activated receptor (PPAR) activity of telmisartan may render this compound more effective in preventing or delaying onset of diabetes: incidence of new diabetes was non-significantly different between telmisartan and ramipril in ONTARGET.

Most recently, the hypothesis has been raised of an association of angiotensin receptor blockers with cancer onset [425]. A much larger meta-analysis, including all major randomized trials investigating all major compounds of the class, has subsequently found no evidence of increased cancer incidence [426], for which there is also no basis from a mechanistic standpoint [427]. Among the well known ancillary properties of ACE inhibitors and angiotensin receptor blockers, are their peculiar effectiveness in reducing proteinuria (see section 6.9) and improving outcomes in chronic heart failure (section 6.11.2).

5.2.1.5 Renin inhibitors

Aliskiren, a direct inhibitor of renin at the site of its activation, is available for treating hypertensive patients, both as monotherapy and when combined with other antihypertensive agents. To date, available evidence shows that, when used alone, aliskiren lowers SBP and DBP in younger and elderly hypertensive patients [428]; that it has a greater antihypertensive effect when given in combination with a thiazide diuretic, a blocker of the RAS at other sites, or a calcium antagonist [429,430]; and that prolonged administration in combination treatment can have a favourable effect (i) on asymptomatic OD, such as urinary protein excretion [431] or (ii) on prognostic biomarkers for heart failure, such as B-type natriuretic peptides [432].

No trial is available on the effect of aliskiren on CV or renal morbid and fatal events in hypertension. A large-scale trial on diabetic patients, ALiskiren Trial In Type 2 Diabetes Using Cardio-renal Endpoints (ALTITUDE), in which aliskiren was administered on top of a RAS blocker, has recently been stopped because, in these patients at high risk of CV and renal events, there was a higher incidence of adverse events, renal complications (ESRD and renal death), hyperkalaemia and hypotension [433]. This treatment strategy is therefore contra-indicated in such specific conditions, similar to the contra-indications for the ACE inhibitor-angiotensin receptor blocker combination resulting from the ONTARGET trial (see Section 5.2.2) [331]. Another large-scale trial, A Randomized Controlled Trial of Aliskiren in the Prevention of Major Cardiovascular Events in Elderly People (APOLLO), in which aliskiren was used alone or in combination with a thiazide diuretic or a calcium channel blocker, has also been stopped, despite no evidence of harm in the aliskiren-treated group. No aliskiren-based antihypertensive trials with hard endpoints are expected in the near future. No beneficial effect on mortality and hospitalization has recently been shown by adding aliskiren to standard treatment in heart failure [434].

5.2.1.6 Other antihypertensive agents

Centrally active agents and alpha-receptor blockers are also effective antihypertensive agents. Nowadays, they are most often used in multiple drug combinations. The alpha-blocker doxazosin has effectively been used as third-line therapy in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). This will be further discussed in the section on resistant hypertension (6.14).

5.2.1.7 Antihypertensive agents and visit-to-visit blood pressure variability

Attention has recently been drawn to the association of visit-to-visit variability of intra-individual BP during antihypertensive treatment and the incidence of CV events (particularly stroke) in high-risk patients [435]. In coronary hypertensive patients, consistency of BP control between visits is accompanied by less-frequent CV morbidity and mortality, independently of the mean BP level [436]. However, in the mild hypertensive, low-CV-risk patients of the ELSA trial, mean on-treatment BP, rather than visit-to-visit BP variations, predicted both the progression of

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carotid atherosclerosis and the incidence of CV events [437]. Thus the clinical importance of visit-to-visit BP variability within treated individuals, vis-a-vis the achieved long-term average BP level, is not yet indisputably proven.

An analysis of the ASCOT trial has suggested that visit-to-visit BP variability may be lower with the combination of a calcium antagonist and an ACE inhibitor, than with the combination of a beta-blocker and a diuretic [438]. Additionally, from a meta-analysis of several trials, the conclusion has been reached that visit-to-visit BP variability is more pronounced in patients under beta-blockade than with other drug classes [439,440]. Yet, the underlying cause of visit-to-visit BP variability is not known—whether it is really pharmacologically driven or, rather, a marker of treatment adherence. Also, the abovementioned meta-analyses based their results on inter-individual BP variability (i.e. the range of the BP effects of treatment in the whole group of patients) rather than intra-individual variability. The use of inter-individual BP variability as a surrogate of intra-individual variability to classify antihypertensive agents as associated with greater or lesser visit-to-visit BP variations or more or less consistent BP control [439,440] seems unjustified, since discrepancies have been reported between the two measures [441]. Furthermore, despite any possible correlations, the two types of variability are unlikely to measure the same phenomena [442]. In practical terms, until intra-individual visit-to-visit BP variability from new large-scale trials is analysed, inter-individual visit-to-visit variability should not be used as a criterion for antihypertensive drug choice. It remains, however, an interesting subject for further investigation.

5.2.1.8 Should antihypertensive agents be ranked in order of choice?

Once it is agreed that (i) the major mechanism of the benefits of antihypertensive therapy is lowering of BP per se, (ii) the effects on cause-specific outcomes of the various agents are similar or differ by only a minor degree, (iii) the type of outcome in a given patient is unpredictable, and (iv) all classes of antihypertensive agents have their advantages but also contra-indications (Table 14), it is obvious that any all-purpose ranking of drugs for general antihypertensive usage is not evidence-based [141,443]. Rather than indulging in an all-purpose ranking, the Task Force decided to confirm (with small changes) the table published in the 2007 ESH/ESC Guidelines [2], with the drugs to be considered in specific conditions, based on the fact that some classes have preferentially been used in trials in specific conditions or have shown greater effectiveness in specific types of OD (see Mancia *et al*. for detailed evidence) [2] (Table 15). However, no evidence is available that different choices should be made based on age or gender (except for caution in using RAS blockers in women with child bearing potential because of possible teratogenic effects) [444,445]. In any case, physicians should pay attention to adverse drug effects—even those purely subjective—as they are powerful deterrents to treatment adherence. If necessary, doses or drugs should be changed in order to combine effectiveness with tolerability.

TABLE 14. Compelling and possible contra-indications to the use of antihypertensive drugs

Drug	Compelling	Possible
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalaemia
Beta-blockers	Asthma A–V block (grade 2 or 3)	Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease (except for vasodilator beta-blockers)
Calcium antagonists (dihydropyridines)		Tachyarrhythmia Heart failure
Calcium antagonists (verapamil, diltiazem)	A–V block (grade 2 or 3, trifascicular block) Severe LV dysfunction Heart failure	
ACE inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Mineralocorticoid receptor antagonists	Acute or severe renal failure (eGFR <30 mL/min) Hyperkalaemia	

A-V, atrio-ventricular; eGFR, estimated glomerular filtration rate; LV, left ventricular.

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TABLE 15. Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CV, cardiovascular; ESRD, end-stage renal disease; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy.

5.2.2 Monotherapy and combination therapy

5.2.2.1 Pros and cons of the two approaches

The 2007 ESH/ESC Guidelines underlined that, no matter which drug is employed, monotherapy can effectively reduce BP in only a limited number of hypertensive patients and that most patients require the combination of at least two drugs to achieve BP control [2]. Therefore, the issue is not whether combination therapy is useful, but whether it should always be preceded by an attempt to use monotherapy, or whether—and when—combination therapy may be the initial approach.

The obvious advantage of initiating treatment with monotherapy is that of using a single agent, thus being able to ascribe effectiveness and adverse effects to that agent. The disadvantages are that, when monotherapy with one agent is ineffective or insufficiently effective, finding an alternative monotherapy that is more effective or better tolerated may be a painstaking process and discourage adherence. Additionally, a meta-analysis of more than 40 studies has shown that combining two agents from any two classes of antihypertensive drugs increases the BP reduction much more than increasing the dose of one agent [446]. The advantage of initiating with combination therapy is a prompter response in a larger number of patients (potentially beneficial in high-risk patients), a greater probability of achieving the target BP in patients with higher BP values, and a lower probability of discouraging patient adherence with many treatment changes. Indeed, a recent survey has shown that patients receiving combination therapy have a lower drop-out rate than patients given any monotherapy [447]. A further advantage is that there are physiological and pharmacological synergies between different classes of agents, that may not only justify a greater BP reduction but also cause fewer side-effects and may provide larger benefits than those offered by a single agent. The disadvantage of initiating with drug combinations is that one of the drugs may be ineffective.

On the whole the suggestion, given in the 2007 ESH/ESC Guidelines [2], of considering initiation with a drug combination in patients at high risk or with markedly high baseline BP can be reconfirmed.

When initiating with monotherapy or with a two-drug combination, doses can be stepped up if necessary to achieve the BP target; if the target is not achieved by a two-drug combination at full doses, switching to another two-drug combination can be considered or a third drug added. However, in patients with resistant hypertension,

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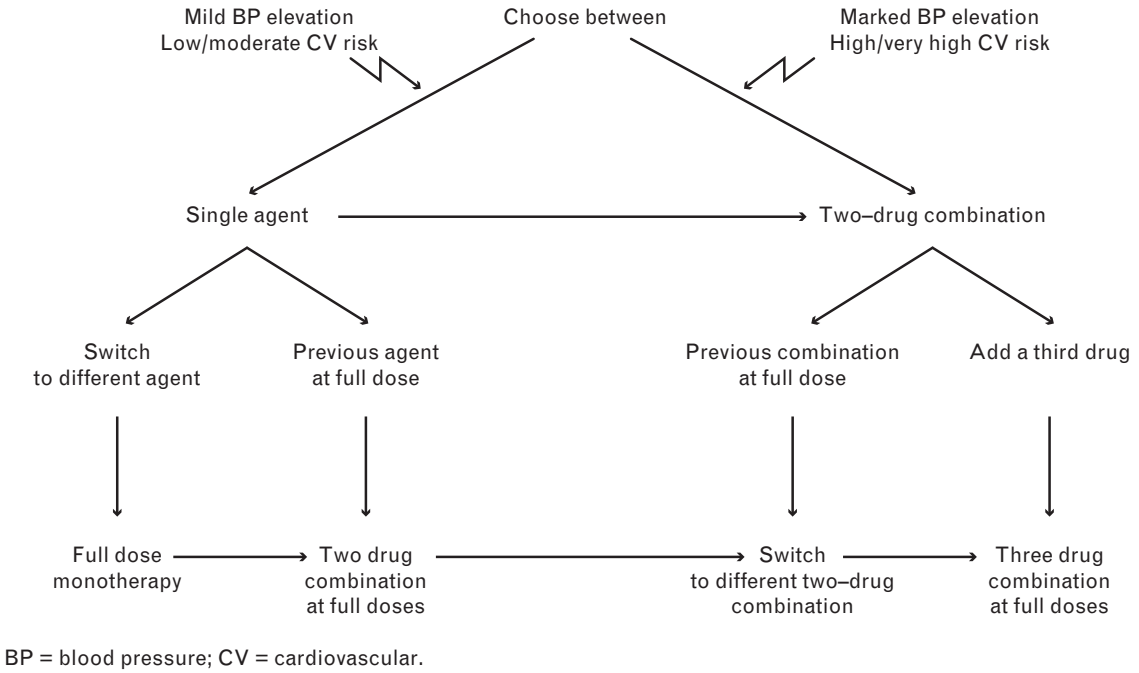

FIGURE 3 Monotherapy vs. drug combination strategies to achieve target BP. Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved.

adding drugs to drugs should be done with attention to results and any compound overtly ineffective or minimally effective should be replaced, rather than retained in an automatic step-up multiple-drug approach (Fig. 3).

5.2.2.2 Preferred drug combinations

Only indirect data are available from randomized trials giving information on drug combinations effective in reducing CV outcomes. Among the large number of RCTs of antihypertensive therapy, only three systematically used a given two-drug combination in at least one arm: the ADVANCE trial compared an ACE inhibitor and diuretic combination with placebo (but on top of continued background therapy) [276], FEVER compared a calcium antagonist and diuretic combination with diuretic alone (plus placebo) [269] and ACCOMPLISH compared the same ACE inhibitor in combination with either a diuretic or a calcium antagonist [414]. In all other trials, treatment was initiated by monotherapy in either arm and another drug (and sometimes more than one drug) was added in some patients. In some trials, the second drug was chosen by the investigator among those not used in the other treatment arms, as in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart ATtack (ALLHAT) [448].

With this important reservation, Table 16 shows that, with the exception of an angiotensin receptor blocker and a calcium antagonist (never systematically used in an outcome trial), all combinations were used in at least one active arm of placebo-controlled trials in which the active arm was associated with significant benefit [269,276,287,296,449–454]. In trials comparing different regimens, all combinations have been used in a larger or smaller proportion of patients, without major differences in benefits [186,445,448,455,456,458–461]. The only exceptions are two trials in which a large proportion of the patients received either an angiotensin receptor blocker-diuretic combination or a calcium antagonist-ACE inhibitor combination [423,457], both of which were superior to a beta-blocker-diuretic combination in reducing CV events. Admittedly, a beta-blocker-diuretic combination was as effective as other combinations in several other trials [448,455,460,461], and more effective than placebo in three trials [449,453,454]. However, the beta-blocker- diuretic combination appears to elicit more cases of new-onset diabetes in susceptible individuals, compared with other combinations [462].

The only trial directly comparing two combinations in all patients (ACCOMPLISH) [414] found significant superiority of an ACE inhibitor-calcium antagonist combination over the ACE inhibitor-diuretic combination despite there being no BP difference between the two arms. These unexpected results deserve to be repeated, because trials comparing a calcium antagonist-based therapy with a diuretic-based therapy have never shown superiority of the calcium antagonist. Nonetheless, the possibility that ACCOMPLISH results may be due to a more effective reduction of central BP by the association of an RAS blocker with a calcium antagonist deserves to be investigated [398,399,464].

The only combination that cannot be recommended on the basis of trial results is that between two different

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TABLE 16. Major drug combinations used in trials of antihypertensive treatment in a step-up approach or as a randomized combination

Trial	Comparator	Type of patients	SBP diff (mmHg)	Outcomes
ACE-I and diuretic combination				
PROGRESS[296]	Placebo	Previous stroke or TIA	–9	–28% strokes ($P < 0.001$)
ADVANCE[276]	Placebo	Diabetes	–5.6	–9% micro/macro vascular events ($P = 0.04$)
HYVET[287]	Placebo	Hypertensives aged ≥80 years	–15	–34% CV events ($P < 0.001$)
CAPPP[455]	BB + D	Hypertensives	+3	+5% CV events (P = NS)
Angiotensin receptor blocker and diuretic combination				
SCOPE[450]	D + placebo	Hypertensives aged ≥70 years	–3.2	–28% non fatal strokes ($P = 0.04$)
LIFE[457]	BB + D	Hypertensives with LVH	–1	–26% stroke ($P < 0.001$)
Calcium antagonist and diuretic combination				
FEVER[269]	D + placebo	Hypertensives	–4	–27% CV events ($P < 0.001$)
ELSA[186]	BB + D	Hypertensives	0	NS difference in CV events
CONVINCE[458]	BB + D	Hypertensives with risk factors	0	NS difference in CV events
VALUE[456]	ARB + D	High-risk hypertensives	–2.2	–3% CV events (P = NS)
ACE-I and calcium antagonist combination				
SystEur[451]	Placebo	Elderly with ISH	–10	–31% CV events ($P < 0.001$)
SystChina[452]	Placebo	Elderly with ISH	–9	–37% CV events ($P < 0.004$)
NORDIL[461]	BB + D	Hypertensives	+3	NS difference in CV events
INVEST[459]	BB + D	Hypertensives with CHD	0	NS difference in CV events
ASCOT[423]	BB + D	Hypertensives with risk factors	–3	–16% CV events ($P < 0.001$)
ACCOMPLISH[414]	ACE-I + D	Hypertensives with risk factors	–1	–21% CV events ($P < 0.001$)
BB and diuretic combination				
Coope & Warrender[453]	Placebo	Elderly hypertensives	–18	–42% strokes ($P < 0.03$)
SHEP[449]	Placebo	Elderly with ISH	–13	–36% strokes ($P < 0.001$)
STOP[454]	Placebo	Elderly hypertensives	–23	–40% CV events ($P = 0.003$)
STOP 2[460]	ACE-I or CA	Hypertensives	0	NS difference in CV events
CAPPP[455]	ACE-I + D	Hypertensives	–3	–5% CV events (P = NS)
LIFE[457]	ARB + D	Hypertensives with LVH	+1	+26% stroke ($P < 0.001$)
ALLHAT[448]	ACE-I + BB	Hypertensives with risk factors	–2	NS difference in CV events
ALLHAT[448]	CA + BB	Hypertensives with risk factors	–1	NS difference in CV events
CONVINCE[458]	CA + D	Hypertensives with risk factors	0	NS difference in CV events
NORDIL[461]	ACE-I + CA	Hypertensives	–3	NS difference in CV events
INVEST[459]	ACE-I + CA	Hypertensives with CHD	0	NS difference in CV events
ASCOT[423]	ACE-I + CA	Hypertensives with risk factors	+3	+16% CV events ($P < 0.001$)
Combination of two renin–angiotensin–system blockers /ACE-I + ARB or RAS blocker + renin inhibitor				
ONTARGET[463]	ACE-I or ARB	High-risk patients	–3	More renal events
ALTITUDE[433]	ACE-I or ARB	High-risk diabetics	–1.3	More renal events

ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CA, calcium antagonist; CHD, coronary heart disease; CV, cardiovascular; D, diuretic; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy; NS, not significant; RAS, renin angiotensin system; TIA, transient ischaemic attack.

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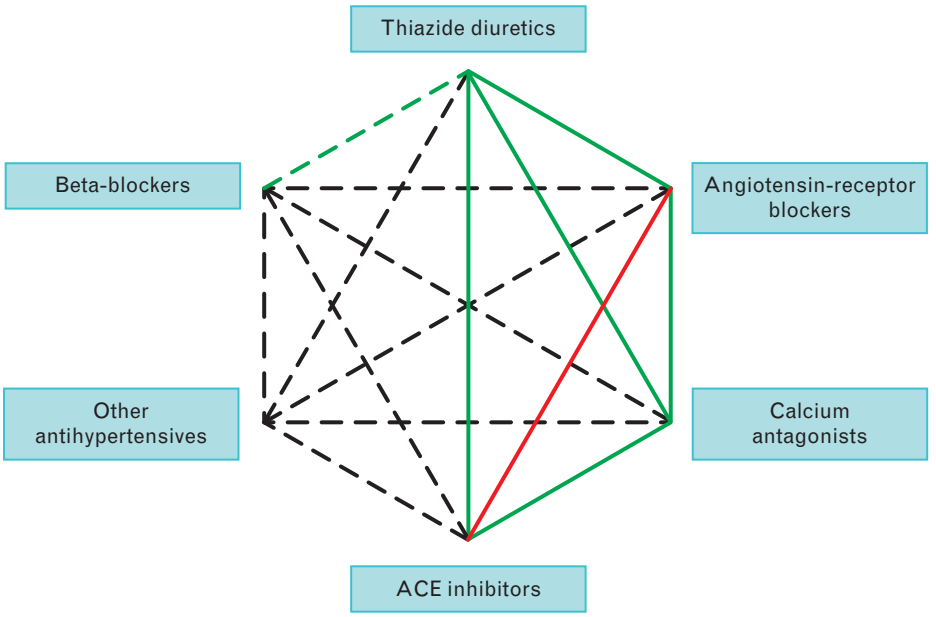

ACE = angiotensin-converting enzyme.

FIGURE 4 Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well tested combinations; red continuous line: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.

blockers of the RAS. Findings in ONTARGET [331,463], that the combination of an ACE inhibitor and an angiotensin receptor blocker are accompanied by a significant excess of cases of ESRD, have recently been supported by the results of the ALTITUDE trial in diabetic patients [433]. This trial was prematurely interrupted because of an excess of cases of ESRD and stroke in the arm in which the renin inhibitor aliskiren was added to preexisting treatment using an ACE inhibitor or an angiotensin receptor blocker. It should be noted, however, that BP was less closely monitored for hypotension in ALTITUDE. Two-drug combinations most widely used are indicated in the scheme shown in Fig. 4.

5.2.2.3 Fixed-dose or single-pill combinations

As in previous guidelines, the 2013 ESH/ESC Guidelines favour the use of combinations of two antihypertensive drugs at fixed doses in a single tablet, because reducing the number of pills to be taken daily improves adherence, which is unfortunately low in hypertension, and increases the rate of BP control [465,466]. This approach is now facilitated by the availability of different fixed-dose combinations of the same two drugs, which minimizes one of its inconveniences, namely the inability to increase the dose of one drug independently of the other. This holds also for fixed- dose combinations of three drugs (usually a blocker of the RAS, a calcium antagonist and a diuretic), which are increasingly becoming available. Availability extends to the so-called polypill (i.e. a fixed-dose combination of several antihypertensive drugs with a statin and a low-dose aspirin), with the rationale that hypertensive patients often present with dyslipidaemia and not infrequently have a high CV risk [12,13]. One study has shown that, when combined into the polypill, different agents maintain all or most their expected effects [467]. The treatment simplification associated with this approach may only be considered, however, if the need for each polypill component has been previously established [141].

5.2.3 Summary of recommendations on treatment strategies and choice of drugs

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Treatment strategies and choice of drugs

Recommendations	Class[a]	Level[b]	Ref.[c]
Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other.	I	A	284, 332
Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of OD.	IIa	C	-
Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk.	IIb	C	-
The combination of two antagonists of the RAS is not recommended and should be discouraged.	III	A	331, 433, 463
Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable.	IIa	C	-
Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.	IIb	B	465

ACE, angiotensin-converting enzyme; BP, blood pressure; CV, cardiovascular; OD, organ damage; RAS, renin-angiotensin system.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6. TREATMENT STRATEGIES IN SPECIAL CONDITIONS

6.1 White-coat hypertension

If the evidence favouring drug treatment in grade 1 hypertensives at low-to-moderate risk is scant (see Section 4.2.3), evidence is even weaker in white-coat hypertensives. In these individuals, no randomized trial has ever investigated whether administration of BP-lowering drugs leads to a reduction in CV morbid and fatal events. To date, information is largely limited to a subgroup analysis of the SYSTolic Hypertension in Europe (SYSTEUR) trial, which concluded that drug treatment reduces ambulatory BP and CV morbidity and mortality less in white-coat than in sustained hypertensive individuals, based on a small number of events [468].

The following considerations may help orientating the therapeutic decision in individual cases. Subjects with white-coat hypertension may frequently have dysmetabolic risk factors and some asymptomatic OD (see Section 3.1.3), the presence of which raises CV risk. In these higher-risk individuals with white-coat hypertension, drug treatment may be considered in addition to appropriate lifestyle changes. Both lifestyle changes and drug treatment may be considered also when normal ambulatory BP values are accompanied by abnormal home BP values (or vice versa) because this condition is also characterized by increased CV risk [105]. In the absence of additional CV risk factors, intervention may be limited to lifestyle changes only, but this decision should be accompanied by a close follow-up of the patients (including periodical out-of-office BP monitoring) because, in white-coat hypertensive subjects, out-of-office BP is often higher than in truly normotensive subjects and white-coat hypertensives have a greater risk of developing OD and to progress to diabetes and sustained hypertension (see Section 3.1.3). Consideration should also be given to the fact that, because of its high prevalence (particularly in mild-to-moderate hypertension), white-coat hypertension was presumably well represented in antihypertensive drug trials that have established clinic BP reduction as the guidance for treatment. Recommendations on treatment strategies in white-coat hypertension are listed below.

6.2 Masked hypertension

Isolated ambulatory or masked hypertension is infrequently diagnosed because finding a normal clinic BP only exceptionally leads to home or ambulatory BP measurements. When this condition is identified, however, both lifestyle measures and antihypertensive drug treatment should be considered because masked hypertension has consistently been found to have a CV risk very close to that of in-office and out-of-office hypertension [109,112, 117,469]. Both at the time of treatment decision and during follow-up, attention to dysmetabolic risk factors and OD should be considered since these conditions are much more common in masked hypertension than in normotensive individuals. Efficacy of antihypertensive treatment should be assessed by ambulatory and/or home BP measurements.

6.2.1 Summary of recommendations on treatment strategies in white-coat and masked hypertension

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Treatment strategies in white-coat and masked hypertension

Recommendations	Class[a]	Level[b]
In white-coat hypertensives without additional risk factors, therapeutic intervention should be considered to be limited to lifestyle changes only, but this decision should be accompanied by a close follow-up.	IIa	C
In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic OD, drug treatment may be considered in addition to lifestyle changes.	IIb	C
In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension.	IIa	C

CV, cardiovascular; OD, organ damage.
[a]Class of recommendation.
[b]Level of evidence.

6.3 Elderly

In previous sections (4.2.5 and 4.3.3) we mentioned that there is strong evidence of benefits from lowering of BP by antihypertensive treatment in the elderly, limited to individuals with initial SBP of >160 mmHg, whose SBP was reduced to values <150 but not <140 mmHg. Therefore the recommendation of lowering SBP to <150 mmHg in elderly individuals with SBP >160 mmHg is strongly evidence-based. However, at least in elderly individuals younger than 80 years, antihypertensive treatment may be considered at SBP values >140 mmHg and aimed at values <140 mmHg, if the individuals are fit and treatment is well tolerated.

Direct evidence of the effect of antihypertensive treatment in elderly hypertensives (older than 80 years) was still missing at the time the 2007 ESH/ESC Guidelines were prepared. The subsequent publication of the HYpertension in the Very Elderly Trial (HYVET) results [287], comparing active treatment (the diuretic indapamide supplemented, if necessary, by the ACE inhibitor perindopril) with placebo in octogenarians with entry SBP >160 mmHg, reported a significant reduction in major CV events and all-cause deaths by aiming at SBP values <150 mmHg (mean achieved SBP: 144 mmHg). HYVET deliberately recruited patients in good physical and mental conditions and excluded ill and frail individuals, who are so commonplace among octogenarians, and also excluded patients with clinically relevant orthostatic hypotension. The duration of follow-up was also rather short (mean: 1.5 years) because the trial was interrupted prematurely by the safety monitoring board.

RCTs that have shown beneficial effects of antihypertensive treatment in the elderly have used different classes of compounds and so there is evidence in favour of diuretics [287,449,454,470,471], beta-blockers [453,454], calcium antagonists [451,452,460], ACE inhibitors [460], and angiotensin receptor blockers [450]. The three trials on isolated systolic hypertension used a diuretic [449] or a calcium antagonist [451,452].

A prospective meta-analysis compared the benefits of different antihypertensive regimens in patients younger or older than 65 years and confirmed that there is no evidence that different classes are differently effective in the younger vs. the older patient [444].

6.3.1 Summary of recommendations on antihypertensive treatment strategies in the elderly

Antihypertensive treatment strategies in the elderly

Recommendations	Class[a]	Level[b]	Ref.[c]
In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.	I	A	141, 265
In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated.	IIb	C	-
In individuals older than 80 years with an initial SBP ≥160 mmHg it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.	I	B	287
In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment.	I	C	-
Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian.	IIa	C	-
All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension.	I	A	444, 449, 451, 452

SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.4 Young adults

In young adults with moderately high BP it is almost impossible to provide recommendations based directly on evidence from intervention trials, since outcomes are delayed by a period of years. The results of an important observational study on 1.2 million men in Sweden, initially investigated at a mean age of 18.4 years at the time of military conscription examination and followed-up for a median of 24 years, have recently been reported [472]. The relationship of SBP to total mortality was U-shaped with a

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nadir at approximately 130 mmHg, but the relationship with CV mortality increased monotonically (the higher the BP the higher the risk). In these young men (without stiff, diseased arteries) the relationship of DBP to total and CV mortality was even stronger than that of SBP, with an apparent threshold around 90 mmHg. Approximately 20% of the total mortality in these young men could be explained by their DBP. Young hypertensives may sometimes present with an isolated elevation of DBP. Despite absence of RCT evidence on the benefits of antihypertensive treatment in these young individuals, their treatment with drugs may be considered prudent and, especially when other risk factors are present, BP should be reduced to <140/90 mmHg. The case may be different for young individuals in whom brachial SBP is elevated with normal DBP values (<90 mmHg). As discussed in sections 3.1.6 and 4.2.4 these individuals sometimes have a normal central SBP, and can be followed with lifestyle measures only.

6.5 Women

The representation of women in RCTs in hypertension is 44% [473], but only 24% of all CV trials report sex-specific results [474–475]. A subgroup analysis by sex of 31 RCTs including individuals found similar BP reductions for men and women and no evidence that the two genders obtain different levels of protection from lowering of BP, or that regimens based on ACE inhibitors, calcium antagonists, angiotensin receptor blockers or diuretics/beta-blockers were more effective in one sex than the other [445].

In women with child-bearing potential, ACE inhibitors and angiotensin receptor blockers should be avoided, due to possible teratogenic effects. This is the case also for aliskiren, a direct renin inhibitor, although there has not been a single case report of exposure to aliskiren in pregnancy.

6.5.1 Oral contraceptives

Use of oral contraceptives (OCs) is associated with some small but significant increases in BP and with the development of hypertension in about 5% of users [476,477]. Notably, these studies evaluated older-generation OCs, with relatively higher oestrogen doses compared with those currently used (containing <50 mg oestrogen, ranging most often from 20–35 mg of ethinyl estradiol and a low dose of second- or third-generation progestins). The risk of developing hypertension decreased quickly with cessation of OCs and past users appeared to have only a slightly increased risk [2]. Similar results were later shown by the Prevention of REnal and Vascular ENdstage Disease (PREVEND) study in which second- and third- generation OCs were evaluated separately [478]: in this study, after an initial increase, urinary albumin excretion fell once OC therapy had been stopped. Drospirenone (3 mg), a newer progestin with an antimineralocorticoid diuretic effect, combined with ethinyl estradiol at various doses, lowered SBP by 1–4 mmHg across the groups [479]. Unfortunately, there is growing evidence that drospirenone is associated with a greater risk of venous thrombo-embolism than levonorgestrel (a second-generation synthetic progestogen) [480].

The association between combined OCs and the risk of myocardial infarction has been intensively studied and the conclusions are controversial. Earlier prospective studies consistently showed an increased risk of acute myocardial infarction among women who use OCs and particularly in OC users who smoke, and extended this observation to past smokers on OCs [481]. Two case-control studies using the second- and third-generation OCs exist, but with conflicting results [482,483]. A large-scale, Swedish, population-based, prospective study, in which most of the current OC users were taking low-dose oestrogen and second- or third-generation progestins, did not find use of OCs to be associated with an increased risk of myocardial infarction [484]. Data from observational studies with progestogen-only OCs suggest no increase in risk of myocardial infarction [485].

Three separate meta-analyses summarizing over 30 years of studies have shown that OC users have about a two-fold increased risk of stroke over nonusers [486–488]. In an Israeli population-based cohort study, drospirenone-containing OCs were not associated with an increased risk of TIAs and stroke [489].

There are no outcome data on the newest non-oral formulations of hormone contraception (injectable, topical, vaginal routes). However, transdermal patches and vaginal rings have been found to be associated with an increased risk of venous thrombosis, compared with age-matched controls [490].

Although the incidence of myocardial infarction and ischaemic stroke is low in the age group of OC users, the risk of OCs is small in absolute terms but has an important effect on women's health, since 30–45% of women of reproductive age use OCs. Current recommendations indicate that OCs should be selected and initiated by weighing risks and benefits for the individual patient [491]. BP should be evaluated using properly taken measurements and a single BP reading is not sufficient to diagnose hypertension [492]. Women aged 35 years and older should be assessed for CV risk factors, including hypertension. It is not recommended that OCs be used in women with uncontrolled hypertension. Discontinuation of combined OCs in women with hypertension may improve their BP control [493]. In women who smoke and are over the age of 35 years, OCs should be prescribed with caution [494].

6.5.2 Hormone replacement therapy

Hormone replacement therapy (HRT) and selective oestrogen receptor modulators should not be used for primary or secondary prevention of CVD [495]. If occasionally treating younger, perimenopausal women for severe menopausal symptoms, the benefits should be weighed against potential risks of HRT [490,496]. The probability is low that BP will increase with HRT in menopausal hypertensive women [497].

6.5.3 Pregnancy

Hypertensive disorders in pregnancy have been reviewed recently by the ESC Guidelines on the management of CVD during pregnancy [498], and by other organizations [499]. In the absence of RCTs, recommendations can only be guided by expert opinion. While there is consensus that drug treatment of severe hypertension in pregnancy (>160 for

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SBP or >110 mmHgfor DBP) is required and beneficial, the benefits of antihypertensive therapy are uncertain for mildly to moderately elevated BP in pregnancy (<160/110 mmHg), either preexisting or pregnancy-induced, except for a lower risk of developing severe hypertension [500]. International and national guidelines vary with respect to thresholds for starting treatment and BP targets in pregnancy. The suggestion, in the 2007 ESH/ESC Guidelines [2], of considering drug treatment in all pregnant women with persistent elevation of BP >150/95 mmHg is supported by recent US data, which show an increasing trend in the rate of pregnancy-related hospitalizations with stroke—especially during the postpartum period—from 1994 to 2007 [501], and by an analysis of stroke victims with severe preeclampsia and eclampsia [502]. Despite lack of evidence, the 2013 Task Force reconfirms that physicians should consider early initiation of antihypertensive treatment at values >140/90 mmHg in women with (i) gestational hypertension (with or without proteinuria), (ii) preexisting hypertension with the superimposition of gestational hypertension or (iii) hypertension with asymptomatic OD or symptoms at any time during pregnancy.

No additional information has been provided, after publication of the previous Guidelines [2], on the antihypertensive drugs to be used in pregnant hypertensive women: therefore the recommendations to use methyldopa, labetalol and nifedipine as the only calcium antagonist really tested in pregnancy can be confirmed. Beta-blockers (possibly causing foetal growth retardation if given in early pregnancy) and diuretics (in preexisting reduction of plasma volume) should be used with caution. As mentioned above, all agents interfering with the renin-angiotensin system (ACE inhibitors, ARBs, renin inhibitors) should absolutely be avoided. In emergency (preeclampsia), intravenous labetalol is the drug of choice with sodium nitroprusside or nitroglycerin in intravenous infusion being the other option.

There is a considerable controversy regarding the efficacy of low-dose aspirin for the prevention of preeclampsia. Despite a large meta-analysis reporting a small benefit of aspirin in preventing preeclampsia [503], two other very recent analyses came to opposing conclusions. Rossi and Mullin used pooled data from approximately 5000 women at high risk and 5000 at low risk for preeclampsia and reported no effect of low-dose aspirin in the prevention of the disease [504]. Bujold *et al*. [505], however, pooled data from over 11 000 women enrolled in RTCs of low-dose aspirin in pregnant women and concluded that women who initiated treatment at <16 weeks of gestation had a significant and marked reduction of the relative risk for developing preeclampsia (relative risk: 0.47) and severe preeclampsia (relative risk: 0.09) compared with control [505]. Faced with these discrepant data, only prudent advice can be offered: women at high risk of preeclampsia (from hypertension in a previous pregnancy, CKD, autoimmune disease such as systemic lupus erythematosus, or antiphospholipid syndrome, type 1 or 2 diabetes or chronic hypertension) or with more than one moderate risk factor for preeclampsia (first pregnancy, age >40 years, pregnancy interval of >10 years, BMI >35 kg/m^2 at first visit, family history of preeclampsia and multiple pregnancy), may be advised to take 75 mg of aspirin daily from 12 weeks until the birth of the baby, provided that they are at low risk of gastrointestinal haemorrhage.

6.5.4 Long-term cardiovascular consequences in gestational hypertension

Because of its CV and metabolic stress, pregnancy provides a unique opportunity to estimate a woman's lifetime risk; preeclampsia may be an early indicator of CVD risk. A recent large meta-analysis found that women with a history of preeclampsia have approximately double the risk of subsequent ischaemic heart disease, stroke and venous thrombo-embolic events over the 5–15 years after pregnancy [506]. The risk of developing hypertension is almost four-fold [507]. Women with early-onset preeclampsia (delivery before 32 weeks of gestation), with stillbirth or foetal growth retardation are considered at highest risk. Risk factors before pregnancy for the development of hypertensive disorders are high maternal age, elevated BP, dyslipidaemia, obesity, positive family history of CVD, antiphospholipid syndrome and glucose intolerance. Hypertensive disorders have been recognized as an important risk factor for CVD in women [495]. Therefore lifestyle modifications and regular check-ups of BP and metabolic factors are recommended after delivery, to reduce future CVD.

6.5.5 Summary of recommendations on treatment strategies in hypertensive women

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Treatment strategies in hypertensive women

Recommendations	Class[a]	Level[b]	Ref.[c]
Hormone therapy and selective oestrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks.	III	A	495, 496
Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended.	I	C	-
Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical OD or symptoms.	IIb	C	-
In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal haemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered.	IIb	B	503, 504, 505
In women with child-bearing potential RAS blockers are not recommended and should be avoided.	III	C	-
Methyldopa, labetolol and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetolol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia).	IIa	B	498

BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; OD, organ damage; RAS, renin–angiotensin system; SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.6 Diabetes mellitus

High BP is a common feature of both type 1 and type 2 diabetes and masked hypertension is not infrequent [121], so that monitoring 24-h ambulatory BP in apparently normotensive patients with diabetes may be a useful diagnostic procedure. Previous sections (4.2.6 and 4.3.4) have mentioned that there is no clear evidence of benefits in general from initiating antihypertensive drug treatment at SBP levels <140 mmHg (high normal BP), nor there is evidence of benefits from aiming at targets <130 mmHg. This is due to the lack of suitable studies correctly investigating these issues. Whether the presence of microvascular disease (renal, ocular, or neural) in diabetes requires treatment initiation and targets of lower BP values is also unclear. Microalbuminuria is delayed or reduced by treatment but trials in diabetic populations, including normotensives and hypertensives, have been unable to demonstrate consistently that proteinuria reduction is also accompanied by a reduction in hard CV outcomes (see also Section 6.9) [274,276,329]. No effect of antihypertensive therapy on diabetic retinopathy has been reported in normotensive and hypertensive patients in the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial [508], and in the normotensive type-1 diabetics of the DIabetic REtinopathy Candesartan Trials (DIRECT) [509]. Finally, antihypertensive drugs do not appear to substantially affect neuropathy [510]. Therefore, evidence-based recommendations are to initiate antihypertensive drug treatment in all patients with diabetes whose mean SBP is >160 mmHg. Treatment is also strongly recommended in diabetic patients when SBP is >140 mmHg, with the aim to lower it consistently to <140 mmHg. As mentioned in section 4.3.4.1, DBP target between 80–85 mmHg is supported by the results of the HOT and United Kingdom Prospective Diabetes Study (UKPDS) studies [290,293]. How far below 140 mmHg the SBP target should be in patients with diabetes is not clear, since the only two large trials showing CV outcome reduction in diabetes by SBP reduction to <140 mmHg actually reduced SBP to an average of 139 mmHg [270,275]. Comparison of CV event reductions in various trials indicates that, for similar SBP differences, the benefit of more intensive lowering of SBP becomes gradually smaller when the SBP differences are in the lower part of the 139–130 mmHg range [314]. Supportive evidence against lowering SBP <130 mmHg comes from the ACCORD trial [295], a post-hoc analysis of RCTs and a nationwide register-based observational study in Sweden, which suggest that benefits do not increase below 130 mmHg [326,511,512]. The case of the diabetic patient with increased urinary protein excretion is discussed in Section 6.9.

The choice of antihypertensive drugs should be based on efficacy and tolerability. All classes of antihypertensive agents are useful, according to a meta-analysis [394], but the individual choice should take co-morbidities into account to tailor therapy. Because BP control is more difficult in diabetes [324], most of the patients in all studies received combination therapy and combination therapy should most often be considered when treating diabetic hypertensives. Because of a greater effect of RAS blockers on urinary protein excretion (see Section 6.9) [513], it appears reasonable to have either an ACE inhibitor or an ARB in the combination. However, the simultaneous administration of two RAS blockers (including the renin inhibitor, aliskiren) should be avoided in high-risk patients because of the increased risk reported in ALTITUDE and ONTARGET [433,463]. Thiazide and thiazide-like diuretics are useful and are often used together with RAS blockers. Calcium antagonists have been shown to be useful, especially when combined with an RAS blocker. Beta-blockers, though potentially impairing insulin sensitivity, are useful for BP control in combination therapy, especially in patients with CHD and heart failure.

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6.6.1 Summary of recommendations on treatment strategies in patients with diabetes

Treatment strategies in patients with diabetes

Recommendations	Class[a]	Level[b]	Ref.[c]
While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg.	I	A	275, 276 290–293
A SBP goal <140 mmHg is recommended in patients with diabetes.	I	A	270,275, 276,295
The DBP target in patients with diabetes is recommended to be <85 mmHg.	I	A	290, 293
All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria.	I	A	394, 513
It is recommended that individual drug choice takes comorbidities into account.	I	C	-
Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.	III	B	433

DBP, diastolic blood pressure; RAS, renin–angiotensin system; SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.7 Metabolic syndrome

The metabolic syndrome is variably defined, especially because of different definitions of central obesity, although a so-called harmonized definition was presented in 2009 [514]. Whether the metabolic syndrome is a useful clinical concept is currently disputed, largely because it has been hard to prove that it adds anything to the predictive power of individual factors [515,516]. High normal BP and hypertension constitute a frequent possible component of the metabolic syndrome [517], although the syndrome can also be diagnosed in the absence of a raised BP. This is consistent with the finding that hypertension, high normal BP and white-coat hypertension are often associated with increased waist circumference and insulin resistance. Coexistence of hypertension with metabolic disturbances increases global risk and the recommendation (Section 4.2.3) to prescribe antihypertensive drugs (after a suitable period of lifestyle changes) to individuals with a BP >140/90 mmHg should be implemented with particular care in hypertensive patients with metabolic disturbances. No evidence is available that BP-lowering drugs have a beneficial effect on CV outcomes in metabolic syndrome individuals with high normal BP [277,278]. As the metabolic syndrome can often be considered as a 'prediabetic' state, agents such as RAS blockers and calcium antagonists are preferred, since they potentially improve—or at least do not worsen—insulin sensitivity, while beta-blockers (with the exception of vasodilating beta-blockers) [407–409] and diuretics should only be considered as additional drugs, preferably at low doses. If diuretics are used, the association with a potassium-sparing agent should be considered [409], as there is evidence that hypokalaemia worsens glucose intolerance [518]. Lifestyle changes, particularly weight loss and increased physical exercise, are recommended to all individuals with the metabolic syndrome. This will improve not only BP but also the metabolic components of the pattern and delay the onset of diabetes [369,519,520].

6.7.1 Summary of recommendations on treatment strategies in hypertensive patients with metabolic syndrome

Treatment strategies in hypertensive patients with metabolic syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset.	I	B	**369, 519, 520**
As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating beta-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent.	IIa	C	-
It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg.	I	B	**141**
BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP.	III	A	**277, 278**

BP, blood pressure; RAS, renin–angiotensin system.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.8 Obstructive sleep apnoea

This topic has recently been the subject of a consensus document from the ESH and the European Respiratory Society [521]. The association between obstructive sleep

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apnoea and hypertension is well documented, particularly when nocturnal hypertension is concerned. Obstructive sleep apnoea appears to be responsible for a large proportion of cases of BP increase or absence of BP reduction at night-time. Although a few prospective studies have linked severe obstructive sleep apnoea to fatal and nonfatal CV events and all-cause mortality, this association appears to be closer for stroke than CHD and to be weak with obstructive sleep apnoea of mild-to-moderate severity [521]. Whether monitoring CV and respiratory variables during night sleep should be employed systematically in individuals with resistant hypertension is open to question and no cost-effectiveness analysis has been carried out. At present, these complex methods should be preceded by ABPM showing BP abnormalities during the night or by overnight oximetry. Because of the relationship between obesity and obstructive sleep apnoea, weight loss and exercise are commonly recommended, but unfortunately no large-scale controlled trials are available [521]. Continuous, positive airway pressure therapy is a successful procedure for reducing obstructive sleep apnoea; however, on the basis of four available meta-analyses, the effect of prolonged, continuous, positive airway pressure therapy on ambulatory BP is very small (1–2 mmHg reduction) [522–525]. This may be due to poor adherence to this complex procedure or a limited follow-up period but a recent study with a follow-up longer than 3 years has found no difference in BP or in drug usage between sleep apnoea patients who continued, or those who quitted positive air pressure therapy [526]. However, two recent prospective studies have reported that (i) normotensive subjects with obstructive sleep apnoea were characterized over a 12-year follow-up by a significant increase in the risk of developing hypertension [527], and (ii) the risk of new-onset hypertension was lower in subjects treated with continuous positive air pressure [528], although the benefit seemed restricted to those with daytime sleepiness [527].

In conclusion, despite the potential health impact of obstructive sleep apnoea, well designed therapeutic studies are too few. The two more urgent issues to be investigated are whether obstructive sleep apnoea really increases the CV risk of hypertension and whether long-term therapeutic correction of obstructive sleep apnoea leads to a reduction in BP and CV events [529].

6.9 Diabetic and non-diabetic nephropathy

In observational studies, the relationship between BP and progression of CKD and incident ESRD is direct and progressive [530]. Also, in the Japanese male population in general, high normal BP was associated with increased prevalence of CKD [531]. Likewise, in a meta-analysis of intervention trials in patients with non-diabetic nephropathy, the progression of CKD correlated with achieved BP, with the slowest progression observed in patients with treated SBP in the range 110–119 mmHg [532]. Unfortunately (see Section 4.3.4.3), these observational data are not supported by the results of three trials in which CKD patients were randomized to a lower (<125–130 mmHg) or higher (<140 mmHg) BP target [304–306]: no difference in renal failure or death was found between the two arms, except in the observational follow-up of two of these trials, in which the groups initially randomized to the lower BP had fewer cases of ESRD or death, provided that proteinuria was present [307,308,313]. In patients with diabetic or non-diabetic renal disease, SBP should be lowered to <140 mmHg and when overt proteinuria is present values <130 mmHg may be pursued, provided that changes in eGFR are monitored.

In patients with ESRD under dialysis, a recent meta-analysis showed a reduction in CV events, CV death and all-cause mortality by lowering of SBP and DBP [533]. However, no information on the absolute BP values achieved was provided and reduction of mortality was seen in patients with heart failure only. Hence a recommendation on a precise BP target cannot be provided.

Reduction of proteinuria (both microalbuminuria and overt proteinuria) is widely considered as a therapeutic target, since observational analyses of data from RCTs have reported that changes in urinary protein excretion are predictors of adverse renal and CV events [534–536]. Once again, solid evidence is lacking from trials comparing CV or renal outcomes in groups randomized to more or less aggressive reductions of proteinuria. Several RCTs have clearly indicated that RAS blockade is more effective in reducing albuminuria than either placebo or other antihypertensive agents in diabetic nephropathy, non-diabetic nephropathy and patients with CVD [513,537], and is also effective in preventing incident microalbuminuria [329,538]. None of these trials had sufficient statistical power to evaluate effects on CV outcomes.

Achieving BP targets usually requires combination therapy and RAS blockers should be combined with other antihypertensive agents. A sub-analysis of the ACCOMPLISH trial has reported that the association of an ACE inhibitor with a calcium antagonist, rather than a thiazide diuretic, is more effective in preventing doubling serum creatinine and ESRD, though less effective in preventing proteinuria [539]. As reported in Section 6.6, combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not generally recommended [433,463]. Mineralocorticoid receptor antagonists cannot be recommended in CKD, especially in combination with an RAS blocker, because of the risk of excessive reduction in renal function and hyperkalemia [540]. Loop diuretics should replace thiazides if serum creatinine is 1.5 mg/dL or eGFR is <30 ml/min/1.73 m^2.

6.9.1 Summary of recommendations on therapeutic strategies in hypertensive patients with nephropathy

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Therapeutic strategies in hypertensive patients with nephropathy

Recommendations	Class[a]	Level[b]	Ref.[c]
Lowering SBP to <140 mmHg should be considered.	IIa	B	303, 313
When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored.	IIb	B	307, 308, 313
RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria.	I	A	513, 537
Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents.	I	A	446
Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended.	III	A	331, 433, 463
Aldosterone antagonists cannot be recommended in CKD, especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalaemia.	III	C	-

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system; SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.9.2 Chronic kidney disease stage 5D

Hypertension is a ubiquitous finding in haemodialysis patients and has major implications for survival. Detailed recommendations on how to manage high BP in patients on haemodialysis are available in guidelines issued by nephrological scientific societies and only few general considerations will be made here. Firstly, accurate measurement of BP is essential for the management of haemodialysis patients. However, a pre-haemodialysis BP may not reflect the average BP experienced by the patient. Thus, the question of how and where the measurements should be made is of particular importance, with clear evidence for the superiority of self-measured BP at home over pre-haemodialysis BP values. Secondly, the BP to be pursued by treatment in patients on haemodialysis has not been clearly established in this context. A distinct difficulty is that large alterations in sodium and water balance make BP particularly variable and that the extent of BP reductions may depend on the presence of complications such as cardiomyopathy rather that drug-induced BP control. Thirdly, all antihypertensive drugs except diuretics can be used in the haemodialysis patients, with doses determined by the haemodynamic instability and the ability of the drug to be dialysed. Drugs interfering with homeostatic adjustments to volume depletion (already severely impaired in renal insufficiency) should be avoided to minimize hypotension during the fast and intensive reduction of blood volume associated with the dialytic manoeuvres.

RCTs are rare in haemodialysis and should be encouraged. Longer or more frequent dialysis may solve the haemodynamic problems associated with salt restriction and short dialysis time [541].

6.10 Cerebrovascular disease

6.10.1 Acute stroke

BP management during the acute phase of stroke is a matter of continuing concern. The results of a small trial called Controlling Hypertension and Hypertension Immediately Post-Stroke (CHHIPS) suggested a beneficial impact in administering lisinopril or atenolol in patients with acute stroke and a SBP >160 mmHg [542]. The same was the case for the Acute Candesartan Cilexetil Therapy in Stroke Survival (ACCESS) study [543], which suggested benefits of candesartan given for 7 days after acute stroke. This latter hypothesis was properly tested in the Angiotensin-Receptor Blocker Candesartan for Treatment of Acute STroke (SCAST) trial involving more than 2000 acute stroke patients [544]. SCAST was neutral for functional outcomes and CV endpoints, including recurrent stroke, and could not identify any subgroup with significant benefit. A recent review gives a useful update of this difficult area [545].

6.10.2 Previous stroke or transient ischaemic attack

Sections 4.2.6 and 4.3.4.2 have mentioned data from three major placebo-controlled RCTs of antihypertensive treatment in patients with a recent (but not acute) stroke or TIA [279,296,297], which provide somewhat conflicting evidence. No evidence is yet available that recurrent stroke is prevented by initiating therapy when BP is in the high normal range, nor is there evidence for reducing SBP to <130 mmHg.

As prevention of stroke is the most consistent benefit of antihypertensive therapy and has been observed in almost all large RCTs using different drug regimens, all regimens are acceptable for stroke prevention provided that BP is effectively reduced [546]. Meta-analyses and meta-regression analyses suggest that calcium antagonists may have a slightly greater effectiveness on stroke prevention [284,395,421], but the two successful trials in secondary stroke prevention used a diuretic or a diuretic in combination with an ACE inhibitor [279,296]. Greater cerebrovascular protective effects have also been reported for ARBs vs. a variety of other drugs in single trials and meta-analyses [547,548].

6.10.3 Cognitive dysfunction and white matter lesions

The importance of hypertension in predicting vascular dementia has been confirmed in a recent, carefully conducted observational study in Japan [549], but evidence on the effects of lowering of BP is scanty and confusing. Little information was added by a cognition sub-study of HYVET in hypertensive octogenarians because of the inadequate

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duration of follow-up and an accompanying meta-analysis showed very limited benefit [550]. Trials are urgently needed on preventing cognitive dysfunction and on delaying dementia when cognitive dysfunction has begun. Although white matter lesions (hyperintensities at MRI) are known to be associated with increased risk of stroke, cognitive decline and dementia (see Section 3.7.5), almost no information is available as to whether antihypertensive treatment can modify their evolution. A small sub-study of PROGRESS and a recent prospectively observational study suggest that preventing white matter hyperintensities by lowering BP is possible [551,552], but this suggestion requires verification in a large RCT.

6.10.4 Summary of recommendations on therapeutic strategies in hypertensive patients with cerebrovascular disease

Therapeutic strategies in hypertensive patients with cerebrovascular disease

Recommendations	Class[a]	Level[b]	Ref.[c]
It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values.	III	B	544, 545
Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or TIA, even when initial SBP is in the 140–159 mmHg range.	I	B	280, 296
In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered.	IIa	B	280, 296, 297
In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher.	IIb	B	141, 265
All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced.	I	A	284

BP, blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.11 Heart disease

6.11.1 Coronary heart disease

Several risk factors contribute to CHD, but the level of BP over a large and continuous range is one of the important factors, with a steeper association above a SBP of about 140 mmHg. The Effect of Potentially Modifiable Risk Factors associated with Myocardial Infarction in 52 Countries (INTERHEART) study showed that about 50% of the population-attributable risk of a myocardial infarction can be accounted for by lipids, with hypertension accounting for about 25% [553]. Several risk factors for CHD, and particularly SBP and DBP, are strongly related to BMI [554], a finding emphasizing the urgency of halting the present inexorable rise of obesity in the general population.

Sections 4.2.6 and 4.3.4.2 mentioned that RCTs of antihypertensive treatment do not provide consistent evidence that SBP target should be <130 mmHg in hypertensive patients with overt CHD, nor is there consistent evidence that antihypertensive treatment should be initiated with high normal BP. On the contrary, a number of the correlative analyses raising suspicion about the existence of a J-curve relationship between achieved BP and CV outcomes included a high proportion of CHD patients [317,318,322,323], and it is not unreasonable that, if a J-curve occurs, it may occur particularly in patients with obstructive coronary disease. The recommendation to lower SBP to <140 mmHg is indirectly strengthened by a post-hoc analysis of the INternational VErapamil SR/T Trandolapril (INVEST) study (examining all patients with CHD) showing that outcome incidence is inversely related to consistent SBP control (i.e. <140 mmHg) throughout follow-up visits [436].

As to which drugs are better in hypertensive patients, there is evidence for greater benefits from beta-blockers after a recent myocardial infarction [284], a condition in which ACE inhibitors have also been successfully tested [555,556]. Later on, all antihypertensive agents can be used [284]. Beta-blockers and calcium antagonists are to be preferred, at least for symptomatic reasons, in cases of angina.

6.11.2 Heart failure

Hypertension is the leading attributable risk factor for developing heart failure, which is today a hypertension-related complication almost as common as stroke [557]. Preventing heart failure is the largest benefit associated with BP-lowering drugs [395], including in the very elderly [287]. This has been observed using diuretics, beta-blockers, ACE inhibitors and ARBs, with calcium antagonists apparently being less effective in comparative trials, at least in those trials in which they replaced diuretics [395]. In ALLHAT [448] an ACE inhibitor was found to be less effective than a diuretic, but the study design implied initial diuretic withdrawal and the small excess of early heart failure episodes may have resulted from this withdrawal. In the Prevention Regimen for Effectively Avoiding Secondary Strokes (PROFESS) and Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) trials [297,558], an ARB did not reduce hospitalizations for heart failure below those occurring on placebo (in which treatment consisted of non-RAS-blocking agents) and in ONTARGET [463]. an ARB appeared (non-significantly) less effective than an ACE inhibitor.

Whilst a history of hypertension is common in patients with heart failure, a raised BP can disappear when heart failure with LV systolic dysfunction develops. No RCT has been carried out in these patients with the specific intent of testing the effects of reducing BP (in most trials of antihypertensive therapy heart failure patients have usually been excluded). In these patients evidence in favour of the administration of beta-blockers, ACE inhibitors, ARBs

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and mineralocorticoid receptor antagonists has been obtained from trials, in which these agents were aimed at correcting cardiac overstimulation by the sympathetic system and the RAS, rather than at lowering of BP (and indeed in a number of these trials BP changes were not reported) [411]. In a meta-analysis of 10 prospective observational studies of heart failure patients, a higher SBP was found to be associated with better outcomes [559].

Hypertension is more common in heart failure patients with preserved LV ejection fraction. However, in outcome trials specifically including these patients, few had uncontrolled hypertension, probably because they received a large background therapy of BP-lowering agents. In one of these trials, Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) [560], the angiotensin receptor blocker irbesartan failed to lessen CV events compared with placebo. However, randomized therapy was added to optimize existing antihypertensive therapy (including 25% of ACE inhibitors) and initial BP was only 136/76 mmHg, thus further strengthening the question as to whether lowering SBP much below 140 mmHg is of any further benefit.

6.11.3 Atrial fibrillation

Hypertension is the most prevalent concomitant condition in patients with atrial fibrillation, in both Europe and the USA [561]. Even high normal BP is associated with the development of atrial fibrillation [562], and hypertension is likely to be a reversible causative factor [154]. The relationships of hypertension and antihypertensive therapy to atrial fibrillation have recently been discussed by a position paper of an ESH working group [563].

Hypertensive patients with atrial fibrillation should be assessed for the risk of thromboembolism by the score mentioned in the recent ESC Guidelines [561] and, unless contra-indications exist, the majority of them should receive oral anticoagulation therapy to prevent stroke and other embolic events [564,565]. Current therapy is based on vitamin K antagonists but newer drugs, either direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban,apixaban) have been shown to be non-inferior and sometimes superior to warfarin [561,563]. They are promising newcomers in this therapeutic field, although their value outside clinical trials remains to be demonstrated. In patients receiving anticoagulant therapy, good control of BP has the added advantage of reducing bleeding events [566].

Most patients show a high ventricular rate when in atrial fibrillation [565]. Beta-blockers and non-dihydropyridine calcium antagonists are hence recommended as antihypertensive agents in patients with atrial fibrillation and high ventricular rate.

The consequences of atrial fibrillation include increased overall mortality, stroke, heart failure and hospitalizations; therefore prevention or retardation of new atrial fibrillation is desirable [154]. Secondary analyses of trials in patients with LVH and hypertension have found that ARBs (losartan, valsartan) are better in preventing first occurrence of atrial fibrillation than beta-blocker (atenolol) or calcium antagonist (amlodipine) therapy, consistent with similar analyses in patients with heart failure [567–571]. This finding has not been confirmed in some more-recent trials in high-risk patients with established atherosclerotic disease, such as PRoFESS and TRANSCEND [297,558]; and irbesartan did not improve survival in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE I) trial in patients with established atrial fibrillation [572]. ARBs have not prevented recurrences of paroxysmal or persistent atrial fibrillation [CAndesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) [573], Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) [574], and ANgioTensin II Antagonist In Paroxysmal Atrial Fibrillation (ANTIPAF) [575] trials]. Given the heterogeneity of the available data, it has been suggested that the beneficial effects of ARBs may be limited to the prevention of incident atrial fibrillation in hypertensive patients with structural heart disease, such as LV hypertrophy or dysfunction or high risk in general, but no history of atrial fibrillation [568,576]. In patients with heart failure, beta-blockers and mineralocorticoid antagonists may also prevent atrial fibrillation [577,578]. The suggestion is indirectly supported by the results of a general practice database in the UK, with approximately 5 million patient records, reporting that ACE inhibitors and ARBs were associated with a lower risk of atrial fibrillation, compared with calcium antagonists [579]. This has been shown also for beta-blockers in heart failure. Hence, these agents may be considered as the preferred antihypertensive agents in hypertensive patients with cardiac OD, to prevent incident atrial fibrillation.

6.11.4 Left ventricular hypertrophy

The 2009 ESH re-appraisal document summarized the evidence on why LVH, especially of the concentric type, is associated with a CVD risk higher than 20% in 10 years (i.e. high CV risk) [141]. A number of smaller studies, but in particular the LIFE study [330], reported that LVH reduction is closely related to BP reduction. For similar BP reductions, ARBs, ACE inhibitors and calcium antagonists have been found, in randomized comparative studies, to be more effective than beta-blockers [580]. In the LIFE study, which selected only hypertensive patients with LVH, the therapeutically induced reduction of LV mass was significantly associated with CV event reduction [261]. This topic is further discussed in Section 8.4.

6.11.5 Summary of recommendations on therapeutic strategies in hypertensive patients with heart disease

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Therapeutic strategies in hypertensive patients with heart disease

Recommendations	Class[a]	Level[b]	Ref.[c]
In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered.	IIa	B	141, 265
In hypertensive patients with a recent myocardial infarction beta-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but beta-blockers and calcium antagonists are to be preferred, for symptomatic reasons (angina).	I	A	284
Diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe LV dysfunction to reduce mortality and hospitalization.	I	A	411
In patients with heart failure and preserved EF, there is no evidence that antihypertensive therapy per se or any particular drug, is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with beta-blockers, etc.) should also be considered.	IIa	C	-
ACE inhibitors and angiotensin receptor blockers (and beta-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation.	IIa	C	-
It is recommended that all patients with LVH receive antihypertensive agents.	I	B	458
In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers and calcium antagonists.	IIa	B	580

ACE, angiotensin-converting enzyme; CHD, coronary heart disease; EF, ejection fraction; LV, left ventricle; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.12 Atherosclerosis, arteriosclerosis, and peripheral artery disease

6.12.1 Carotid atherosclerosis

The 2007 ESH/ESC Guidelines concluded that progression of carotid atherosclerosis can be delayed by lowering BP [2], but calcium antagonists have a greater efficacy than diuretics and beta-blockers [186], and ACE inhibitors more than diuretics [581]. Very few data are available on whether calcium antagonists have a greater effect on carotid IMT than RAS blockers.

6.12.2 Increased arterial stiffness

All antihypertensive drugs reduce arterial stiffness, since the reduction of BP unloads the stiff components of the arterial wall, leading to a passive decrease of PWV. A recent meta-analysis and meta-regression analysis of RCTs documented that ACE inhibitors and ARBs reduce PWV [582,583]. However, owing to the lack of high-quality and properly powered RTCs, it is not clear whether they are superior to other antihypertensive agents in their effect on arterial stiffness. The ability of RAS blockers to reduce arterial stiffness as assessed by PWV seems to be independent of their ability to reduce BP [582–584]. However, although the amlodipine-valsartan combination decreased central SBP more effectively than the amlodipine-atenolol combination, in the Amlodipine-Valsartan Combination Decreases Central Systolic Blood Pressure more Effectively than the Amlodipine-Atenolol Combination (EXPLOR) trial, both combinations decreased PWV by 0.95 m/s with no significant differences over the trial 24-week duration [399]. Also, in a randomized study in mild-to-moderate hypertension, the vasodilating beta-blocker nebivolol decreased central pulse pressure to a larger extent than the nonvasodilating beta-blocker metoprolol after 1 year of treatment, although no significant changes in the augmentation index or carotid-femoral PWV were detected with either drug [406]. Improvement of arterial stiffness with treatment has been documented over the long term [585]. A relationship between a reduction of arterial stiffness and reduced incidence of CV events has been reported in only one study, on a limited number of patients with advanced renal disease [586].

6.12.3 Peripheral artery disease

A prospective observational analysis of the UKPDS shows that the incidence of PAD-related amputation and death in patients with diabetes is strongly and inversely associated with the SBP achieved by treatment [315,587]. The choice of the antihypertensive agent is less important than actual BP control in patients with PAD [199]. ACE inhibitors have shown benefit in a subgroup analysis of more than 4000 patients with PAD enrolled in the Heart Outcomes Prevention Evaluation (HOPE) study [588], but the arm receiving the ACE inhibitor had a lower BP than the comparative arm.

There has been concern that the use of beta-blockers in patients with PAD may worsen the symptoms of claudication. Two meta-analyses of studies published in PAD patients with mild-to-moderate limb ischaemia did not confirm the intake of beta-blockers to be associated with exacerbation of PAD symptoms [589,590].

The incidence of renal artery stenosis is increased in patients with PAD. Thus, this diagnosis must be kept in mind when resistant hypertension is encountered in these patients [587].

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6.12.4 Summary of recommendations on therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease

Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease

Recommendations	Class[a]	Level[b]	Ref.[c]
In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and beta-blockers.	IIa	B	186, 581
In hypertensive patients with a PWV above 10 m/s all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved.	IIa	B	138, 582, 586
Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death.	I	A	284
Though a careful follow up is necessary, beta-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.	IIb	A	589, 590

ACE, angiotensin-converting enzyme; BP, blood pressure; CV, cardiovascular; PAD, peripheral artery disease; PWV, pulse wave velocity.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

6.13 Sexual dysfunction

Sexual dysfunction is more prevalent in hypertensive than normotensive individuals, but available information mostly concerns men. Erectile dysfunction is considered to be an independent CV risk factor and an early diagnostic indicator for asymptomatic or clinical OD [591]. Hence, a full history should include sexual dysfunction. Lifestyle modifications may ameliorate erectile function [592]. Compared with older antihypertensive drugs, newer agents (ARBs, ACE inhibitors, calcium antagonists and vasodilating beta-blockers) have neutral or even beneficial effects on erectile function [593]. Phospho-diesterase-5 inhibitors may be safely administered to hypertensives, even those on multiple drug regimens (with the possible exception of alpha-blockers and in absence of nitrate administration) [594] and may improve adherence to antihypertensive therapy [595]. Studies on the effects of hypertension and antihypertensive therapy on female sexual dysfunction are in their infancy and should be encouraged [596].

6.14 Resistant hypertension

Hypertension is defined as resistant to treatment when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower SBP and DBP values to <140 and 90 mmHg, respectively. Depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been reported to range from 5–30% of the overall hypertensive population, with figures less than 10% probably representing the true prevalence. Resistant hypertension is associated with a high risk of CV and renal events [597–600].

Resistant hypertension can be real or only apparent or spurious. A frequent cause of spurious resistant hypertension is failure to adhere to the prescribed treatment regimen, a notoriously common phenomenon that is responsible for the poor rate of BP control in the hypertensive population worldwide. Lack of BP control may, however, also depend on (i) persistence of an alerting reaction to the BP-measuring procedure, with an elevation of office (although not of out-of-office) BP (ii) use of small cuffs on large arms, with inadequate compression of the vessel and (iii) pseudohypertension, i.e. marked arterial stiffening (more common in the elderly, especially with heavily calcified arteries), which prevents occlusion of the brachial artery.

True resistant hypertension may originate from: (i) lifestyle factors such as obesity or large weight gains, excessive alcohol consumption (even in the form of binge drinking) and high sodium intake, which may oppose the BP-lowering effect of antihypertensive drugs via systemic vasoconstriction, sodium and water retention and, for obesity, the sympatho-stimulating effect of insulin resistance and increased insulin levels; (ii) chronic intake of vasopressor or sodium-retaining substances; (iii) obstructive sleep apnoea (usually but not invariably associated with obesity) [521], possibly because nocturnal hypoxia, chemoreceptor stimulation and sleep deprivation may have a long-lasting vasoconstrictor effect; (iv) undetected secondary forms of hypertension and (v) advanced and irreversible OD, particularly when it involves renal function or leads to a marked increase in arteriolar wall-lumen ratio or reduction of large artery distensibility.

A correct diagnostic approach to resistant hypertension requires detailed information on the patient's history (including lifestyle characteristics), a meticulous physical examination and laboratory tests to detect associated risk factors, OD and alterations of glucose metabolism, as well as of advanced renal dysfunction opposing—via sodium retention—the effect of BP-lowering drugs. The possibility of a secondary cause of hypertension should always be considered: primary aldosteronism may be more frequent than was believed years ago [601], and renal artery stenoses of an atherosclerotic nature have been shown to be quite common in the elderly. Finally, ABPM should be performed regularly, not only to exclude spurious resistance but also to quantify to a better degree the BP elevation and the subsequent effect of the treatment modifications [598,602].

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In clinical practice, identification of low adherence to treatment may present special difficulties, because (i) information provided by the patient may be misleading and (ii) methods to objectively measure adherence to treatment have little applicability in day-to-day medicine. An unhealthy lifestyle may represent a clue, as may a patient's expression of negative feelings about medicines in general. Ultimately, physicians may have to consider stopping all current drugs and restart with a simpler treatment regimen under close medical supervision. This approach may also avoid futile use of ineffective drugs. Although hospitalization for hypertension is regarded as inappropriate in most European countries, a few days in hospital may be necessary to check the BP effect of antihypertensive drugs under strict control.

Although resistant hypertension may show a BP reduction if the diuretic dose is further increased (see below), most patients with this condition require the administration of more than three drugs. Subgroup analyses of large-scale trials and observational studies have provided evidence that all drug classes with mechanisms of action partially or totally different from those of the existing three drug regimens can lower BP in at least some resistant hypertensive individuals [603]. A good response has been reported to the use of mineralocorticoid receptor antagonists, i.e. spironolactone, even at low doses (25–50 mg/day) or eplerenone, the alpha-1-blocker doxazosin and a further increase in diuretic dose [604–608], loop diuretic replacing thiazides or chlorthalidone if renal function is impaired. Given that blood volume may be elevated in refractory hypertension [609], amiloride may add its effect to that of a previously administered thiazide or thiazide-like diuretic, although its use may favour hyperkalaemia and is not indicated in patients with marked reduction of eGFR. The BP response to spironolactone or eplerenone may be accounted for by the elevated plasma aldosterone levels frequently accompanying resistant hypertension, either because aldosterone secretion escapes the early reduction associated with RAS blockade [610] or because of undetected primary aldosteronism.

At variance from an earlier report [611], endothelin antagonists have not been found to effectively reduce clinic BP in resistant hypertension and their use has also been associated with a considerable rate of side-effects [612]. New BP-lowering drugs (nitric oxide donors, vasopressin antagonists, neutral endopeptidase inhibitors, aldosterone synthase inhibitors, etc.) are all undergoing early stages of investigation [613]. No other novel approach to drug treatment of resistant hypertensive patients is currently available.

6.14.1 Carotid baroreceptor stimulation

Chronic field electrical stimulation of carotid sinus nerves via implanted devices has recently been reported to reduce SBP and DBP in resistant hypertensive individuals [614–616]. The reduction was quite marked when initial BP values were very high and the effect included ambulatory BP and persisted for up to 53 months [615]. However, longer-term observations have so far involved only a restricted number of patients and further data on larger numbers of individuals with an elevation of BP unresponsive to multiple drug treatments are necessary to confirm the persistent efficacy of the procedure. Although only a few remediable side-effects of a local nature (infection, nerve damage, pain of glossopharyngeal nerve origin, etc) have so far been reported, a larger database is also needed to conclusively establish its safety. Ongoing technical improvements to reduce the inconvenience represented by the surgical implantation of the stimulating devices, and to prolong the duration of the battery providing the stimulation, are being tested.

6.14.2 Renal denervation

A growing non-drug therapeutic approach to resistant hypertension is bilateral destruction of the renal nerves travelling along the renal artery, by radiofrequency ablation catheters of various design, percutaneously inserted through the femoral artery [617–621]. The rationale for renal denervation lays in the importance of sympathetic influences on renal vascular resistance, renin release and sodium re-absorption, the increased sympathetic tone to the kidney and other organs displayed by hypertensive patients [622–624], and the pressor effect of renal afferent fibres, documented in experimental animals [625,626]. The procedure has been shown to induce a marked reduction in office BP which has been found to be sustained after one year and in a small number of patients two and three years following the denervation procedure. Limited reductions have been observed on ambulatory and home BP, and need of antihypertensive drugs [627], while some evidence of additional benefit, such as decrease of arterial stiffening, reversal of LVH and diastolic dysfunction, renal protection and improvement of glucose tolerance, has been obtained [628–630]. Except for the rare problems related to the catheterization procedure (local haematoma, vessel dissection, etc) no major complications or deterioration of renal function have been reported.

At present, the renal denervation method is promising, but in need of additional data from properly designed long-term comparison trials to conclusively establish its safety and persistent efficacy vs. the best possible drug treatments. Understanding what makes renal denervation effective or ineffective (patient characteristics or failure to achieve renal sympathectomy) will also be important to avoid the procedure in individuals unlikely to respond. A position paper of the ESH on renal denervation should be consulted for more details [631].

6.14.3 Other invasive approaches

Research in this area is ongoing and new invasive procedures are under study. Examples are creation of a venous-arterial fistula and neurovascular decompression by surgical interventions, which has been found to lower BP in a few cases of severe resistant hypertension (presumably by reducing central sympathetic overactivity) with, however, an attenuation of the effect after 2 years [632]. New catheters are also available to shorten the renal

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ablation procedure and to achieve renal denervation by means other than radiofrequency, e.g. by ultrasounds.

Overall, renal denervation and carotid baroreceptor stimulation should be restricted to resistant hypertensive patients at particularly high risk, after fully documenting the inefficacy of additional antihypertensive drugs to achieve BP control. For either approach, it will be of fundamental importance to determine whether the BP reductions are accompanied by a reduced incidence of CV morbid and fatal events, given the recent evidence from the FEVER and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) studies that, in patients under multidrug treatment, CV risk (i) was greater than in patients on initial randomized monotherapy and (ii) did not decrease as a result of a fall in BP [633,634]. This raises the possibility of risk irreversibility, which should be properly studied.

6.14.4 Follow-up in resistant hypertension

Patients with resistant hypertension should be monitored closely. Office BP should be measured at frequent intervals and ambulatory BP at least once a year. Frequent home BP measures can also be considered and measures of organ structure and function (particularly of the kidney) instituted on a yearly basis. Although mineralocorticoid receptor antagonists at low doses have been associated with relatively few side-effects, their use should prompt frequent assessment of serum potassium and serum creatinine concentrations, because these patients may undergo acutely or chronically an impairment of renal function, especially if there is concomitant treatment with an RAS blocker. Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, implementation of these procedures should be restricted to experienced operators, and diagnosis and follow-up restricted to hypertension centres [631].

6.14.5 Summary of recommendations on therapeutic strategies in patients with resistant hypertension

Therapeutic strategies in patients with resistant hypertension

Recommendations	Class[a]	Level[b]	Ref.[c]
In resistant hypertensive patients it is recommended that physicians check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal.	I	C	-
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindication exists.	IIa	B	604, 606, 607, 608
In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.	IIb	C	-
Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers.	I	C	-
It is recommended that the invasive approaches are considered only for truly resistant hypertensive patients, with clinic values ≥160 mmHg SBP or ≥110 mmHg DBP and with BP elevation confirmed by ABPM.	I	C	-

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

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6.15 Malignant hypertension

Malignant hypertension is a hypertensive emergency, clinically defined as the presence of very high BP associated with ischaemic OD (retina, kidney, heart or brain). Although its frequency is very low, the absolute number of new cases has not changed much over the past 40 years. The survival rate 5 years after diagnosis of malignant hypertension has improved significantly (it was close to zero 50 years ago), possibly as a result of earlier diagnosis, lower BP targets and availability of new classes of antihypertensive agents [635]. OD may regress—at least partially—under treatment [636], although long-term prognosis remains poor, especially when renal function is severely reduced [637]. Because of its low incidence, no good controlled study has been conducted with recent agents. Current treatment is founded on agents that can be administered by intravenous infusion and titrated, and so can act promptly but gradually in order to avoid excessive hypotension and further ischaemic OD. Labetalol, sodium nitroprusside, nicardipine, nitrates and furosemide are among the intravenous agents most usually employed but in these severely ill patients, treatment should be individualized by the physician. When diuretics are insufficient to correct volume retention, ultrafiltration and temporary dialysis may help.

6.16 Hypertensive emergencies and urgencies

Hypertensive emergencies are defined as large elevations in SBP or DBP (>180 mmHg or >120 mmHg, respectively) associated with impending or progressive OD, such as major neurological changes, hypertensive encephalopathy, cerebral infarction, intracranial haemorrhage, acute LV failure, acute pulmonary oedema, aortic dissection, renal failure, or eclampsia. Isolated large BP elevations without acute OD (hypertensive urgencies)—often associated with treatment discontinuation or reduction as well as with anxiety—should not be considered an emergency but treated by reinstitution or intensification of drug therapy and treatment of anxiety. Suspicions have recently been raised on the possible damaging effect of maximum vs. predominant BP values [435]. However, this requires more information and overtreatment should be avoided.

Treatment of hypertensive emergencies depends on the type of associated OD and ranges from no lowering, or extremely cautious lowering, of BP in acute stroke (see Section 6.10) to prompt and aggressive BP reduction in acute pulmonary oedema or aortic dissection. In most other cases, it is suggested that physicians induce a prompt but partial BP decrease, aiming at a <25% BP reduction during the first hours, and proceed cautiously thereafter. Drugs to be used, initially intravenously and subsequently orally, are those recommended for malignant hypertension (see Section 6.15). All suggestions in this area, except those for acute stroke, are based on experience because of the lack of any RCTs comparing aggressive vs. conservative lowering of BP, and the decision on how to proceed should be individualized.

6.17 Perioperative management of hypertension

Presence of hypertension is one of the common reasons for postponing necessary surgery, but it is arguable whether this is necessary [638]. Stratifying the overall CV risk of the surgery candidate may be more important [639]. The question of whether antihypertensive therapy should be maintained immediately before surgery is frequently debated. Sudden withdrawal of clonidine or beta-blockers should be avoided because of potential BP or heart-rate rebounds. Both types of agent can be continued over surgery and, when patients are unable to take oral medications, beta-blockers can be given parenterally and clonidine transdermally. Diuretics should be avoided on the day of surgery because of potential adverse interaction with surgery-dependent fluid depletion. ACE inhibitors and ARBs may also be potentiated by surgery-dependent fluid depletion and it has been suggested that they should not be taken on the day of surgery and restarted after fluid repletion has been assured. Post-surgery BP elevation, when it occurs, is frequently caused by anxiety and pain after awakening, and disappears after treating anxiety and pain. All these suggestions are based on experience only (**Class IIb, Level C**).

6.18 Renovascular hypertension

Renovascular artery stenosis secondary to atherosclerosis is relatively frequent, especially in the elderly population, but rarely progresses to hypertension or renal insufficiency [640]. It is still debated whether patients with hypertension or renal insufficiency benefit from interventions: mostly percutaneous renal artery stenting. While there is convincing (though uncontrolled) information favouring this procedure in younger (mostly female) patients with uncontrolled hypertension in fibromuscular hyperplasia (82–100% success, re-stenosis in 10–11%) [641] (**Class IIa, Level B**), the matter is highly controversial in atherosclerotic renovascular hypertension. Two retrospective studies have reported improvements (though not in mortality) in patients with bilateral renal artery stenosis complicated by recurrent episodes of acute heart failure [642]. In all other conditions with renal artery stenosis, uncertainties continue regarding the benefit of angioplasty and stenting, despite several controlled trials. Two RCTs and 21 cohort studies published before 2007 showed no uniform pattern of benefit. The more recent Angioplasty and STenting for Renal Artery Lesions (ASTRAL) trial, including 806 patients randomized between angioplasty and stenting, plus medical therapy vs. medical therapy alone, did not provide any evidence of clinically meaningful benefit on BP, renal function, or CV events [643]. Although no final conclusions can be drawn from ASTRAL because of some limitations in its design (patients with a strong indication for intervention were excluded from randomization) and lack of statistical power, intervention is at present not recommended in atherosclerotic renal artery stenosis if renal function has remained stable over the past 6–12 months and if hypertension can be controlled by an acceptable medical regimen (**Class ill, Level B**). Suitable medical regimens can include RAS blockers, except in bilateral renal artery stenosis or in unilateral artery stenosis with evidence of functional importance by ultrasound examinations or scintigraphy.

6.19 Primary aldosteronism

In documented unilateral primary aldosteronism, caused either by aldosterone-producing adenoma or unilateral

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adrenal hyperplasia, the treatment of choice is unilateral laparoscopic adrenalectomy, whereas treatment with mineralocorticoid receptor antagonists is indicated in patients with bilateral adrenal disease (idiopathic adrenal hyperplasia and bilateral adenoma). Glucocorticoid-remediable aldosteronism is treated with a low dose of a long-acting glucocorticoid, e.g. dexamethasone.

Surgical treatment in patients with unilateral primary aldosteronism shows improvement of postoperative serum potassium concentrations in nearly 100% of patients [644], when diagnosis of—and indication for—adrenalectomy are based on adrenal venous sampling. Hypertension is cured (defined as BP <140/90 mmHg without antihypertensive medication) in about 50% (range: 35–60%) of patients with primary aldosteronism after unilateral adrenalectomy. Cure is more likely in patients having no more than one first-degree relative with hypertension, preoperative use of two antihypertensive drugs at most, younger age, shorter duration of hypertension and no vascular remodelling [645,646].

Mineralocorticoid receptor antagonists (spironolactone, eplerenone) are indicated in patients presenting with bilateral adrenal disease and in those who, for various reasons, do not undergo surgery for unilateral primary aldosteronism. The starting dose for spironolactone should be 12.5–25 mg daily in a single dose; the lowest effective dose should be found, very gradually titrating upwards to a dose of 100 mg daily or more. The incidence of gynaecomasty with spironolactone is dose-related whereas the exact incidence of menstrual disturbances in premenopausal women with spironolactone is unknown. A small dose of a thiazide diuretic, triamterene or amiloride, can be added to avoid a higher dose of spironolactone, which may cause side-effects.

Eplerenone is a newer, selective mineralocorticoid receptor antagonist without antiandrogen and progesterone agonist effects, thus reducing the rate of side-effects; it has 60% of the antagonist potency of spironolactone. Because of its shorter duration of action, multiple daily dosing is required (with a starting dose of 25 mg twice daily). In a recent 16-week, double-blind, randomized study comparing the antihypertensive effect of eplerenone (100–300 mg once daily) and spironolactone (75–225 mg once daily), spironolactone was significantly superior to eplerenone in reducing BP in primary aldosteronism [647].

7. TREATMENT OF ASSOCIATED RISK FACTORS

7.1 Lipid-lowering agents

Patients with hypertension, and especially those with type 2 diabetes or metabolic syndrome, often have atherogenic dyslipidemia, characterized by elevated triglycerides and LDL-cholesterol with a low HDL-cholesterol [12,13,648]. The benefit of adding a statin to antihypertensive treatment was well established by the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) study [649], as summarized in the 2007 ESH/ESC Guidelines [2]. The lack of statistically significant benefit in the ALLHAT study can be attributed to insufficient lowering of total cholesterol (11% in ALLHAT, compared with 20% in ASCOT) [650]. Further analyses of the ASCOT data have shown that the addition of a statin to the amlodipine-based antihypertensive therapy can reduce the incidence of the primary CV outcome even more markedly than the addition of a statin to the atenolol-based therapy [651]. The beneficial effect of statin administration to patients without previous CV events [targeting a low-density lipoprotein cholesterol value <3.0 mmol/L; (115 mg/dL)] has been strengthened by the findings of the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study [652], showing that lowering low-density lipoprotein cholesterol by 50% in patients with baseline values <3.4 mmol/L (130 mg/dL) but with elevated C-reactive protein reduced CV events by 44%. This justifies use of statins in hypertensive patients who have a high CV risk.

As detailed in the recent ESC/EAS Guidelines [653], when overt CHD is present, there is clear evidence that statins should be administered to achieve low-density lipoprotein cholesterol levels <1.8 mmol/L (70 mg/dL) [654]. Beneficial effects of statin therapy have also been shown in patients with a previous stroke, with low-density lipoprotein cholesterol targets definitely lower than 3.5 mmol/L (135 mg/dL) [655]. Whether they also benefit from a target <1.8 mmol/L (70 mg/dL) is open to future research. This is the case also for hypertensive patients with a low-moderate CV risk, in whom evidence of the beneficial effects of statin administration is not clear [656].

7.2 Antiplatelet therapy

In secondary CV prevention, a large meta-analysis published in 2009 showed that aspirin administration yielded an absolute reduction in CV outcomes much larger than the absolute excess of major bleedings [657]. In primary prevention, however, the relationship between benefit and harm is different, as the absolute CV event reduction is small and only slightly greater than the absolute excess in major bleedings. A more favourable balance between benefit and harm of aspirin administration has been investigated in special groups of primary prevention patients. Studies on diabetes have so far failed to establish a favourable benefit-harm ratio, whereas a sub-study of the HOT trial, in which hypertensive patients were classified on the basis of eGFR at randomization, showed aspirin administration to be associated with a significant trend for a progressive reduction in major CV events and death, the lower the baseline eGFR values. This reduction was particularly marked in hypertensive patients with eGFR <45 mL/min/1.73 m^2. In this group of patients the risk of bleeding was modest compared with the CV benefit [658]. Aspirin therapy should be given only when BP is well controlled.

In conclusion, the prudent recommendations of the 2007 ESH/ESC Guidelines can be reconfirmed [2]: antiplatelet therapy, particularly low-dose aspirin, should be prescribed to controlled hypertensive patients with previous CV events and considered in hypertensive patients with reduced renal function or a high CV risk. Aspirin is not recommended in low-to-moderate risk hypertensive patients in whom absolute benefit and harm are equivalent. It is noteworthy that a recent meta-analysis has shown lower incidences of cancer and mortality in the aspirin (but not the warfarin) arm of primary prevention trials [659]. If confirmed, this additional action of aspirin may lead to a more liberal

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reconsideration of its use. Low-dose aspirin in the prevention of preeclampsia is discussed in Section 6.5.3.

7.3 Treatment of hyperglycaemia

The treatment of hyperglycaemia for prevention of CV complications in patients with diabetes has been evaluated in a number of studies. For patients with type 1 diabetes, the Diabetes Control and Complications (DCCT) study convincingly showed that intensive insulin therapy was superior for vascular protection and reduction of events, compared with standard treatment [660,661]. In type 2 diabetes, several large-scale studies have aimed at investigating whether a tight glycaemic control, based on oral drugs and/or insulin, is superior to less-tight control for CV prevention. In UKPDS, tighter glycaemic control could prevent microvascular—but not macrovascular—complications [662], except in a subgroup with obesity, treated with metformin [663]. The appropriate target for a glycaemic control has been explored recently in the ADVANCE [664], ACCORD [665], and Veterans' Affairs Diabetes Trial (VADT) [666] studies, which randomized one study arm to very low HbA_{1c} targets (<6.5 or 6.0%). None of these individual studies showed a significant reduction of the composite endpoint of combined CVD events, but a number of later meta-analyses have documented that more intensive glycaemic control is likely to reduce non-fatal coronary events and myocardial infarction, as well as nephropathy, but not stroke or all-cause or CV mortality [667–669]. However, especially in ACCORD, the lower HbA_{1c} target arm was associated with an excess of hypoglycaemic episodes and all-cause mortality. Based on these data, the American Diabetology Association and the European Association for the Study of Diabetes (EASD) [670] have jointly taken a similar, prudent attitude, recommending that physicians individualize treatment targets and avoid overtreatment of fragile, higher-risk patients by restricting more stringent control of hyperglycaemia to younger patients with recent diabetes, absent or minor vascular complications and long life-expectancy (HbA_{1c} target <7.0%), while considering a less-stringent HbA_{1c} of 7.5–8.0%, or even higher in more complicated and fragile patients, particularly in elderly patients with cognitive problems and a limited capacity for self care [670,671]. The ESC/EASD Guidelines for the treatment of diabetes should be consulted for more details [672].

7.4 Summary of recommendations on treatment of risk factors associated with hypertension

Treatment of risk factors associated with hypertension

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to use statin therapy in hypertensive patients at moderate to high CV risk, targeting a low-density lipoprotein cholesterol value <3.0 mmol/L (115 mg/dL).	I	A	649, 652
When overt CHD is present, it is recommended to administer statin therapy to achieve low-density lipoprotein cholesterol levels <1.8 mmol/L (70 mg/dL).	I	A	654
Antiplatelet therapy, in particular low-dose aspirin, is recommended in hypertensive patients with previous CV events.	I	A	657
Aspirin should also be considered in hypertensive patients with reduced renal function or a high CV risk, provided that BP is well controlled.	IIa	B	658
Aspirin is not recommended for CV prevention in low-moderate risk hypertensive patients, in whom absolute benefit and harm are equivalent.	III	A	657
In hypertensive patients with diabetes, a HbA_{1c} target of <7.0% is recommended with antidiabetic treatment.	I	B	670
In more fragile elderly patients with a longer diabetes duration, more comorbidities and at high risk, treatment to a HbA_{1c} target of <7.5–8.0% should be considered.	IIa	C	-

BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; HbA1c, glycated haemoglobin.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence.

8. FOLLOW-UP

8.1 Follow-up of hypertensive patients

After the initiation of antihypertensive drug therapy, it is important to see the patient at 2- to 4-week intervals to evaluate the effects on BP and to assess possible side-effects. Some medications will have an effect within days

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or weeks but a continued delayed response may occur during the first 2 months. Once the 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 [673]. Depending on the local organization of health resources, many of the later visits may be performed by non-physician health workers, such as nurses [674]. For stable patients, HBPM and electronic communication with the physician (SMS, E-mail, social media, or automated telecommunication of home BP readings) may also provide an acceptable alternative [675–677]. It is nevertheless advisable to assess risk factors and asymptomatic OD at least every 2 years.

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

Individuals with high normal BP or white-coat hypertension frequently have additional risk factors, including asymptomatic OD, with a higher chance of developing office or sustained hypertension, respectively [285,351, 678–681] (see Section 3.1.3). Even if 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. Regular annual visits should also serve the purpose of reinforcing recommendations on lifestyle changes, which represent the appropriate treatment in many of these patients.

8.3 Elevated blood pressure at control visits

Patients and physicians have a tendency to interpret an uncontrolled BP at a given visit as due to occasional factors and thus to downplay its clinical significance. This should be avoided and 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 drugs or substances that raise BP or oppose the antihypertensive effect of treatment (e.g. alcohol, nonsteroidal anti-inflammatory drugs). This may require tactful but stringent questioning of the patient (and his/her relatives), as well as repeated measurements of BP, to attenuate the initial alerting response to the BP-measuring procedures. If ineffective treatment is regarded as the reason for inadequate BP control, the treatment regimen should be modified without delay to avoid clinical inertia—major contribution to poor BP control worldwide [682,683]. Consideration should be given to the evidence that visit-to-visit BP variability may be a determinant of CV risk, independently of the mean BP levels achieved during long-term treatment, and that, thus, CV protection may be greater in patients with consistent BP control throughout visits.

8.4 Continued search for asymptomatic organ damage

Several studies have shown that the regression of asymptomatic OD occurring during treatment reflects the treatment-induced reduction of morbid and fatal CV events, thereby offering valuable information on whether patients are more or less effectively protected by the treatment strategies adopted. This has been shown for the treatment-induced regression of electrocardiographic LVH (voltage or strain criteria), the echocardiographic LVH and the echocardiographically derived measures of LVM and left atrial size [150,151,261,684–686]. Lower incidence of CV events and slower progression of renal disease have also been repeatedly associated with treatment-induced reduction in urinary protein excretion in both diabetic and nondiabetic patients [227,262,535,536,687,688] but, especially for microalbuminuria, discordant results have also been reported [329,331]. This has also been the case in a recent sub-analysis of the ACCOMPLISH trial, in which the combination of an ACE inhibitor and a calcium antagonist was more effective than an ACE inhibitor-diuretic combination in preventing the doubling of serum creatinine or ESRD while reducing proteinuria to a lesser degree [539]. A recent analysis of the ELSA study has, on the other hand, failed to consistently document a predictive value for CV events of treatment-induced reductions in carotid IMT (possibly because the changes are minimal and their impact masked by large between-subject differences) [188]. This conclusion is supported by meta-analyses [689–691], though some of them have been discussed [692]. Evidence on the predictive power of treatment-induced changes in other measures of OD (eGFR, PWV and ABI) is either limited or absent. On the whole, it appears reasonable to search for at least some asymptomatic OD, not only for the initial stratification of CV risk, but also during follow-up.

A cost-effectiveness analysis of which signs of OD should best be assessed in the follow-up of hypertensive patients has never been done. Assessment of urinary protein excretion can be reliably quantified in a morning urine sample and has a low cost, wide availability and ability to show a treatment-induced effect within a few months. Also, the low cost and wide availability suggest regular repetition of an electrocardiogram, although detection of its LVH-dependent change is less sensitive. Treatment-induced changes are also slow for echocardiographic measures of LVM, which also carries the disadvantage of reduced availability, higher cost, extra-time and need of refined expertise for proper assessment. The information available on assessment of OD during antihypertensive treatment is summarized in Fig. 5. In addition, follow-up measurements should include lipid profile, blood glucose, serum creatinine and serum potassium and, regardless of their greater or smaller ability to accurately and quickly detect regression with treatment, all measures of OD may provide useful information on the progression of hypertension-dependent abnormalities, as well as on the appearance of conditions requiring additional therapeutic interventions, such as arrhythmias, myocardial ischaemia, stenotic plaques and heart failure.

8.5 Can antihypertensive medications be reduced or stopped?

In some patients, in whom treatment is accompanied by an effective BP control for an extended period, it may be possible to reduce the number and dosage of drugs. This may be particularly the case if BP control is accompanied by

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Marker of organ damage	Sensitivity for changes	Time to change	Prognostic value of changes
LVH/ECG	Low	Moderate (>6 months)	Yes
LVH/echo	Moderate	Moderate (>6 months)	Yes
LVH/cardiac magnetic resonance	High	Moderate (>6 months)	No data
eGFR	Moderate	Very slow (years)	No data
Urinary protein excretion	High	Fast (weeks–months)	Moderate
Carotid wall thickness	Very low	Slow (>12 months)	No
Pulse wave velocity	High	Fast (weeks–months)	Limited data
Ankle/ brachial index	Low	No data	No data

ECG = electrocardiogram; echo = echocardiogram; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; OD = organ damage.

FIGURE 5 Sensitivity to detect treatment-induced changes, time to change and prognostic value of change by markers of asymptomatic OD.

healthy lifestyle changes, such as weight loss, exercise habits and a low-fat and low-salt diet, which remove environmental pressor influences. Reduction of medications should be made gradually and the patient should frequently be checked because of the risk of reappearance of hypertension.

9. IMPROVEMENT OF BLOOD PRESSURE CONTROL IN HYPERTENSION

Despite overwhelming evidence that hypertension is a major CV risk factor and that BP-lowering strategies substantially reduce the risk, studies performed outside Europe and in several European countries [16,683] consistently show that (i) a noticeable proportion of hypertensive individuals are unaware of this condition or, if aware, do not undergo treatment [693,694], (ii) target BP levels are seldom achieved, regardless of whether treatment is prescribed or patients are followed by specialists or general practitioners [695,696] (iii), failure to achieve BP control is associated with persistence of an elevated CV risk, [697,698] and (iv) the rate of awareness of hypertension and BP control is improving slowly or not at all—and this is the case also in secondary prevention [699,700]. Because, in clinical trials, antihypertensive treatment can achieve BP control in the majority of the patients [701], these data reflect the wide gap that exists between the antihypertensive treatment potential and real-life practice. As a consequence, high BP remains a leading cause of death and CV morbidity in Europe, as elsewhere in the world [702]. Thus there is a strong need to detect and treat more hypertensive patients, as well as improve the efficacy of ongoing treatment.

Overall, three main causes of the low rate of BP control in real life have been identified: (i) physician inertia [703]; (ii) patient low adherence to treatment [704,705], and (iii) deficiencies of healthcare systems in their approach to chronic diseases. However, delayed initiation of treatment when OD is irreversible or scarcely reversible is also likely to be an important factor [272]. Physician inertia (i.e. lack of therapeutic action when the patient's BP is uncontrolled) is

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generated by several factors: doubts about the risk represented by high BP (particularly in the elderly), fear of a reduction in vital organ perfusion when BP is reduced (the J-curve phenomenon) and concern about side-effects. Several physicians also maintain a sceptical attitude towards guidelines because of their multiplicity and origin from different sources (international and national scientific societies, governmental agencies, local hospitals, etc.), which make their recommendations sometimes inconsistent. Recommendations are also often perceived as unrealistic when applied to the environment where physicians operate [706].

Low adherence to treatment is an even more important cause of poor BP control because it involves a large number of patients and its relationship with persistence of elevated BP values and high CV risk has been fully documented [704–710]. Non-adherence has been classified into 'discontinuers' (patients who discontinue treatment) and 'bad users' [i.e. those who take treatment irregularly because of delays in drug(s) intake or repeated short interruptions of the prescribed therapeutic strategy]. Discontinuers represent a greater problem because their behaviour is normally intentional and, once discontinued, treatment resumption is more difficult. Bad users, however, are at higher risk of becoming discontinuers, and thus their identification is important.

Low adherence is extremely common for lifestyle changes but importantly extends to drug prescriptions, for which it develops quite rapidly: after 6 months, more than one-third and after 1 year about half of the patients may stop their initial treatment; furthermore, on a daily basis, 10% of patients forget to take their drug [704,705]. For hypertension (and other chronic diseases), investigating adherence to treatment is now facilitated by electronic methods of measuring adherence and by the availability of administrative databases that provide information for the entire population [709,711].

Several approaches have been proposed to reduce physician inertia, unawareness of hypertension and non-adherence to treatment. Physician training programmes notably reduce inertia although perhaps with less than expected benefits [712–714], and there is consensus that making simple, informative material available in the lay press, the physician's office, pharmacies, schools and other public places may have a favourable effect on information and motivation by interested individuals [715]. Emphasis should be placed on the importance of measuring and reporting BP values, even at visits not connected with hypertension or problems of a CV nature, in order to collate information on BP status over the years. Adherence to treatment can also be improved by simplification of treatment [716] and use of self-measured BP at home [66]; an additional favourable effect might be gained through the use of telemetry for transmission of recorded home values [98,99].

Health providers should facilitate guidelines implementation as a means of educating physicians about recent scientific data, rather than primarily as an instrument to contain cost. They should also foster a multidisciplinary approach to CV prevention, which could mean that physicians receive the same motivating message from different perspectives. The most serious attempt by a healthcare system to improve the diagnostic and treatment aspects of hypertension has been done in the UK, based on the pay-per-performance principle, i.e. to give incentives to physicians rewarding the appropriate diagnosis and care of chronic diseases, including hypertension. The impact on the quality and outcomes of care for hypertension is uncertain. An early report showed that the implementation was associated with an increased rate of BP monitoring and control among general practitioners [717], whereas later reports showed that the trend was not sustained. Furthermore, no statistically significant changes in the cumulative incidence of major hypertension-related adverse outcomes or mortality have been observed after implementation of pay-for-performance for the subgroups of already treated and newly treated patients [718,719].

A list of the interventions associated with improved patient adherence to treatment in shown in Table 17.

TABLE 17. Methods to improve adherence to physicians' recommendations

Patient level
Information combined with motivational strategies (see Section 5.1.6 on smoking cessation).
Group sessions.
Self-monitoring of blood pressure.
Self-management with simple patient-guided systems.
Complex interventions.[a]
Drug treatment level
Simplification of the drug regimen.
Reminder packaging.
Health system level
Intensified care (monitoring, telephone follow-up, reminders, home visits, telemonitoring of home blood pressure, social support, computer-aided counselling and packaging).
Interventions directly involving pharmacists.
Reimbursement strategies to improve general practitioners' involvement in evaluation and treatment of hypertension.

[a]Almost all of the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, supportive care, worksite- and pharmacy-based programmes.

10. HYPERTENSION DISEASE MANAGEMENT

While there is strong evidence that antihypertensive treatment has a protective effect (see Section 4.1), it is less clear how care for hypertensive patients should be organized and delivered in the community [720]. However, there seems to be little doubt that, for effective disease management, a multidisciplinary approach is required. This means the involvement of a variety of healthcare providers [720–722]: the general practitioner, who should

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take care of the majority of hypertensive patients; medical specialists from various fields depending on the nature of the hypertension and the difficulty posed by its treatment; specifically trained nurses to closely follow the patient during his or her lifetime treatment; and pharmacists who handle physicians' prescriptions and often have to deal directly with the patients' problems and reply to his or her questions. In an ideal setting, all healthcare providers should co-operate in a successful lifetime intervention against this condition. In a review of the results of 13 studies, interpretation of disease management programmes resulted in a significantly greater SBP and DBP reduction, compared with controls. The effect was equivalent to an about 5 mmHg and >4 mmHg greater effect on SBP and DBP, respectively [723].

10.1 Team approach in disease management

Wide variations exist in the organization of healthcare systems across Europe but, in most countries, hypertension is usually diagnosed and managed in primary care (i.e. by general practitioners). In some countries, practice-based specialists take care of more complex examinations (ultrasounds etc.) and the more difficult-to-treat cases, while in other countries only hospital-based specialists and hypertension units are available for referral. In a few countries, specially educated and trained nurses assist physicians in the prescription, consultation, referral and even hospital admission of individuals with raised BP. In most countries, however, nurses have little or no role-sharing with physicians.

Several studies are available to show that team-based care can reduce BP by several mmHg more than standard care [724], with a greater SBP reduction of about 10 mmHg (median value) and an approximately 22% greater rate of BP control in a meta-analysis from 37 comparisons between team-based and standard-treatment groups [725]. Compared with standard care, team-based care has been found to be effective if it involves nurses and/or pharmacists either within a clinic or in the community [724]. The beneficial effect of the involvement of pharmacists and nurses in the management of hypertension has been obtained when their task involved patient education, behavioural and medical counselling, assessment of adherence to treatment, and, for pharmacists, interaction with physicians in the area of guideline-based therapy [724,726,727]. In a review of 33 RCTs published between 2005 and 2009, BP targets were more commonly achieved when interactions included a step-care treatment algorithm administered by nurses, as well as the involvement of nurses in patient monitoring by telephone [726,728,729]. Clearly, team-based strategies offer an important potential method for improvement of antihypertensive treatment compared with strategies involving physicians alone. Physicians, nurses and pharmacists should all be represented and general practitioners should interact, when needed, with specialists from various areas, such as internists, cardiologists, nephrologists, endocrinologists and dieticians. The contribution of nurses may be particularly important for implementation of lifestyle changes, for which long-term adherence is, notoriously, extremely low. Details on how team work for hypertension management may be organized are available in a recent publication on ESH Excellence Centres [730].

10.2 Mode of care delivery

Care is normally delivered on a face-to-face basis i.e. during an office visit in the primary care setting, in a specialist's office, or in hospital. Other methods for the delivery of care are, however, available, such as telephone interviews and advanced telemedicine (including videoconferences). Telephone contacts are effective in changing patient behaviours, with the additional potential advantage that, compared with face-to-face contact [726] (i) more patients can be reached, (ii) little or no time or working hours are lost, and (iii) contacts can be more frequent, with a greater chance of addressing patients' concerns in a timely manner, tailoring treatment and ultimately improving adherence. It is nevertheless important to emphasize that these new models of care delivery do not represent a substitute for office visits, but rather offer a potentially useful addition to the strategy of establishing a good relationship between the patient and the healthcare providers.

10.3 The role of information and communication technologies

Studies using communication technologies have shown that there are many new ways by which healthcare teams can communicate with patients, with the theoretical advantage of timely and effective adjustment of care plans. Home BP telemonitoring represents an appropriate example: several studies have shown that electronic transmission of self-measured BP can lead to better adherence to treatment regimen and more effective BP control [677,728,731,732]. Other examples include the use of smart phones, cell phones, Bluetooth, texting, personal electronic health records and patient portals, all aimed at favouring self-monitoring of treatment efficacy, adherence to prescription and feedback to healthcare personnel. It should be noted, however, that for no such device has effectiveness been proven in an RCT; thus their advantage over classical medical approaches remains to be established [723,724,731–734].

The impact of information and communication technologies in general, and of computerized decision-support systems in particular, on patient risk management and safety is analysed in detail in the e-Health for Safety report published by the European Commission in 2007 (review.epractice-en/en/library/302671). The report maintains that these systems can (i) prevent medical errors and adverse events, (ii) initiate rapid responses to an event, enable its tracking and provide feedback to learn from, (iii) provide information that can ease diagnostic and therapeutic decisions, and (iv) favour involvement of the patient in the decision-making process with an advantage to his or her co-operation and adherence [735].

Connecting the patient's health records to a variety of electronic health records (from different providers, pharmacies, laboratories, hospitals, or insurers) may foster the development of tailored tools for the individual patient,

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enhancing his or her engagement in care and disease prevention and improving health outcomes and patient satisfaction. Further developments are the incorporation of computerized technology that may help in the decision-making process to manage high BP.

11. GAPS IN EVIDENCE AND NEED FOR FUTURE TRIALS

Based on the review of the evidence available for the 2013 Guidelines on hypertension, it is apparent that several therapeutic issues are still open to question and would benefit from further investigation:

1. Should antihypertensive drug treatment be given to all patients with grade 1 hypertension when their CV risk is low-to-moderate?
2. Should elderly patients with a SBP between 140 and 160 mmHg be given antihypertensive drug treatments?
3. Should drug treatment be given to subjects with white-coat hypertension? Can this condition be differentiated into patients needing or not needing treatment?
4. Should antihypertensive drug treatment be started in the high normal BP range and, if so, in which patients?
5. What are the optimal office BP values (i.e. the most protective and safe) for patients to achieve by treatment in different demographic and clinical conditions?
6. Do treatment strategies based on control of out-of-office BP provide an advantage (reduced clinical morbidity and mortality, fewer drugs, fewer side-effects) over strategies based on conventional (office) BP control?
7. What are the optimal out-of-office (home and ambulatory) BP values to be reached with treatment and should targets be lower or higher in high risk hypertensives?
8. Does central BP add to CV event prediction in untreated and treated hypertensive patients?
9. Do invasive procedures for treatment of resistant hypertension compare favourably with the best drug treatment and provide long-term BP control and reduction of morbid and fatal events?
10. Do treatment-induced changes in asymptomatic OD predict outcome? Which measures—or combinations of measures—are most valuable?
11. Are lifestyle measures known to reduce BP capable of reducing morbidity and mortality in hypertensive patients?
12. Does a treatment-induced reduction of24 h BP variability add to CV protection by antihypertensive treatment?
13. Does BP reduction substantially lower CV risk in resistant hypertension?

While RCTs remain the 'gold standard' for solving therapeutic issues, it is equally clear that it would be unreasonable to expect that all these questions can realistically be answered by RCTs in a foreseeable future. Approaching some of these questions, such as those of the reduction of CV morbid and fatal events by treating grade 1 hypertensive individuals at low risk for CVD or the CV event reduction of lifestyle measures, would require trials involving many thousands of individuals for a very extended period and may also raise ethical problems. Others, such as the benefit of drug treatment for white-coat hypertensives or the additional predictive power of central vs. peripheral BP may require huge investigational efforts for small prospective benefits. It appears reasonable, at least for the next years, to focus RCTs upon important—as well as more easily approachable—issues, like the optimal BP targets to be achieved by treatment, the BP values to be treated and achieved in elderly hypertensive individuals, clinical reduction of morbidity and fatal events by new approaches to treating resistant hypertension and the possible benefits of treating high-risk individuals with high normal BP. Other important issues, e.g. the predictive value of out-of-office BP and that of OD, can be approached more realistically by adding these measurements to the design of some of the RCTs planned in the near future.

APPENDIX 1

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