2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH)

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Abbreviations: AAA, abdominal aortic aneurysm; ABI, ankle–brachial index; ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting-enzyme inhibitor; ACR, albumin–creatinine ratio; ADL, activity daily living; ADR, adverse drug reactions; AGB, adjustable gastric banding; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprylisin inhibitor; ARR, aldosterone–renin ratio; ARVD, atherosclerotic renal vascular disease; AS, aortic stenosis; ASCVD, atherosclerotic cardiovascular disease; AVatrio, -ventricular; baPWV, brachial–ankle pulse wave velocity; BB, beta blocker; BNP, brain natriuretic peptide; BP, blood pressure; BSA, body surface area; CAC, coronary arterial calcium; CAD, coronary or ischemic heart disease; CCB, calcium channel blocker; cfPWV, carotid–femoral pulse wave velocity; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration Equation; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CV, cardiovascular; CVD, cardiovascular disease; DDim, diastolic dimension; DOAC, direct oral anticoagulants; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; ESKD, end-stage kidney disease; ET1, endothelin 1; FEV1, forced expiratory volume in 1s; FLAIR-MRI, fluid-attenuated inversion recovery magnetic resonance imaging; FMD, fibromuscular dysplasia; FU, follow-up; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GLS, global longitudinal strain; HbA1c, hemoglobinA_{1c}; HBPM, home blood pressure monitoring; HDL, high-density lipoprotein; HDP, hypertensive disorders in pregnancy; HELLP, Hemolysis, Elevated liver enzymes, Low platelet count syndrome; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV, Human Immuno-deficiency Virus; HMOD, hypertension-mediated organ damage; IDH, isolated diastolic hypertension; IMID, immune-mediated inflammatory diseases; IMT, intima–media thickness; INOCA, Ischemia with non obstructive coronary arteries; ISH, isolated systolic hypertension; ISHY, isolated systolic hypertension of the young; IVT, intravenous thrombolysis; KTR, kidney transplant recipients; KWB, Keith Wagener Barger; LA, left atrium; LAV, left atrial volume; LEAD, lower extremity artery disease; LGE, late gadolinium enhancement; LMIC, low-income and middle-income countries; LV, left ventricle; LVDD, left ventricular diastolic dysfunction; LVDP, left ventricular diastolic pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVSD, left ventricular systolic dysfunction; LVSP, left ventricular systolic pressure; MACE, major adverse cardiovascular events; MAS, middle aortic syndrome; MH, masked hypertension; MI, mitral insufficiency; MINOCA, myocardial infraction with nonobstructive coronary arteries; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MRA, mineralocorticoid receptor antagonist; MT, mechanical thrombectomy; MUCH, masked uncontrolled hypertension; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Study; NOAC, non-Warfarin oral anticoagulants; NRI, Net Reclassification Index; NSAIDS, nonsteroidal antiinflammatory drugs; Nt-pro BNP, inactive-pro brain

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natriuretic peptide; OBPM, office blood pressure monitoring; OSA, obstructive sleep apnea; PA, primary aldosteronism; PAC, plasma aldosterone concentration; POAG, primary open angle glaucoma; PRA, plasma renin activity; PRC, plasma renin concentration; PTRA, percutaneous transluminal renal angioplasty; PTSD, posttraumatic stress disease; PWV, pulse wave velocity; RAS, renin–angiotensin system; RCT, randomized controlled trial; RDN, renal denervation; RTKIs, receptor tyrosine kinase inhibitors; RVH, renovascular hypertension; RWT, relative wall thikness; RYGB, Roux-en-Y gastric bypass; SCr, serum creatinine; SIADH, syndrome of inappropriate antidiuretic hormone; SLE, systemic lupus erythematosus; SNS, sympathetic nervous system; SNV, single nucleotide variant; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack; UACR, urinary albumin creatinine ratio; UPCR, urinary protein–creatinine ratio; VEGF, vascular endothelium growth factor; VEGFI, vascular endothelium growth factor inhibitor; WCE, white-coat effect; WCH, white-coat hypertension; WML, white matter lesion; WUCH, white-coat uncontrolled hypertension

Acronyms of trials, observational studies, medical associations etc.: AASK, African American study on kidney disease; ACC, American College of Cardiology; ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ACCORD, Action to control cardiovascular risk in diabetes; ADVANCE, Action in Diabetes and VAscular Disease – PreterAx and DiamicroN Controlled Evaluation; AHA, American Heart Association; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints; AMBER, Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease; AMI, US Association for Advance in Medical Instrumentation; ANBP-2, Second Australian National Blood Pressure Study; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ATTACH-2, Antihypertensive Treatment of Acute Cerebral Hemorrhage II; BUMP-1, Blood Pressure Monitoring in High Risk Pregnancy to Improve the Detection and Monitoring of Hypertension-1; BUMP-2, Blood Pressure Monitoring in High Risk Pregnancy to Improve the Detection and Monitoring of Hypertension-2; CALM-FIM, Controlling and Lowering Blood Pressure With the MobiusHD – First in Man; CAPP, The Captopril Prevention Project Study; CARDIA, Coronary Artery Risk Development in Young Adults; CHAP, Chronic Hypertension and Pregnancy; CHIPS, Control of Hypertension in Pregnancy Study; CLICK, Chlorthalidone in Chronic Kidney disease trial; COLM, Combination of OLMesartan and a calcium channel blocker or diuretic in Japanese elderly patients trial; CONVINCE, Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints; COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CREOLE, Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DASH, Dietary Approaches to Stop Hypertension; DCP, Diuretic Comparison Project; EASD, European Association for the Study of Diabetes; ELSA, European Lacidipine Study on Atherosclerosis; EMPA KIDNEY TRIAL, The Study of Heart and Kidney Protection With Empagliflozin trial; ESC, European Society of Cardiology; ESH, European Society of Hypertension; EUCLID, EURODIAB Controlled Trial of Lisinopril in Insulin-dependent Diabetes Mellitus; EUROPA, Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease; FEVER, Felodipine Event Reduction; FIDELIO DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIDELITY, The Finerenone in chronic kiDney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis; FIGARO DKD, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; GATEWAY, Gastric Bypass to Treat Obese Patients With Steady Hypertension; GRADE, Grade of Recommendation, Assessment, Development and Evaluation; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; HOPE-3, Heart Outcomes Prevention Evaluation-3; HOT, Hypertension Optimal Treatment; HYVET, Hypertension in the Very Elderly Trial; IDACO, International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome.; IDNT, Irbesartan diabetic nephropathy trial; INTERACT-2, Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial; INVEST, INternational Verapamil SR TRandolapril STudy; ISO, International Organization for Standardization; LEGEND, Large-scale Evidence Generation and Evaluation across a Network of Databases; LIFE, Losartan Intervention For Endpoint reduction in hypertension; MATCH, Is Metomidate PET-CT superior to Adrenal vein sampling in predicting ouTCome from adrenalectomy in patients with primary Hyperaldosteronism; MDRD, Modification of diet in renal disease; MODERATO I, Moderato System in Patients With Hypertension I; MODERATO II, Moderato System in Patients With Hypertension II; NORDIL, Nordic Diltiazem; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; OSCAR, The OlmeSartan and Calcium Antagonists Randomized study; PAMELA, Pressioni Arteriose Monitorate e Loro Associazioni; PATHWAY-1, Optimum Treatment for Drug-Resistant Hypertension -1; PATHWAY-2, Optimum Treatment for Drug-Resistant Hypertension -2; PATS, Post-stroke Antihypertensive Treatment Study; PEACE, Prevention of Events with Angiotensin Converting Enzyme Inhibition; PHYLLIS, Plaque Hypertension Lipid Lowering Italian Study; PRAISE, Prospective Randomized Amlodipine Survival Evaluation study; PREDIVA, Prevention of dementia by intensive vascular care; PROGRESS, perindopril protection against recurrent stroke study; PROSIT, Project on Stroke Services in Italy; RADIANCE HTN SOLO, A Study of the ReCor Medical Paradise System in Clinical Hypertension – SOLO; RADIANCE HTN-TRIO, A Study of the ReCor Medical Paradise System in Clinical Hypertension -TRIO; RE-HOT, Resistant Hypertension Optimal Treatment; RENAAL, Reduction of endpoints in NIDDM with angiotensin II antagonist losartan; REQUIRE, Renal Denervation on Quality of 24-hr BP Control by Ultrasound In Resistant Hypertension; ROX CONTROL HTN, ROX Coupler in Patients With Resistant Hypertension study; SCOPE, Study on Cognition and Prognosis in the Elderly; SCORE-2, Systemic coronary risk evaluation; SCORE-2-OP, Systemic coronary risk evaluation – Older Persons; SHEP, Systolic Hypertension in the Elderly Program; SOS, Swedish obese individual study; SPRINT, Systolic Blood Pressure Intervention Trial; SPRINT-MIND, Systolic Blood Pressure Intervention Trial – Memory and Cognition in Decreased Hypertension; SPYRAL HTN Off Med, catheter-based renal denervation

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in the absence of antihypertensive medications, multicentre, randomised, sham-controlled trial; SPYRAL HTN – On Med, catheter-based renal denervation in the presence of antihypertensive medications, multicentre, randomised, sham-controlled trial; SSa, Subsaharian Africa; STOP-1, Swedish Trial in Old Patients-1; STOP-2, Swedish Trial in Old Patients-2; STRIDE BP, Science and Technology for Regional Innovation and Development in Europe – Blood Pressure; SYMPLICITY-3 HTN, Renal Denervation in Patients With Uncontrolled Hypertension trial; SYST-CHINA, Systolic Hypertension in China; SYST-EUR, Systolic Hypertension in Europe; TAIM, Trial on antihypertensive intervention and management; TIME, Treatment in Morning vs Evening study; TOMHS, Treatment of Mild Hypertension Study; TONE, Trial on nonpharmacological intervention in the elderly; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; TOPH, Trials of Hypertension Prevention; TRANSCEND, Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; UKPDS, United Kingdom prospective diabetes study; VALISH, Valsartan in elderly isolated systolic hypertension study; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation; WHL, World Heart Federation; WHO, World Health Organization

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INTRODUCTION

The year 2023 marks the 20th anniversary of the hypertension guidelines of the European Society of Hypertension (ESH), which were published for the first time in 2003, following a proposal by Professor Alberto Zanchetti (Fig. 1). Professor Zanchetti thought that it was time for Europe to express its view on diagnostic and treatment aspects of this crucially important medical condition rather than referring, as in the past, to guidelines issued by the WHO, with or without the ISH or the scientific societies in the USA. He played a fundamental role in these first guidelines [1] as coordinator of the Writing Committee appointed by the ESH, and this was rewarded by an unexpected large success, which made these guidelines the fifth most widely quoted paper in the world across all research areas and the most quoted in the medical area. ESH offered to share these hypertension guidelines with the European Society of Cardiology (ESC), which accepted after the manuscript had already been completed, without sharing its publication in the ESC Society Journal. Subsequently, the ESH and the ESC enjoyed an equal collaboration, resulting in three further successful and also widely quoted guidelines in 2007 [2], 2013 [3] and 2018 [4] that were published in the official journals of the two Societies, except for a 2009 reappraisal of the 2007 guidelines, which was prompted by new evidence in the hypertension area and prepared only by the ESH [5].

These 2023 hypertension guidelines have also been prepared only by the ESH. The rules of these guidelines, however, are largely, although not entirely, the same as those that were followed in the previous guidelines. That is, in the 2023 guidelines: (i) the members of the Task Force have been appointed by the ESH, based on recognized scientific and clinical expertise in one or more areas covered by the guidelines as well as on the documented absence of relevant conflicts of interest; (ii) selected members were initially asked to write a section or sections of the guidelines related to her or his main scientific expertise, and a small Steering Committee was appointed to harmonize the material received; (iii) multiple revisions of the text were made by back and forth interactions between the Task Force members, with a final collective critical review of the text and (iv) the final manuscript has been sent to external reviewers and further revised according to their suggestions and criticism. Particular attention has been given to the scoring of the strength of the diagnostic and treatment recommendations, which have been graded according to criteria partly different from those used in previous guidelines, i.e. with consideration for the study design but also for the quality of the collected data (Section 1). Because of the questionable scientific value of voting, disagreements on treatment recommendations have not been resolved that way but by consensus on a shared text. Conflicting evidence or interpretation of the data have been openly admitted.

The similarity of the present and past guidelines extends to the scientific principles on which the guidelines have been based. The 2023 guidelines have been developed after careful search for new studies in the hypertension and related areas. Furthermore, as in the past, RCTs have been assigned a top value while also mentioning their limits when appropriate. However, all other relevant sources of knowledge (from observational studies down to clinical case series) have been considered, and even mechanistic studies have not been ignored, given their relevance for diagnostic and treatment decisions in individual groups of patients. Particular attention has been given to real-world studies, which play a growing role in hypertension research and sometimes provide knowledge in areas that cannot be addressed by RCTs. Like the



FIGURE 1 Alberto Zanchetti.

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previous guidelines, the 2023 guidelines (i) regard their value as educational, which explains why the text addresses the data justifying the recommendations and (ii) emphasize that their recommendations are not invariably prescriptive for individual patients because they are based on average data and address conditions or diseases in general. In individual patients, the most appropriate diagnostic and treatment decisions may differ from those expressed by the guidelines.

The 2023 guidelines (i) contain several conceptual elements of novelty originated by research performed after the 2018 guidelines; (ii) deal more in depth with topics that were only briefly considered in the past and (iii) extend to several conditions that were previously unaddressed by guidelines, although frequently coexisting with hypertension and leading to specific needs for medical management. Although mainly referring to hypertension in adults, they include for the first time essential recommendations on hypertension in children, adolescents and the transition to young hypertensive adult individuals; and (iv) include a detailed index of sections and subsections focused on specific issues that has been prepared to facilitate reading of these various and multiple aspects. Furthermore, while the text addresses the sometimes nonunivocal evidence provided by research on a given issue, each section offers, as is now usual for many guidelines, a simple final list of key statements and recommendations that translate research achievements into practical use. We hope that this structure will make the ESH guidelines useful not only to the practicing physicians but also to hypertension experts and investigators.

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WHAT IS NEW AND WHAT HAS CHANGED IN THE 2023 EUROPEAN SOCIETY OF HYPERTENSION ARTERIAL HYPERTENSION GUIDELINES?

1. Modified and simplified criteria for evidence grading recommendations
2. Pathophysiological background of primary hypertension
3. Clinical BP measurements by different methods and in different settings and clinical conditions
4. Thorough description of office, ambulatory and home BP measurements and value in different demographic and clinical conditions
5. Upgrading of out-of-office BP measurements in hypertension management
6. New HMOD measurements and their clinical value in hypertension work-up
7. New CV risk factors and update on CV risk assessment
8. Update and comprehensive summary of secondary forms of hypertension
9. Update on lifestyle interventions
10. Update on threshold and targets for antihypertensive drug treatment, including their possible heterogeneity in demographic and clinical subgroups of patients
11. Confirmation of preferred use of RAS blockers, CCBs and Thiazide/Thiazide-like diuretics, and their various combinations for BP-lowering treatment. Inclusion of BBs among the major antihypertensive drugs
12. Update on available combination-based drug treatment strategies, including the quadpill and the polypill
13. Emphasis and update on the diagnosis and management of true-resistant hypertension
14. Update on use and position of renal denervation for antihypertensive treatment
15. Impact of hypertension and its treatment on cognitive dysfunction and dementia
16. Management of hypertension in older people according to the frailty and functional level
17. Update on treatment of hypertension in HFrEF and HFpEF
18. New diagnostic approaches to diagnosis and treatment in hypertensive patients with AF
19. Update on treatment in CKD, including kidney transplantation
20. Update and novel treatment approaches to patients with type 2 diabetes
21. Epidemiology, diagnosis and treatment in different BP phenotypes
22. Diagnosis, treatment and follow-up of hypertension in demographic and clinical conditions not or only marginally addressed in previous guidelines:
    a. Children/adolescents and transition to adulthood
    b. Young patients
    c. Sex-related differences
    d. Pregnancy and puerperium
    e. Peripheral artery disease
    f. Aortic aneurism
    g. Valvular heart disease
    h. Treatment of hypertension in acute cerebrovascular diseases
    i. Hypertensive emergencies/urgencies
    j. Perioperative hypertension
    k. Obesity
    l. COVID-19
    m. Chronic inflammatory diseases
    n. Hypertension in oncology
    o. Baroreflex failure and dysautonomia
    p. Glaucoma

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23. Detailed recommendations on patients' follow-up strategies, including assessment and minimization of nonadherence and clinical inertia.
24. Mention of new potential approaches to the treatment of hypertension and containment of hypertension-related workload (tele-health, team-based treatment, role of pharmacists)

1. METHODOLOGY AND DEFINITION OF EVIDENCE

1.1 Methodology of evidence grading

The 2023 ESH guidelines aim to summarize the best available evidence for all aspects of hypertension management. The guidelines were developed by a Task Force of 59 experts form European countries, representing the areas of internal medicine, cardiology, nephrology, endocrinology, general medicine, geriatrics, pharmacology and epidemiology. Each topic was assigned to a small group of Task Force members responsible for reviewing and summarizing the available evidence within that topic. The 'class of recommendation' (CoR) and 'level of evidence' (LoE) for all recommendations were reviewed by an Evidence Grading Committee to make sure that they complied with the predefined criteria outlined in the following. Draft versions were reviewed by the Steering Committee, Task Force members and external reviewers. The final version was approved by all Task Force members.

In accordance with previous versions of the ESH guidelines, a similar system separating CoR and LoE was applied [3,4]. CoR indicates how strong a recommendation is, considering the assumed benefit versus risks and costs on a scale from I to III. Recommendation classes I and III each convey a clear message, namely a general consensus that a measure is either useful (CoR I) or not useful or even harmful (CoR III). If there is no general consensus or only doubtful evidence, an optional recommendation is conveyed with CoR II. In contrast to previous guidelines [3,4], these guidelines find that a further subdivision of the CoR II into two subclasses (IIa and IIb) adds little value and, for the sake of simplification and for conveying a clearer message, and did not use this subdivision. The LoE indicates how reliable the evidence underlying each recommendation is on a scale from A to C (Fig. 2). Importantly, the CoR and LoE are independent of each other, e.g. strong recommendations may build on weak evidence if the assumed benefit of an intervention or a diagnostic procedure greatly outweighs the potential risks.

1.2 Level of evidence

The 2023 ESH guidelines employ the same terminology as in the 2018 ESC/ESH guidelines but with updated criteria for assessing the LoE. This revision was influenced primarily by the recommendations from the GRADE working group [6,7], but also by the most recent evidence definition used by the AHA/ACC [7].

Class of Recommendation		Level of Evidence		
	Definition		Definition	Interpretation
I	Evidence or general agreement that a treatment/test/procedure is beneficial, useful or effective AND that potential benefits clearly outweigh potential risk	A	- RCT or meta-analysis of RCTs with CVD outcomes - Single trial enough if sufficient power and without important limitations[a]	Strong evidence. Evidence of high certainty. Unlikely that future studies will change the effect estimate substantially
II	Conflicting evidence oropinion about the benefit, usefulness and effectiveness of a treatment/ test/procedure OR uncertainty about benefit-risk balance	B	- RCT with surrogate measures (BP, HMOD) - Observational studies with CVD outcomes and no major limitations[a] - Meta-analyses including the above study types	Moderate evidence. Evidence with some Future studies may modify, at least the magnitude of, the effect estimate
III	Evidence or general agreement that a treatment/test/procedure is not beneficial, useful or effective OR that potential risks outweigh the potential benefit	C	- Observational studies of surrogate measures - Any study type may be downgraded to level C due to limitations[a] - Expert opinion (EO)	Weak evidence. Evidence of low certainty. Future studies may change the effect estimate substantially

FIGURE 2 Class of recommendation (CoR) and level of evidence (LoE). BP, blood pressure, CVD, cardiovascular disease, HMOD, hypertension mediated organ damage, RCT, randomized controlled trial. [a]Limitations affecting level of evidence include (but may not be limited to) high risk of bias, inability to account for important confounding factors in observational studies, questionable external validity and uncertain effect estimates (confidence intervals including negligible effect).

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The most important difference compared with the previous guidelines is the priority given to patient-important CV outcomes, such as stroke, MI, HF, ESKD and CV or total mortality, acknowledging that the primary aim of antihypertensive treatment is to reduce the risk of clinical outcomes and not only BP. Although BP reduction is strongly associated with a reduction in clinical events, interventions affecting BP may also affect other physiological systems with beneficial or harmful effects, and the benefit/harm ratio cannot be firmly established without clinical outcome trials.

Furthermore, risk of bias and statistical precision were considered when assigning the LoE. This means that recommendations supported by well conducted RCTs with CV outcomes were assigned LoE A, whereas recommendations supported by trials with a similar design and with similar outcomes, were downgraded to LoE B or C if the risk of bias was judged as high, or if effect estimates were imprecise. Meta-analyses may contribute to any level of evidence depending on the type of studies included and the quality of the meta-analysis itself [8].

For diagnostic tests and procedures, we have adopted the strategy recommended by the GRADE working group, assessing the evidence for benefit on patient-important outcomes [9]. Many diagnostic procedures rely on studies of accuracy rather than effect on outcomes, and recommendations building on such evidence is generally downgraded for indirectness even if the studies themselves are without important limitations.

2. PRINCIPLES OF HYPERTENSION PATHOPHYSIOLOGY

Hypertension is divided into a primary (formerly and still also currently referred to as 'essential') and secondary forms. Secondary hypertension originates from specific causes and can be detected in only a small fraction of hypertensive patients (see Section 6). Primary hypertension covers the remaining large fraction of the hypertensive population, and its origin depends on the complex interaction between a genetic background, a large number of environmental factors [10–12] and the aging process. Both genetic and environmental factors operate through alterations of CV regulatory systems, leading to an increase of systemic vascular resistance, which is the hallmark hemodynamic abnormality responsible for BP elevation in almost all hypertensive patients [13]. In the last few years, important new evidence has been obtained on the genetic background of hypertension, with more than 1000 genetic factors being identified [11,12], together with, in some instances, the biochemical and pathophysiological paths they work through [14]. New environmental factors (e.g. air pollution and noise) have been added to those already documented by older research [15–17]. Furthermore, new experimental and clinical studies have confirmed that alterations of several major CV control systems may contribute to chronic BP elevation. As shown in Fig. 3, primary hypertension may be accompanied by alterations of the renin–angiotensin–aldosterone system, central and peripheral autonomic cardiac and vascular regulation, the endothelin system and other systems controlling vascular function, including nitric oxide and natriuretic peptides [13,18,19–22]. More recently, pressogenic effects (increased sodium sensitivity) of gut microbial dysbiosis have also been reported [23,24]. In addition, the immune system is likely to play a pathophysiologic role, with effects that are possibly primarily mediated by inflammation, and involve not only BP regulation (and thus development of hypertension) but also the initiation and progression of HMOD [25,26]. There is extensive experimental and clinical evidence that hypertension is associated with inflammation and immune cell

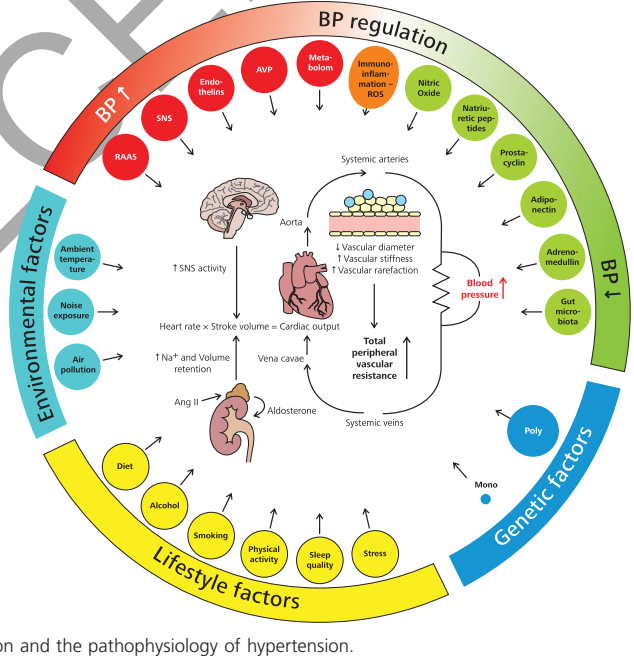


FIGURE 3 Mechanisms involved in BP reguation and the pathophysiology of hypertension.

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activation, two processes that are driven in large part by oxidative stress. Immune cell activation is characterized by excessive production of reactive oxygen species and an altered oxidation–reduction (redox) state [26], and there is evidence that generation of reactive oxygen species is influenced by factors involved in BP regulation, such as Ang II, endothelin-1 (ET-1), aldosterone and salt (sodium) [26]. Furthermore, evidence is also available that alterations of immunoinflammation is promoted by the above-mentioned hypertension promoters such as genetic susceptibility, neurohumoral activation, salt influences and gut microbiome [10–13,18–22,27]. Although this complex interplay makes it impossible to know whether inflammation is causatively related to hypertension or represents a secondary effect of a chronic BP elevation, it is clear that inflammation and the dysregulated immune system are closely linked to each other and that immunoinflammation is involved in hypertension [25,26]. Indeed, the suggestion has been made that oxidative stress and increased generation of reactive oxygen species represent the common molecular basis linking immunoinflammation to hypertension. Alterations in metabolomic pathways, e.g. glucose and lipid metabolism, may also contribute, as exemplified by the sympathostimulating effect of insulin [13,28] and the favoring effect of sympathostimulation on insulin resistance [29]. Regardless of the mechanisms involved, a chronic BP elevation is known to modify the cardiac (e.g. LVH), large artery (increase in collagen and stiffening of the arterial wall) and small artery (increase in wall-to-lumen ratio) structure, which in a later hypertension phase promote the BP increase on a nonspecific anatomical basis [13]. This confirms and expands the former mosaic theory on the pathogenesis of primary hypertension as a multifactorial phenotype, which was already formulated by Page [30] in the pioneer phase of hypertension research more than 70 years ago. To the original theory, modern research has added not only new mechanisms but also, as shown in Fig. 3, strong evidence for the existence of reciprocal influences between different CV control systems, as a result of which alteration of one system may favor or reinforce alterations of the other systems and vice versa [31]. At a practical level, this multimechanistic interactive pathophysiology implies that diagnostic attempts to identify a single responsible mechanism for primary hypertension can often be not only methodologically difficult but also futile. It also explains why an elevated BP can be lowered by drugs with different mechanisms of action as well as why a combination of mechanistically different drugs lowers BP much more effectively than monotherapy.

CENT DRAFT

3. DEFINITION OF HYPERTENSION AND BP CLASSIFICATION

3.1 Definition of hypertension

According to the previous 2018 European and current international guidelines [32–34], hypertension is defined based on repeated office SBP values ≥140 mmHg and/or DBP ≥90 mmHg. However, there is a continuous relationship between BP and CV or renal morbid or fatal events starting from an office SBP >115 mmHg and a DBP >75 mmHg [35]. Therefore, this definition is arbitrary and has mainly the pragmatic purpose of simplifying the diagnosis and decision on hypertension management. In this context, the above office threshold BP values correspond to the level of BP at which the benefits of intervention (lifestyle interventions or drug treatment) exceed those of inaction, as shown by outcome-based RCTs. Based on available evidence [36] the definition of hypertension remains unchanged from the previous guidelines [4].

3.2 Classification of hypertension

The classification of office BP and definition of hypertension grades also remain the same from previous guidelines (Table 1).

In addition to grades of hypertension, which are based on BP values, we also distinguish stages of hypertension as

TABLE 1. Classification of office BP and definitions of hypertension grades

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and	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[a]	≥140	and	<90
Isolated diastolic hypertension[a]	<140	and	≥90

The BP category is defined by the highest level of BP, whether systolic or diastolic.
[a]Isolated systolic or diastolic hypertension is graded 1, 2 or 3 according to SBP and DBP values in the ranges indicated. The same classification is used for adolescents ≥16 years old (Section 15.1).

follows:

Stage 1: Uncomplicated hypertension (i.e. without HMOD or established CVD, including CKD stage 1 and 2).
Stage 2: Presence of HMOD or CKD grade 3 or diabetes.
Stage 3: Established CVD or CKD stages 4 or 5.

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Definition of BP categories, hypertension grades and stages according to office BP

Recommendations and statements	CoR	LoE
It is recommended that BP is classified as optimal, normal, high normal, or grade 1, 2 or 3 hypertension, according to office BP.	I	C
In addition to grades of hypertension, which are based on BP values, it is recommended to distinguish stage 1, 2, and 3 hypertension. Stage 1: Uncomplicated hypertension without HMOD, diabetes, CVD and without CKD ≥ stage 3 Stage 2: Presence of HMOD, diabetes, or CKD stage 3 Stage 3: Presence of CVD or CKD stage 4 or 5	I	C

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3.3 Prevalence of hypertension

Hypertension is the most prevalent CV disorder in the world and according to the WHO, it affects 1.28 billion adults aged 30–79 years worldwide, two-thirds living in low-income and middle-income countries. In 2019, the global age-standardized average prevalence of hypertension in adults aged 30–79 years was reported to be 34% in men and 32% in women [37]. In European countries, the prevalence is similar, with between-country differences and values lower than average in Western and above average in Eastern European countries [37]. At younger ages (<50 years), hypertension is more prevalent in men, whereas a steeper increase of SBP in women from their third decade (and more so following menopause) makes the prevalence of hypertension greater in women in older age categories (>65 years) [38,39]. SBP increases progressively with age while DBP rises only until the age of 50–60 years, followed by a short period of stagnation and a subsequent mild decrease [40]. This results in an increase of pulse pressure (difference between SBP and DBP) with age [38].

3.4 BP relationship with risk of cerebral, cardiovascular and kidney events

There is a continuous relationship between the increase in BP and the risk of stroke, CAD, HF and development and progression of CKD. This applies to all ages and ethnic groups [41]. In 2002, the Prospective Studies Collaboration Group found that, for each 20 mmHg elevation of office SBP or 10 mmHg elevation of office DBP, the risk for fatal CAD or stroke doubled [35]. SBP is a better predictor of events than DBP after the age of 50 years. In addition to previous studies suggesting that elevated DBP is associated with increased risk in young individuals [42], more recent studies indicate increased risk of CV events for both SBP and DBP elevations in younger adults [43] (Section 15.2). By reflecting an increase of arterial stiffness, increased pulse pressure was found to be associated with an adverse prognostic impact, additional to that associated with SBP elevation in middle-aged and older people [44,45].

3.5 Hypertension and total CV risk assessment

Hypertension is often associated with other risk factors, including dyslipidemia, impaired glucose tolerance and type 2 diabetes, which further increase of CV risk [46,47]. The large number of factors influencing CV risk in patients with hypertension (environmental, lifestyle and clinical CV risk factors plus HMOD and established CVD or CKD categories) are listed in Table 2. Special risk factors apply to women, e.g. hypertension disorders in pregnancy and early-onset menopause [48,49]. HMOD is an important intermediate stage in the CVD continuum between CV risk factors and clinically manifest CVD or advanced CKD stages 4 and 5. HMOD is an important determinant of overall CV risk [1], which is usually high in the presence of HMOD [4]. Diabetes mellitus is listed (Fig. 4) as a separate condition that impacts on CV risk, regardless of the concomitance of HMOD, CVD or CKD. Only diabetic patients with well controlled, short-standing duration of the disease (less than 10 years), no evidence of HMOD and no additional CV risk factors are categorized as at moderate risk [33].

Estimation of total CV risk is recommended in each hypertensive patient because of its relevance for hypertension management. Computerized methods have been developed for estimating total CV risk, i.e. the likelihood of developing a CV event, usually within the following 10 years. Many risk stratification systems are based on the Framingham study, estimating the 10-year risk for both fatal and nonfatal CAD by SBP and the presence of other risk factors [50]. The Framingham risk stratification is applicable to some European populations [51], but this requires re-calibration [52,53], due to geographic differences in the incidence of coronary and stroke events between the European and US populations. Because of these limitations, the SCORE (Systemic Coronary Risk Evaluation) method, based on a large European database, has been

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TABLE 2. Factors that influence CV risk in patients with hypertension

Parameter for risk stratification, which are included in SCORE2 and SCORE2-OP
Sex (men >women)
Age
Level of SBP[a]
Smoking – current or past history
Non-HDL cholesterol
Established and suggested novel risk factors
Family or parental history of early onset hypertension
Personal history of malignant hypertension
Family history of premature CVD (men aged <55 years; women aged <65 years)
Heart rate (resting values >80 bpm)
Low birth weight
Sedentary lifestyle
Overweight or Obesity
Diabetes
Uric acid
Lp(a)
Adverse outcomes of pregnancy (recurrent pregnancy loss, preterm delivery, hypertensive disorders, gestational diabetes)
Early-onset menopause
Frailty
Psychosocial and socioeconomic factors
Migration
Environmental exposure to air pollution or noise
Additional clinical conditions or comorbidities
Resistant hypertension
Sleep disorders (including OSA)
COPD
Gout
Chronic inflammatory diseases
Nonalcoholic fatty liver disease (NASH)
Chronic infections (including long COVID-19)
Migraine
Depressive syndromes
Erectile dysfunction
Hypertension-mediated organ damage (HMOD)
Increased large artery stiffness:
Pulse pressure (in older people) ≥60 mmHg
Carotid–femoral PWV >10 m/s (if available)
ECG LVH (Sokolow–Lyon index >35 mm, or R in aVL ≥11 mm; Cornell voltage-duration product (+6 mm in women) >2440 mm∗ms, or Cornell voltage >28 mm in men or >20 mm in women)
Echocardiographic LVH (LV mass index: men >50 g/m$^{2.7}$; women >47 g/m$^{2.7}$ (m = height in meters);
Indexation for BSA may be used in normal-weight patients: >115 g/m^2 in men and >95/m^2 in women
Moderate increase of albuminuria 30–300 mg/24 h or elevated ACR (preferably in morning spot urine) 30–300 mg/g
CKD stage 3 with eGFR 30–59 ml/min/1.73 m^2
Ankle–brachial index <0.9
Advanced retinopathy: hemorrhages or exudates, papilloedema
Established cardiovascular and kidney disease
Cerebrovascular disease: ischemic stroke, cerebral hemorrhage, TIA
Coronary artery disease: myocardial infarction, angina, myocardial revascularization
Presence of atheromatous plaque on imaging
Heart failure, including heart failure with preserved ejection fraction
Peripheral artery disease
Atrial fibrillation
Severe albuminuria > 300 mg/24 h or ACR (preferably in morning urine) >300 mg/g
CKD stage 4 and 5, eGFR < 30 mL/min/1.73m^2

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LV, left ventricle; OSA, obstructive sleep apnea.
[a]DBP is not included in the SCORE2/SCORE2-OP tool to estimate CV risk.

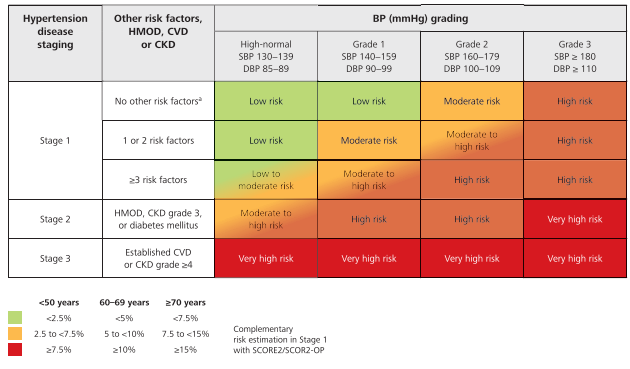


FIGURE 4 Cardiovascular risk according to grade and stage of hypertension.

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developed [54]. SCORE charts estimate the risk of death from CV (not only coronary) disease over 10 years in either high-risk and low-risk European countries [54] and modified charts can, thus, be used for individual countries. The 2021 European Guidelines on CVD prevention made use of SCORE2, which is an updated version of the original SCORE that estimates an individual's 10-year risk of fatal and nonfatal CV events in apparently healthy individuals aged 40–69 years with risk factors that are untreated or have been stable for several years [55]. For older people (age 70–89 years), a corresponding SCORE2-OP algorithm for older people is available [56]. SCORE2 and SCORE2-OP are calibrated for four clusters of countries (low, moderate, high, and very high CV risk) that are grouped according to national CV mortality rates published by the WHO.

Estimating a person's 10-year CV risk by SCORE2 and SCORE2-OP is done by first selecting the correct country group and its corresponding risk stratification table [33]. Within the table, the risk is estimated based on sex, age, level of SBP, smoking status, and non-HDL cholesterol level (total cholesterol – HDL cholesterol, Table 2). DBP is not included in the SCORE2/SCORE2-OP tool, which is a weakness. Overall risk should be stratified in all patients as shown in Fig. 4. Risk stratification is particularly important in individuals with a high-normal BP or grade 1 hypertension, in whom it may influence the decision of whether or how fast to initiate BP-lowering drug treatment. In patients with grade 2 and 3 hypertension, drug treatment should be used regardless of the CV risk level, but risk stratification is nevertheless important for several treatment aspects and follow-up strategies. The disadvantage of this and other approaches to CV risk quantification is that the estimated risk is usually low in younger adults, particularly in young women who may be stratified as being at low risk even if they have more than one risk factor. Indeed the SCORE2 system does not even provide risk estimations for adult women and men younger than 40 years. By contrast, most older men are considered at high risk, despite being at little increased risk relative to their peers. For young adults, it may be more useful to estimate lifetime risk of CVD and potential CVD-free life-years gained through risk factor optimization [57]. In addition, methods for total CV risk stratification usually underestimate the primary importance of asymptomatic HMOD for the CV risk quantification. In hypertensive patients, HMOD usually indicates a high risk regardless of the organ where the damage is located, and its assessment is, therefore, important for management, particularly in patients who – according to age and general risk stratification – are at apparently low risk [1] (see Section 5).

Risk assessment in hypertension with SCORE2 and SCORE2-OP

CV risk assessment with the SCORE2 and SCOR2-OP system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD or CKD, long-lasting or complicated diabetes, severe HMOD (e.g. LVH) or a markedly elevated single risk factor (e.g. cholesterol, albuminuria).	I	B

3.6 Screening versus case finding in the detection of hypertension

Because of the high prevalence of hypertension in the general population and its major role as cause of death and morbidity, its detection is crucially important for public health. Studies performed in different countries have almost universally shown that a considerable fraction of hypertensive individuals is unaware of their condition, with an adverse reflection on the number of patients undergoing treatment and achieving BP control [37]. There is evidence that screening policies can substantially increase the number of individuals in whom hypertension is although data on outcome benefit and harm from randomized controlled trials or observational studies at low risk of bias are lacking [58]. However, participation in the screening procedures may be less in some categories (e.g. men, younger individuals, people with lower socioeconomic backgrounds) than in others [59]. In the USA, the US Preventive Services Task Force suggests screening for hypertension in adults aged 18 years or older [60]. Despite limited evidence on the optimal frequency of screening, they recommend yearly screening in adults ≥40 years old and in those at increased risk for developing hypertension such as blacks, individuals with high-normal BP and people who are overweight or obese [60]. Opportunistic BP measurements are now also encouraged in several countries [59] and have been recently supported in USA by the increased detection, treatment and control of hypertension associated with BP measurements in barber shops or by pharmacists [61]. Based on the available evidence, we recommend opportunistic screening for hypertension in all adults (i.e. ≥18 years old). Regular BP measurements is particularly important in adults from the age of 40 years and in adults at increased risk for hypertension (special ethnic groups, individuals with high-normal BP, overweight or obesity). Attention should be paid to postmenopausal women and women with a history of gestational hypertension and preeclampsia. BP should always be part of any medical visit even in individuals below 18 years of age.

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Screening for hypertension

Recommendations and statements	CoR	LoR
Case finding or opportunistic screening for hypertension is recommended in all adults.	I	C
Regular BP measurements are recommended in adults from the age of 40 years or earlier in patients at high-risk.	I	C
In individuals without hypertension, intervals for repeated BP measurement should be scheduled depending on the BP level, the risk of hypertension and CV risk. In patients with high risk, annual follow-up is recommended.	I	C

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3.7 Confirming the diagnosis of hypertension

Because of the variability of BP, an elevation of office BP (SBP ≥140 mmHg or DBP ≥90 mmHg) should be confirmed by at least two to three visits, unless the BP values recorded during the first visit are markedly elevated (grade 3 hypertension) or CV risk is high, including the presence of HMOD. Although available evidence has some diagnostic limitations and in clinical practice, collecting ABPM or HBPM data on a large scale may be difficult, out-of-office BP measurements are a source of important clinical information. Therefore, ABPM, HBPM or data should be collected whenever feasible when office BP is elevated, to confirm the diagnosis of hypertension and identify specific BP phenotypes. ABPM and/or HBPM can be especially important when office BP data visit provide variable results. These issues are addressed in detail Section 4.

4. BP MEASUREMENT AND MONITORING

4.1 Devices for blood pressure measurement

4.1.1 Standard cuff-based devices

The accurate determination of BP is the cornerstone for the diagnosis and management of hypertension [62]. Intra-arterial BP measurement is the only method, which provides true arterial BP values, but its invasive nature prevents any wide clinical use. Furthermore, a noninvasive device that provides finger beat-to-beat BP values close to intra-arterial values has been available for many years, but its use has remained largely confined to research [63–65], except for its helpful diagnostic information in people with autonomic failure or orthostatic hypotension. Thus, for clinical purposes, BP measurement almost entirely relies on indirect noninvasive methods, originally described more than a century ago, that are based on a pneumatic cuff for occluding the brachial artery, the radial artery pulse assessment or a stethoscope for detecting the Korotkoff sounds [66,67]. With some theoretical and practical improvements, these methods are still almost universally used today, and their adoption in clinical trials has laid the basis of diagnostic and treatment recommendations. The different types of noninvasive cuff BP measuring devices available on the market are shown in Table 3.

TABLE 3. Noninvasive arm cuff BP measuring devices[a]

Manual auscultatory devices	Automated electronic devices
• Mercury sphygmomanometer • Aneroid sphygmomanometer • Hybrid device (LED or LCD display, or digital countdown)	• Automated oscillometric (also wrist cuff devices) • Automated auscultatory • Semiautomated (manual inflation)

[a]Cuffless BP devices are currently not recommended for clinical use.

The manual auscultatory BP measurement using a mercury or mercury-free sphygmomanometer is still the gold standard method for validation studies testing the accuracy of novel BP measurement technology [62]. However, due to environmental issues related to mercury toxicity, mercury devices have been banned from clinical use [66]. Hybrid manual auscultatory devices (LED or LCD display, or digital countdown), or good-quality (shock resistant) aneroid devices can be used, although they are subject to observer-related errors, such as terminal digit preference, observer prejudice and bias [62]. The automated cuff-based BP measurement method (mostly oscillometric) has been developed to avoid the observer-related errors of the manual auscultatory method [62]. This method is currently the one used for ABPM and self-home monitoring devices used for HBPM and is the preferred method for OBPM as well [62]. When BP cannot be measured by an upper arm cuff device, a validated electronic wrist-cuff device may be used [62].

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4.1.2 Cuffless blood pressure measuring devices

All cuff BP measurement methods have limitations, mainly because they provide snapshot BP values in static conditions and ignore the dynamic nature of BP, i.e. its variability in response to different daily challenges and activities [68,69]. Moreover, errors due to inadequate cuff size, shape and positioning are common, and the limb compression during cuff inflation may cause discomfort, particularly at work and during sleep [68,70]. Novel cuffless BP measuring devices, which use sensors, signal processing, machine learning and other technologies embedded in wearable devices, smartphones, pocket devices or other types of devices are already available on the market [68,71] and have considerable potential to improve awareness, diagnosis and treatment of hypertension. However, there are several issues that need to be adequately addressed before these devices can be recommended for clinical use [68,71]. A major concern is that the AAMI/ESH/ISO Universal Standard protocols [68,72], which are used for validating cuff BP devices, are inadequate for cuffless devices which means that their accuracy remains unproven. Furthermore, there is still no agreed standard of performance for these novel technologies [68]. Finally, most cuffless BP devices require periodic calibration using BP values measured by a standard arm cuff device. Some of them also require information on the user such as age, sex and other characteristics [73]. Basically, these devices do not 'measure' BP but track BP changes compared to the calibration BP or attempt to predict BP using demographics and machine learning technology [68,74]. For these reasons, at the present time, cuffless BP devices should not be used for the diagnosis or management of hypertension in clinical practice [68].

4.1.3 Validation of blood pressure measuring devices

In the last 30 years, several scientific societies and associations have developed validation protocols for the evaluation of the accuracy of BP measuring devices [75], the most widely used one being the ESH International Protocol validation [76]. In 2018, a Universal Standard for global use was agreed by the US Association for the Advancement of Medical Instrumentation (AAMI), the ESH and the International Organization for Standardization (ISO) [72]. It should be noted that an electronic BP monitor, which is accurate in adults, may not be accurate in some special populations, e.g. in children or pregnant women, which means that under these circumstances, a separate validation process and dedicated devices for these conditions are required for BP monitoring [72].

Unfortunately, validation for accuracy is not mandatory prior to the distribution of BP devices in the market [75,77]. Thus, established protocols have been used and published in fewer than 10% of BP devices [62,78]. Healthcare professionals, patients and the public, should check for lists of accurate devices, which are available on the internet [62]. STRIDE BP (www.stridebp.org) an international organization endorsed by the ESH, the International Society of Hypertension (ISH) and the World Hypertension League (WHL), presents updated lists of validated BP monitors for office, home and ambulatory BP measurement in adults, children and pregnant women in English, Spanish and Chinese. Other national online sources for validated BP monitors are those by the British & Irish Hypertension Society (https://bihsoc.org/bp-monitors/), the German League of Hypertension (www.hochdruckliga.de/betroffene/blutdruckmessgeraete-mit-pruefsiegel), the American Medical Association (www.validatebp.org), the Hypertension Canada (www.hypertension.ca/bpdevices) and the Japanese Society of Hypertension (www.jpnsh.jp/com_ac_wg1.html) [62].

Periodic calibration is necessary, particularly for aneroid devices, whereas for electronic devices, the performance of the BP measurement algorithm is not affected by use, and what is mainly needed is maintenance of the device parts (e.g. cuffs, tubes or connections). Checking for maintenance is advisable once a year for professional office and ambulatory BP devices and less frequently for home devices [72,79].

Devices for BP measurement

Recommendations and statements	CoR	LoR
Automatic electronic, upper-arm cuff devices are recommended for office and out-of-office BP measurement (home and ambulatory).	I	B
Hybrid manual auscultatory devices with LCD or LED display, or digital countdown, or shock-resistant aneroid devices can be used for office BP measurement if automated devices are not available.	I	B
Only properly validated devices should be used. www.stridebp.org	I	B
Cuffless BP devices should not be used for the evaluation or management of hypertension in clinical practice.	III	C

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4.2 Standard office blood pressure measurement

Conventional or standard OBPM is the most well studied method for assessing BP and the one by which the diagnosis of hypertension, BP classification, the role of BP as a CV risk factor, the protective effect of antihypertensive treatment and the BP thresholds and targets of therapeutic interventions have been established [4,62,80]. Despite several limitations, and the increasing use of out-of-office BP measurements, OBPM remains the most widely used method for hypertension diagnosis and management [4,62,81].

Despite its widespread long time adoption, use of OBPM is often poorly standardized, leading to inaccurate BP estimations, which often consists of an overestimation of BP and overdiagnosis and overtreatment of hypertension [4,62,81]. A systematic review of 328 articles identified 29 potential sources of inaccuracy related to the patient, the device, the procedure and the observer, which can influence the BP levels and lead to unreliable diagnosis [82]. Thus, it is of utmost importance to use a standardized OBPM methodology that allows uniformity of the setting and the conditions of measurement, the patient position, the device, the measurement schedule and the interpretation of the results [62]. Office BP should be measured on a bare arm. An appropriate cuff size is crucial for accurate BP measurement and must be selected according to the arm circumference of each individual. A single cuff cannot fit the range of arm sizes of all adults. A smaller than required cuff overestimates BP whereas a larger cuff underestimates it [83]. For manual auscultatory devices, a cuff with an inflatable bladder length and width of 75–100% and 37–50% of the individual middle upper arm circumference, respectively, is required [62,72]. Importantly, for automated electronic devices, the cuff size should be selected according to the device instructions. People with large arms (mid-arm circumference >42 cm) require a conic-shaped cuff because rectangular cuffs may overestimate BP [84]. When BP cannot be measured by an upper arm cuff device, a validated electronic wrist-cuff device may be used [62].

Additional important requirements for the proper use of OBPM are the following. One, diagnosis of hypertension should not be based on a single office visit, unless office BP indicates grade 3 hypertension (≥180/110 mmHg) or the patient is at high or very high risk based on the presence of HMOD or CVD [62] (Fig. 4). In the vast majority of patients, an accurate evaluation of office BP requires at least two to three office visits at 1–4-week intervals (depending on the BP level and CV risk) using the average of the last two out of three readings per visit [62,85–89]. Two, in older persons (>65 years of age), treated hypertensive patients (especially very old patients), diabetic patients, patients with neurodegenerative disorders, or with symptoms suggesting postural hypotension, BP should also be measured 1 and 3 min after standing for detecting orthostatic hypotension [62]. At the initial office visit, BP should be measured in both arms, ideally with electronic devices that can measure them simultaneously. An interarm SBP difference >10 mmHg must be confirmed with repeated measurements. If confirmed, the arm with the higher BP should be used for all subsequent measurements because its values more accurately reflect the BP level in the major arteries. Moreover, using BP taken on the arm with the higher reading seems to improve the outcome prediction [90]. A consistent interarm SBP difference >15 to 20 mmHg may be due to atherosclerosis and restriction of large intrathoracic or upper arm arteries, requiring investigation for arterial disease [62,91].

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Office BP measurements

Recommendations and statements	CoR	LoE
Ofiice BP is recommended for diagnosis of hypertension, because it is the one method by which hypertension-related risk, benefits of antihypertensive treatment, and treatment-related BP thresholds and goals are based.	I	A
Office BP measurements should be performed in standardized conditions, using a standard measurement protocol. Triplicate measurements should be taken and the average of the last two should be referred to as the representative value.	I	C
It is recommended to diagnose hypertension during at least 2 separate office visits (within 4 weeks) unless office BP indicates grade 3 hypertension (≥180/110 mmHg) or patients presents with hypertension related symptoms or there is evidence of HMOD or CVD.	I	C
At the first office visit, BP should be measured in both arms. A consistent between-arm SBP difference >15-20 mmHg suggests atheromatous disease and is associated with increased CV risk. All subsequent measurements should be made on the arm with the highest BP readings.	I	C
Out-of-office BP is a source of multiple BP-related information before and during treatment. It is therefore recommended to obtain additional information on BP values by ABPM or HBPM or both if available.	I	C

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4.3 Unattended office blood pressure measurement

Unattended OBPM performed automatically (three or more readings) without the medical staff being present in the examination room (patient alone) favors a standardized office BP evaluation by ensuring a quiet environment, multiple BP readings and no talking [62,92]. This BP measurement method was used by the SPRINT study, although in a retrospective survey, nonattendance by the healthcare personnel appeared to be variable [93]. Available data agree that absence of medical personnel leads to lower BP values than those associated with standard OBPM, because of a reduction of the alerting response to the medical staff's presence or the white-coat effect [92,94,95]. This can make unattended BP values closer to those obtained by out-of-office BP measurements, although quantitative disagreements with home and daytime mean ambulatory BP have been reported [96]. However, a major problem of unattended OBPM is that evidence of its ability to predict reduction of outcomes by treatment is limited to one trial (SPRINT) [97], which is in contrast with the large and consistent volume of trial-based evidence available for standard OBPM. Furthermore, again in contrast with standard OBPM, little evidence exists on the ability of unattended OBPM to sensitively predict CV events including CV mortality and mortality in the general population [92,98]. Finally, unattended OBPM requires facilities (equipment, space and personnel) that can make it difficult or even unfeasible to accommodate the large number of patients frequently dealt with in general practice and even in dedicated outpatient clinics. Another issue is that the variable difference between unattended and standard OBPM reported in various studies does also not allow to develop a correction factor between the two BP measurement approaches, and thus to meaningfully compare different trials for their threshold and target BP values for treatment. For these reasons, attended OBPM

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using an automated device and a standardized protocol (triplicate measurements in appropriate conditions and position) appears to be the most reasonable and practical BP measurement recommendation for clinical practice.

4.4 Blood pressure during exercise

BP increases during dynamic and static exercise, and the increase is more pronounced for SBP than for DBP [99], although only exercise SBP can be measured reliably with noninvasive methods. The increase in SBP during exercise is related to preexercise resting BP, age, arterial stiffness and abdominal obesity, and is somewhat greater in men than in women [100]. There is some evidence that an excessive rise in BP during exercise predicts the development of hypertension, independently from BP at rest [100]. There is currently no consensus on the normal BP elevation during exercise. According to a consensus document of the European Association of Preventive Cardiology, a BP above 220 mmHg in male and 200 mmHg in female measured at peak exercise during cycle ergometry warrants further clinical evaluation including ABPM [101]. Two interesting recent findings are that (i) the BP response to submaximal exercise may have a greater prognostic significance than BP measured at peak [101] and (ii) exercise hypotension may also be a sign of an underlying CV disease [100]. Nevertheless, exercise testing is not recommended as part of the routine evaluation of hypertension because of various limitations, including lack of standardized methodology and definitions. The BP rise accompanying exercise should not discourage patients with treated or untreated hypertension from engaging in regular exercise, especially aerobic exercise, except in the presence of very high BP values (grade 3 hypertension). Regular exercise represents an important lifestyle intervention to chronically lower BP (Section 7.5).

4.5 Blood pressure measurement in hospital

Because the mercury sphygmomanometer has been banned, mercury-free professional automated BP measurement devices such as digital electronic and hybrid devices (which combine some of the features of both electronic and auscultatory devices) should be used in hospital wards. Multiparametric monitors that measure BP, pulse oximetry, temperature and pulse rate are becoming increasingly popular. Some professional monitors offer a high-speed measurement mode that measures BP in less than 30 s, and others may offer the possibility to determine SBP in a very fast mode [102]. These devices may be especially helpful in emergency units. There are several features that are essential for a BP monitor to be used in hospital [102], two of which are the possibility of being programmed to take multiple BP readings at variable intervals and to have a memory capacity that allows to recall previous measurements. All automatic monitors need regular maintenance and calibration and should be provided with at least two sizes of cuffs for adults, standard and large, and a pediatric cuff. Some devices use a wide-range cuff, which can cover a wide range of arm sizes according to manufacturer instructions [103]. Only devices and cuffs validated by accepted standards should be used [104]. In patients having AF, at least three office BP measurements by auscultation are recommended to account for the varying BP values. Automated oscillatory methods can be also used for BP measurement in AF patients, because they satisfactorily measure SBP and only modestly overestimate DBP. Some devices can apply an AF-specific algorithm [105] that allows to automatically detect AF (Section 17.3).

Automatic oscillometric measurements may also be considered a reasonably good alternative to intra-arterial measurements in ICUs, the resuscitation area or during surgery [106]. Good agreement between the two methods has been documented within the normotensive BP range in critically ill patients [107], while BP underestimations and overestimations have been observed at very low and very high BP values, respectively [108]. The BP underestimation in hypotensive patients is of particular concern because detection and quantification of hypotension in critically ill patients or in other emergency conditions are crucial for detection and prevention of vital organ hypoperfusion. In a meta-analysis of studies with different oscillometric devices that had brachial intraarterial BP for comparison, the mean SBP underestimation at low BP values was 5.7 mmHg [109], with a wide variability of the between-pressure differences in different patients and for different devices. In patients with hypotensive shock, oscillometric mean BP was found to be 13 mmHg higher than the invasively measured BP [110]. Although oscillometric devices are often used for monitoring BP in emergency medicine and perioperatively [106], direct measurement of BP by an arterial catheter should be used in critical conditions, especially in patients suffering from shock, to guide vasopressor and fluid therapy.

4.6 Central blood pressure

Central (aortic) BP can be assessed noninvasively from peripheral BP waveforms, using tonometry or cuff-based devices and dedicated algorithms [111]. Interest in central BP originates from the consideration that (i) central BP is the pressure to which vital organs and vessels developing atherosclerosis are exposed; (ii) peripheral and central BP values differ and (iii) this is also the case for the effects of treatment [112,113]. A meta-analysis of clinical studies showed that central BP is related to LVH, carotid intima–media thickness and albuminuria, independently of peripheral BP [114]. However, studies and meta-analyses on the predictive value of central BP for CV events have led to conflicting results. According to a recent observational study, higher central pulse pressure was associated with increases in CV outcome incidence even after adjustment for several confounders, including peripheral SBP [115]. An association between central BP and CV outcomes was found also in a meta-analysis, but when studies that included both peripheral and central BP in the same model were considered, a similar risk prediction was observed for peripheral and central BP [116]. Elevated brachial and central BP measurements have both also been found to be associated with higher risk of CV events in patients with CKD [117,118]. However, even in this setting, measurement of central BP did not improve the ability to predict CV events or mortality on top of brachial BP measurement. At variance with these results, in a recent individual-level meta-analysis, central hypertension was associated with increased CV and cerebrovascular risk irrespective of the brachial BP status [119]. Thus, the incremental

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prognostic value of central versus conventional office BP measurement is unclear. In addition to the inconsistency of prognostic data, it should be borne in mind that noninvasive central BP measurement is subject to practical limitations. Devices for central BP measurement have to be calibrated with BP values normally obtained by conventional (usually oscillometric) brachial measurements [111]. Furthermore, although some reference data are available [119,120], there is no conclusive information on (i) the cutoff BP values that differentiate normal from high central BP and (ii) the central–brachial BP correspondence in different population and patient strata. Thus, a widespread use of central BP measurement in the management of hypertensive patients cannot be recommended. The main field of application of central BP may be isolated systolic hypertension in the young (ISHY) in which peripheral BP may be disproportionately elevated compared with a normal central BP value. In this setting, central BP assessment can help to distinguish between a 'spurious' benign condition and an ISHY due to early arterial stiffening [121] (Section 14.5). The clinical use of other types of information derived from central waveform characteristics such as the augmentation index or the wave reflection indices needs to be further defined.

4.7 Home blood pressure monitoring

HBPM provides multiple BP readings away from the office, in the usual environment of each individual [62,122]. It is well accepted for long-term use by patients and has a relatively low cost usually covered by the users [62,122]. HBPM data (i) are more reproducible than those provided by office BP [123,124], (ii) predict HMOD, CV outcomes and mortality better than office BP [125–129], (iii) increase the predictive ability for outcomes, albeit to a modest degree, when added to office BP [129,130], (iv) measure day-to-day BP variability, which carries an adverse prognostic significance and (v) identify, like ABPM, hypertension phenotypes such as MH or WCH, which are characterized by CV risk levels different from those associated with sustained or established hypertension. [62,122,131–133]. Although data are not entirely univocal [134], a further possible advantage of HBPM is that it may improve adherence to treatment, thereby favoring hypertension control, especially when combined with education, counselling, self-titration algorithms or digital interventions (Section 21.6) [122,134–136]. Combination with telemonitoring and smartphone applications may offer additional advantages, including the ability to store and transfer home BP data in a digital format and facilitate their evaluation by healthcare professionals [137,138].

HBPM should be performed using automated upper arm cuff devices validated according to an established protocol (www.stridebp.org) [62,122]. Devices with automated storage and averaging of multiple readings, mobile phone, PC or internet link connectivity enabling data transfer may be preferred to facilitate the evaluation of BP values by the physician [62,122]. The measurement conditions and posture should be similar to those described for OBPM [62,122]. Because HBPM is devoid or almost devoid of a white-coat effect in most patients [139,140], its values are lower than office BP values, with a difference that becomes progressively less pronounced as office BP decreases. In the absence of out-of-office BP outcome data from RCTs, the threshold for home hypertension is defined as the value corresponding to an office BP of 140 mmHg SBP or 90 mmHg DBP, i.e. 135 or 85 mmHg, respectively. By analogy, the home BP target is regarded as the value corresponding to the office BP target recommended by guidelines (<130/80 mmHg) (Section 10), which is not well defined but probably just few mmHg lower [141–144]. It is important to mention that these correspondence-based threshold and target home BP values should be interpreted with caution, because office, home and 24 h mean BP values obtained by ABPM have a limited correlation to one another both in untreated and treated patients [145]. Importantly, in single individuals, these difference may widely depart from the above reported mean values.

Home BP values should be collected before planned office visits or whenever a clinically significant change in BP is suspected. Ideally, home BP should be monitored for 7 days and never for less than 3 days, with duplicate measurements (1 min apart) in the morning (before drug intake if treated) and the evening [62,122,146,147]. First-day readings (usually higher and unstable) should be discarded and averages of the remaining values should be considered [62,122,146,147] (Fig. 5). HBPM helps to improve persistence of BP control during long-term treatment [148] (Section 21).

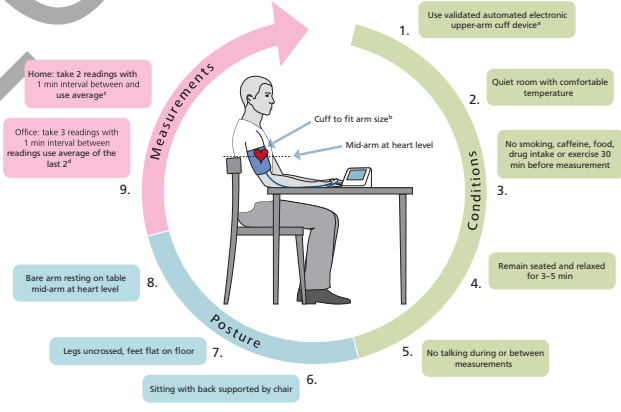


FIGURE 5 Recommendations for BP measurements in the office and at home. Adapted from [62]. [a]Use an automated electronic (oscillometric) device, which is validated according to an established protocol (www.stridebp.org). A device that takes triplicate readings automatically is preferred. [b]The selection of an appropriate cuff size is crucial for accurate BP measurement and depends on the arm circumference of each individual – a smaller than required cuff overestimates BP and a larger underestimates BP. Using automated electronic devices select cuff size according to the device's instructions. At the initial visit, measure BP in both arms. [c]Measure in the morning and the evening for 3–7 days. Use the average of all readings excluding the first day. [d]Strong data linking OBP with CVD. Used in most observational and interventional outcome trials in hypertension.

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Limitations of HBPM are that it requires patient training, is often performed by inaccurate devices, can induce anxiety and lead to overly frequent measurements that may be followed by treatment modifications by the patient [122]. Another limitation is a lack of night-time BP evaluation, which is not a marginal disadvantage, because night-time BP has been shown to predict outcomes more effectively than daytime BP [122]. However, novel HBPM devices allow automated BP measurements during sleep, which provide similar asleep BP values as those provided by ABPM, similar correlations with HMOD [70,149] and have an independent prognostic value [150]. Finally, as mentioned above, a most important limitation (shared with ABPM) is that there are no studies on HBPM-guided treatment and outcomes.

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Home BP monitoring (HBPM)

Recommendations and statements	CoR	LoE
HBPM is recommended in addition to OBPM to improve CV risk prediction due to better reproducibility and prognostic value than OBPM, although lacking data on treatment benefit from RCTs.	IIb	B
HBPM is recommended to identify white-coat hypertension or masked hypertension.	I	B
HBPM is recommended for long-term follow-up of treated hypertension because it improves BP control, especially when combined with education and counselling.	I	B
HBPM should be performed using automated upper arm-cuff BP monitors validated according to an established protocol. www.stridebp.org	I	C
Home BP should be monitored for 7 (not fewer than 3) days with duplicate morning (with 1 minute between them) and evening measurements before office visits. Average home BP should be calculated after discarding readings of the first day.	I	C

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4.8 Ambulatory blood pressure monitoring

Although patients have to remain immobile at the time of the BP measurements, ABPM provides multiple BP readings in conditions that reflect the usual environment, including daily activities and sleep [62]. ABPM has the same advantages over OBPM than those reported for HBPM, i.e. greater reproducibility of 24 h mean BP values, closer association with and prediction of HMOD, better prediction of outcomes and mortality [128,151,152] and the ability to identify WCH and MH. It has as additional advantages the possibility to discriminate between apparent and true-resistant hypertension [153] and to quantify BP characteristics such as 24 h BP variability and the morning BP surge, which have been found to have an adverse prognostic value, independently of 24 h mean BP [133,154,155]. A most important and so far almost unique advantage is the quantification of the dipping status, i.e. the magnitude of nocturnal BP change, which is clinically relevant because night BP reduction and absolute night BP values have been found to predict events better than daytime BP, with a markedly elevated risk in patients with no night-time BP reduction or nocturnal hypertension [156,157]. ABPM may facilitate the identification of daily life hypotensive episodes and the persistency of BP control by treatment during the periods between drug intakes. For research on BP-lowering therapies it has the advantage that its use is accompanied by no or a minimal placebo effect [158]. However, ABPM is not suitable for frequent use, it is rather expensive, it is not widely available in primary care settings, and may cause discomfort to some patients, especially during sleep [62]. As for HBPM, the most important limitations are that (i) no outcome-based RCTs have been conducted to explore the effect of ABPM-guided versus OBPM-guided treatment and (ii) no BP thresholds and goals for treatment have been directly established [159]. Because ABPM does not elicit a white-coat effect [139,140], ambulatory BP values are lower than office values. The threshold for ambulatory hypertension is defined as a 24 h mean SBP of 130 mmHg or a DBP of 80 mmHg corresponding to office BP values of 140 or 90 mmHg, respectively. As for HBPM, in the absence of trials on the effect of ambulatory BP reduction on outcomes, the ambulatory BP values to

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reach with treatment are inferred from their correspondence with the target office BP of <130/80 mmHg, and the ACC/AHA guidelines have tentatively indicated a value <125/75 mmHg [160]. This carries the same limitations as those reported in Section 4.7.

ABPM is performed using fully automated devices programmed to record BP automatically at preselected intervals for 24 h in a usual workday [62,161]. Patients are instructed to keep a diary of their activities, symptoms, meals, drug intake times, sleep times or any unusual problem. Average daytime, night-time and 24 h BP values are provided by the device software [62], which also provides the hourly BP profile. Several guidelines require a minimum of 20 valid awake and seven valid asleep BP readings for a valid 24 h recording [62,162]. However, because some readings may be eliminated by the device software, this may lead to hours without BP values, particularly during the night. Furthermore, there is evidence that measuring BP at 60 min intervals (i.e. a total of 24 values during the 24 h) may provide an incorrect 24 h mean BP [163,164]. To limit the risk that poor quality of the collected data invalidates the advantages of ABPM, an appropriate procedure can be to measure BP every 20 min throughout the day and night. This will avoid the paradox of making BP information more scarce during the prognostically more important fraction of the 24 h (night-time) (Table 4).

TABLE 4. Definitions of hypertension according to the correspondence of home and ambulatory BP values with office BP

Method	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Awake mean	≥135	and/or	≥85
Asleep mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

[a]Refers to standard office BP measurements (not unattended measurements). Data compare the averages from cohorts of untreated and treated individuals. Given the low correlation between office and out-of-office BP values, individuals can have considerable discrepancies from the averages.

Additional indices derived from ABPM recordings have been considered, and some were found to have an independent prognostic value, including indices of BP variability [165–168], the morning BP surge [154] and the ambulatory arterial stiffness index [169–171]. However, their incremental predictive value is still unclear [165]. Thus, at present, these indices should be regarded as research tools with no indication for routine clinical use.

Ambulatory BP monitoring (ABPM)

Specific recommendations and statements	CoR	LoE
ABPM is recommended in addition to OBPM to improve CV risk prediction due to better reproducibility and prognostic value than OBPM, although lacking data on treatment benefit from RCTs.	II	B
ABPM is recommended to identify white-coat hypertension, masked hypertension and nocturnal BP phenotypes. Repeated ABPM may be necessary because these phenotypes have a limited reproducibility.	I	B
ABPM should be used to diagnose true resistant hypertension.	I	B
ABPM should be measured using upper arm-cuff automated BP monitors validated according to an established protocol. www.stridebp.org	I	C
The recommended frequency of measurements is 20 minutes during day and night to minimize the risk of missing day or night periods.	I	C

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TABLE 5. Clinical indications for home and ambulatory BP monitoring

Conditions in which white-coat hypertension is more common, e.g.:
• Grade I hypertension on office BP measurement
• Marked office BP elevation without HMOD
Conditions in which masked hypertension is more common, e.g.:
• High-normal office BP
• Normal office BP in individuals with HMOD or at high total CV risk
In treated individuals:
• Confirmation of uncontrolled and true resistant hypertension
• Evaluation of 24-h BP control (especially in high-risk patients)
• Evaluating symptoms indicating hypotension (especially in older patients)
Suspected postural or postprandial hypotension in treated patients
Exaggerated BP response to exercise
Considerable variability in office BP measurements
Specific indications for ABPM rather than HBPM:
• Assessment of nocturnal BP and dipping status (e.g. sleep apnea, CKD, diabetes, endocrine hypertension, or autonomic dysfunction)
• Patients incapable or unwilling to perform reliable HBPM, or anxious with self-measurement
• Pregnancy
Specific indications for HBPM rather than ABPM:
• Long-term follow-up of treated individuals to improve adherence with treatment and hypertension control
• Patients unwilling to perform ABPM, or with considerable discomfort during the recording
Indications for repeat out-of-office BP evaluation (same or alternative method – HBPM/ABPM)
• Confirmation of white-coat hypertension or masked hypertension in untreated or treated individuals

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; HMOD, Hypertension-mediated organ damage.

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4.9 Clinical indications for HBPM and ABPM

HBPM and ABPM share several clinical indications (Table 5). Both HBPM and ABPM can identify WCH and MH and should be considered when, based on OBPM, the odds of one or the other condition is higher, i.e. in patients with grade 1 hypertension for WCH and with high-normal BP for MH [62]. Either HBPM and ABPM are diagnostically important in patients in whom (i) a normal office BP is accompanied by the presence of HMOD or high CV risk and (ii) elevated office BP (particularly if in the grade 2 or 3 range and long-lasting) is not accompanied by HMOD. A common indication is also the condition in which a large variability of office BP values does not allow to reach a clear decision on the diagnosis of hypertension. Finally, HBPM and ABPM can both identify different treated patient phenotypes, i.e. when there is no control of both office and out-of-office BP, selective control of only one BP or control of both BP values.

There are also selective indications for ABPM or HBPM. ABPM should be performed when postural or postprandial hypotension is suspected, which is more frequently observed in older patients, diabetic patients, patients with dysautonomia, patients developing anxiety with self-BP measurements or patients who are unable to perform and correctly report the results of the procedure. HBPM may be indicated in patients reporting discomfort or sleep problems with ABPM as well for checking long-term BP control during treatment. On the other hand, and despite technological advancement on HBPM, ABPM remains the best approach to characterize nocturnal BP phenotypes, i.e. the dipping status, which is frequently altered in conditions such as diabetes, OSA, obesity and CKD, with a prognostic reflection that extends to the general population. Nevertheless, it is important to know that different dipping patterns and other BP phenotypes based on office and out-of-office BP measurements have a limited reproducibility [172–174]. Thus, these phenotypes should be identified by more than one out-of-office BP monitoring, e.g. at least two monitorings spaced by several days or weeks [172,173].

In conclusion, despite the technological and clinical advances obtained in the last decades, use of out-of-office BP monitoring still faces some unanswered questions. The most important questions are (i) whether the improved prognostic ability associated with addition of out-of-office to office BP is substantial or modest, in particular when OBPM is appropriately measured [129,130], (ii) whether HBPM-guided or ABPM-guided therapy results in greater reductions in morbidity and mortality than conventional office BP-guided treatment and (iii) which are the out-of-office BP thresholds and goals for treatment. The last two questions will need an answer from outcome-based RCTs comparing out-of-office versus office BP-based treatments [4,62]. Yet, the large amount of additional clinical information provided by out-of-office BP measurements cannot be ignored and, therefore, the present guidelines support collection of out-of-office BP data not only for specific indications but more in general as an important source of useful clinical information whenever collection of these data is feasible in the individual patient and compatible with the healthcare organization and resources. Data collection extends to both HBPM and ABPM, because available evidence suggests that their specific indications and clinical value are not redundant, competitive or interchangeable but complementary. HBPM is only performed in a standardized sitting posture at home, whereas ambulatory BP is measured at different postures (sitting, standing and lying), in different environments (work, home, other) and during routine daytime activities and night-time sleep [4,62,122,161]. Data from a general population suggest that the risk of events increases progressively with the progressive elevation of three available BPs (OBPM, HBPM and ABPM) [157]. In the same population, the risk of CV mortality associated with WCH was lower when normality values extended to both HBPM and ABPM compared with when it only involved one of these two out-of-office BP [3].

4.10 Blood pressure variability

Old studies on ambulatory intra-arterial BP monitoring have shown that BP is highly variable during the day and to a lesser extent during the night [175,176] due to the interplay between central factors, humoral influences, local vasoactive

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mechanisms and the buffering influences of the baroreflex [69]. This short-term BP variability was found to be quantitatively related to the BP levels, and thus greater in hypertension than in normotension [176], and to have an adverse effect on the genesis of HMOD [177]. These observations were confirmed by studies with noninvasive ambulatory monitoring, which also showed that 24 h or short-term BP variability is adversely related to the risk of CV outcomes, independently of the 24 h mean BP value [155,167,178,179]. However, although several studies have shown that treatment lowers 24 h BP variability, no study has ever addressed whether a treatment-related reduction of 24 h BP variability attenuates CV risk [155,167,178,179].

A number of studies have also focused on other types of BP variability. Conflicting results have been reported on the prognostic value of within-visit BP variations [180], whereas some studies have reported an association between day-to-day BP variability as assessed by HBPM and the risk of CV outcomes [166,181]. However, the largest body of available evidence relates to what is known as visit-to-visit or long-term BP variability. Post hoc analyses of antihypertensive treatment trials have shown that long-term BP variability such as that measurable as BP differences between visits spaced by 6 or 12 months apart, is associated with CV risk in treated hypertensive patients. In posthoc analyses of three trials, an increase in the number of medical visits in which office BP was reduced to the recommended control value was accompanied by a proportional reduction in the risk of CV outcomes and mortality, independently of the mean office BP reached during the treatment period [182–184]. Furthermore, in trials or treated cohorts of patients with different demographic and clinical characteristics, between-visit office BP variations were found to be associated with the risk of CV and kidney outcomes, also independently of the mean BP values reached during the years of treatment [185–187]. In one study, combined use of on-treatment mean BP and visit-to-visit BP variability identified more accurately the CV risk of treated hypertensive patients than either measure alone [188]. This suggests that in treated patients, protection depends also on time spent under BP control, as more recently confirmed by the relationship between CV events and calculated TTR (time on therapeutic BP range) or BP load (ratio between BP values at BP target and all values during the treatment period) in renal denervated patients and treated diabetic patients, respectively [189,190]. From a practical perspective, this justifies the recommendation to pay attention to consistency of BP control in treated patients, because absence of control at a given visit probably does not represent a fleeting innocent BP elevation but a prolonged period with high BP in the preceding months. Evidence from the ELSA trial shows that an inconsistent BP control is common in treated hypertensive patients [191].

5. PATIENT WORK-UP

The work-up required to obtain the information that is necessary in patients with suspected or established hypertension has been accurately described by previous guidelines [4]. Except for some changes or additions to the list of CV risk factors and measures of HMOD, they have not changed substantially in the last years and will thus be reported in the present guidelines only in table format, with the exception of HMOD, for which a more detailed description has been made available (Tables 6–8).

5.1 Personal and medical history

TABLE 6. Medical and family history[a]

Personal history
• Time of the first diagnosis of hypertension, including records of any previous medical screening, hospitalization
• Stable or rapidly increasing BP
• Recordings of current and past BP values by self BP measurements
• Current/past antihypertensive medications including their effectiveness and intolerance
• Adherence to therapy
• Previous hypertension in pregnancy/preeclampsia
Risk factors[a]
• Family history of hypertension, CVD, stroke or kidney disease
• Smoking history
• Dietary history, alcohol consumption
• Lack of physical exercise/sedentary lifestyle
• Weight gain or loss in the past
• History of erectile dysfunction
• Sleep history, snoring, sleep apnea (information also from partner)
• Distress or eustress with job or at home (subjective stress level)
• Long-term cancer survivor
History and symptoms of HMOD, CVD, stroke and kidney disease
• Brain and eyes: headache, vertigo, syncope, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization, cognitive impairment, memory loss, dementia (in older people)
• Heart: chest pain, shortness of breath, edema, myocardial infarction, coronary revascularization, syncope, history of palpitations, arrhythmias (especially AF), heart failure
• Kidney: thirst, polyuria, nocturia, hematuria, urinary tract infections
• Peripheral arteries: cold extremities, intermittent claudication, pain-free walking distance, pain at rest, ulcer or necrosis, peripheral revascularization
• Patient or family history of CKD (e.g. polycystic kidney disease)
History of possible secondary hypertension
• Young onset of grade 2 or 3 hypertension (<40 years), or sudden development of hypertension or rapidly worsening BP in older patients
• History of repetitive renal/urinary tract disease
• Repetitive episodes of sweating, headache, anxiety or palpitations, suggestive of pheochromocytoma
• History of spontaneous or diuretic-provoked hypokalemia, episodes of muscle weakness and tetany (hyperaldosteronism)
• Symptoms suggestive of thyroid disease or hyperparathyroidism
• History of or current pregnancy, postmenopausal status and oral contraceptive use or hormonal substitution
Drug treatments or use (other than antihypertensive drugs)
• Recreational drug/substance abuse, concurrent therapies including nonprescription drugs, e.g. glucocorticoids, NSAIDs/COX-2 inhibitors, paracetamol (acetaminophen), immunosuppressive drugs, anticancer drugs, nasal vasoconstrictors

[a]Additional factors to be considered are listed in Table 2 (Section 3.5).

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5.2 Physical examination

TABLE 7. Comprehensive physical examination for hypertension[a]

Body habitus
• Weight and height measured on a calibrated scale, with calculation of BMI
• Waist circumference
Signs of hypertension-mediated organ damage
• Neurological examination and cognitive status
• Fundoscopic examination for hypertensive retinopathy in emergencies
• Auscultation of heart and carotid arteries
• Palpation of carotid and peripheral arteries
• Ankle–brachial index
Signs of secondary hypertension (Section 6)
• Skin inspection: cafe-au-lait patches of neurofibromatosis (pheochromocytoma)
• Kidney palpation for signs of renal enlargement in polycystic kidney disease
• Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension
• Signs of Cushing's disease or acromegaly
• Signs of thyroid disease

[a]Can be adapted according to the clinical circumstance.

5.3 Routine clinical chemistry investigations

TABLE 8. Selected standard laboratory tests for work-up of hypertensive patients[a]

• Hemoglobin and/or hematocrit
• Fasting blood glucose and HbA1c
• Blood lipids: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
• Blood potassium and sodium
• Blood uric acid
• Blood creatinine (and/or cystatin C) for estimating GFR with eGFR[a] formulas
• Blood calcium
• Urine analysis (first voided urine in the morning), multicomponent dipstick test in all patients, urinary albumin/creatinine ratio, microscopic examination in selected patients

eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Can be adapted according to the clinical circumstance.

5.4 Other investigations in hypertension

5.4.1 Electrocardiogram

A 12-lead ECG is part of the routine diagnostic evaluation in all hypertensive patients. LVH represents an important and typical HMOD, which increases markedly with long-standing hypertension and its severity [192]. The Sokolow–Lyon voltage criteria and the Cornell voltage-duration product are important criteria for ECG-based LVH (Table 9). The presence of strain (ST-T depression in lateral anterior leads) is the most serious sign of LVH on ECG [193]. Fulfillment

TABLE 9. Assessment of hypertension-mediated organ damage (HMOD)[a]

Basic screening tests for HMOD recommended for all hypertensive patients	Aim
12 lead ECG	Measure HR and AV conduction, detect cardiac arrhythmias, myocardial ischemia and infarction, screen for LVH
Urine albumin : creatinine ratio (UACR)	Detect and classify CKD
Serum creatinine and eGFR	Detect and classify CKD
Extended screening for HMOD	
Echocardiography	Evaluate structure and function of the ventricles and left atrium, detect valvular disease, aortic root diameter and ascending aortic aneurysm
cfPWV or baPWV	Evaluate aortic/large artery stiffness
Carotid artery ultrasound	Determine carotid intima-media thickness, plaque and stenosis
Coronary artery calcium scan	Determine the presence and extent of coronary calcium to predict CAD events
Abdominal aorta ultrasound	Screen for aortic aneurysm
Kidney ultrasound	Evaluate size and structure of kidney, detect renovascular disease, determine RRI (by spectral doppler ultrasonography)
Spectral doppler ultrasonography	Diagnosis of renovascular disease and determination of RRI
ABI	Screen for LEAD
Retina microvasculature	Detect microvascular changes
Cognitive function testing (MMSE, MoCA)	Screen for early stages of dementia
Brain imaging (CT, MRI)	Detect structural brain damage

[a]Can be adapted according to the clinical circumstance.

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of the Sokolow–Lyon criteria for LVH is associated with older age, male gender and high BP, whereas fulfillment of the Cornell voltage-duration criteria is associated with a younger age, female gender, lower BP and obesity. Specificity is high (about 97%) when using the above ECG criteria together, but sensitivity is low, e.g. in the range of about 40–50% of LVH cases in persons above 50 years of age and even lower in younger patients. New diagnostic criteria based on machine learning show a better diagnostic ability [194] but for LVH detection, echocardiography remains more sensitive and preferable (if available), especially in hypertensive patients below 50 years of age but also in the context of a more advanced general work-up (see the following). Nevertheless, it should be considered that ECG-based LVH strongly predicts arrhythmias, including sudden cardiac death, AF, myocardial infarction, HF, stroke and a variety of other cardiac and vascular conditions in a fashion that does not completely overlap with the morbidity and mortality prediction offered by echocardiography [195]. It also provides information about heart rate, cardiac rhythm, AV conduction and normality or abnormality of the repolarization phase, which may influence the selection of antihypertensive therapy, e.g. use of BBs or non-DHP-CCBs. Thus, ECG has an added value both for risk prediction and more, in general, for the clinical evaluation of the hypertensive patient.

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5.4.2 Kidney ultrasound

Due to its low cost and widespread availability, ultrasound imaging of the kidney is commonly used for information on renal morphology (renal size and structure, roughness, adiposity, kidney stones) and, when contrast-enhanced perfusion is added, microstructure, stiffness, inflammation, edema and abscesses [196]. Kidney ultrasound is a valuable method in the presence of CKD and also a noninvasive examination method for detecting renal artery stenosis because, on a gray-scale ultrasound, it can assess the morphology of both the kidney and the renal arteries. Hemodynamic changes in the renal artery and the kidney can be evaluated with color and spectral Doppler ultrasound. Contrast-enhanced ultrasound may directly show a diameter change in the renal artery with intravascular contrast material that is not harmful even to patients with poor renal function [197].

5.4.3 Selected biomarkers and genetic markers

5.4.3.1 Lipoprotein (a)

Epidemiological and genetic studies involving hundreds of thousands of individuals strongly support a causal and continuous association between Lp(a) concentration and CV outcomes in different ethnicities [198–200]. An elevated Lp(a) is a CV risk factor even at very low levels of low-density lipoprotein cholesterol.

5.4.3.2 Cardiac biomarkers

A large number of studies indicate that both high-sensitivity troponins (hs-cTnT and hs-cTnI) and natriuretic peptides (BNP and nt-proBNP) are able to detect individuals that are at higher CV risk.

Studies suggest that on top of their role in the diagnosis and management of several cardiac conditions including asymptomatic LV dysfunction [201], symptomatic HF [202] and acute coronary syndromes [203,204], these markers may also have a role in the detection of early functional and structural cardiac changes associated with hypertension. Their measurement can be extended to primary care patients without the need for high-technology equipment.

5.4.3.3 Kidney markers

Cystatin C, a 13-kDa cysteine proteinase inhibitor protein, is produced by all nucleated cells at a steady rate and is freely filtered by the kidney with near-complete reabsorption and catabolism in the proximal tubule, and thus no significant urinary excretion [205]. Serum cystatin-C levels are much less affected than creatinine levels by patient characteristics such as gender, age, body size and composition, and nutritional status [206]. Cystatin-C has been found to be a more accurate measure of kidney function than serum creatinine and creatinine-based formulas used to calculate eGFR in different patient populations. Cystatin-C captures earlier, more subtle changes in kidney function, which makes its use suitable to identify patients with early impaired function (when serum creatine is in the upper normal or mildly elevated range) and to more sensitively measure the risk of progression toward CKD. Currently, however, cystatin C has a low availability, and the cost-effectiveness and clinical relevance of its possible wider use remain to be determined [207,208]. Bioptic detection of tubulointerstitial damage and fibrosis is highly prognostic for subsequent kidney failure. Considerable research is currently being devoted to biomarkers that reflect noninvasively kidney tubular damage and provide information on the risk of CKD progression and associated adverse clinical outcomes beyond the use of eGFR and urinary albumin excretion.

Available kidney tubule biomarkers can be grouped into those that reflect tubule cell injury (kidney injury molecule 1, epidermal growth factor, monocyte chemoattractant protein one) and those that reflect tubule cell dysfunction (α1-microglobulin and uromodulin). These biomarkers provide new opportunities to monitor the response to treatments in CKD patients [209], and, in hypertension, they can be used to distinguish renal injury from hemodynamic causes of a decline of eGFR. Monitoring these biomarkers serially allows clinicians to monitor persistent beneficial effects of treatment in the presence of benign eGFR declines [210,211].

5.4.3.4 Genetic markers

A positive family history is a frequent feature of hypertensive patients, with hypertension heritability estimates that vary between 35 and 50% in most studies. Rare monogenic forms of hypertension belong to secondary forms of hypertension

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(see Section 6) [12]. There are also inherited forms of phaeochromocytoma and paraganglioma [212], which require genetic testing for early diagnosis and *prognosis as certain mutations are more likely to predict malignancy* (Section 6). Polygenic risk scores, or weighted summations of risk conferred by multiple disease-associated single nucleotide variants, are emerging as tools to improve prediction of common complex CV diseases, including hypertension. For multiple CV diseases, polygenic risk scores are independently associated with respective CVD [213]. Additional potential clinical utility of these scores includes earlier identification for the need of lifestyle interventions, earlier screening for subclinical atherosclerosis, time of initiation of pharmacotherapies and use as a risk-enhancing factor for primary prevention in middle-aged patients at low or moderate conventionally measured 10-year CV risk [214]. However, despite these impressive studies, the role of polygenic risk scores in hypertension, and their possible use in clinical practice should await further clarifications.

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5.5 Assessment of hypertension-mediated organ damage

HMOD refers to structural or functional changes in large and small arteries or end-organs (brain, heart, kidney and eyes), caused by elevated BP and is a marker of preclinical or asymptomatic CV or kidney disease [4]. HMOD is common in severe or long-standing hypertension but can also be found in less severe hypertension. With wider use of imaging, HMOD is becoming increasingly detected in asymptomatic patients [215,216]. CV risk increases with the presence of HMOD, and more so when damage increases progressively and affects multiple organs and functions [4,217,218]. Some types of HMOD can be reversed by antihypertensive treatment, especially when treatment starts early, but with long-standing hypertension, HMOD may become irreversible despite BP control [219]. Nevertheless, BP-lowering treatment is important as it may delay further progression of HMOD and oppose the trend toward a progressive increase of CV risk [215]. Although poor technical provision and cost may limit the search for HMOD in some countries, it is recommended that basic screening for HMOD be performed in all hypertensive patients and that a more detailed assessment be implemented when the presence of HMOD is important for treatment decisions. The examinations that can be used to identify HMOD are shown in Table 9.

5.5.1 HMOD in the heart

In hypertension, the heart is directly exposed to an increased load with consequent development of several structural and functional alterations, which are asymptomatic at an early stage but represent a potent risk factor for subsequent CV events, such as HF with HFpEF or HFrEF, AF, CAD, sudden death and also stroke. Preclinical or asymptomatic hypertensive heart disease includes LVH, LV geometric changes, impaired diastolic and systolic function, LA enlargement and greater incidence of arrhythmias. In clinical practice, most or all parameters indicating hypertensive heart disease should be evaluated in a comprehensive examination, using the ECG and available imaging techniques.

5.5.1.1 Left ventricular mass and geometry

As mentioned above, LVH, as detected by two-dimensional transthoracic echocardiography (2D-TE) is a more sensitive marker of LVH than ECG. It is also a major predictor of morbidity and mortality in both hypertensive patients and the general population [220–222]. LVH significantly reclassifies CV risk when added to CV risk factors in most [223,224], although not all [225] studies. In a population-based sample [226], adding LVH to a commonly used risk score (SCORE) significantly reclassified risk in hypertensive patients. Among a variety of echocardiographic measurements, LV mass index was the single, probably most important predictor of adverse events in patients with hypertension [226]. Furthermore, antihypertensive treatment can be accompanied by a regression of LVH, although only for a fraction of the patients exhibiting this HMOD [219]. Regression of LVH during antihypertensive treatment predicts a better prognosis [193,227–229]. LVH can be detected by different methods, all with advantages and disadvantages (Table 10).

When LVH is detected, it is recommended to follow patients, preferably by echocardiography for monitoring the evolution of LVH and other structural and functional modifications of the heart, the goal being LVH regression. This may take years, cannot always be achieved, and is less achievable in women, and patients with diabetes, obesity and African American ethnicity [230].

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TABLE 10. Advantages and disadvantages of methods to assess LVH in clinical practice

	ECG	ECHO	3D ECHO	CMR
Sensitivity	++	+++	++++	++++
Specificity	+++	+++	++++	++++
Reproducibility	++++	+++	++++	++++
Prognostic significance	++++	++++	+	++++
Availability	++++	+++	++	++
Cost	+	++	++	++++

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5.5.1.2 Transthoracic echocardiography

2D-TE represents the first and most widely used imaging technique to assess LVH. Image quality is the most important factor for reliable measurements. Use of artificial intelligence has been reported to provide a more accurate measurement of cardiac structural and functional alterations [231]. Echocardiographic LVH at baseline has important independent adverse prognostic significance, and adverse or beneficial prognostic changes have also been observed for LVM increases or reductions during FU or antihypertensive treatment [220,228,229]. 2D-TE also permits the evaluation of LV geometry, LA and aortic root dimensions, LV diastolic dysfunction, end diastolic diameter and LV systolic dysfunction [215]. LV concentric geometry is assessed by an increased RWT, and combining RWT and LVM allows to classify the LV geometric adaptation to hypertension as concentric or eccentric, with or without LVH [232]. A significantly higher risk has been observed in patients with concentric nondilated LVH, and the highest risk is exhibited by patients with LV enlargement [229,233]. Regression of LVH during antihypertensive treatment is associated with a reduced risk of CV outcomes but not necessarily with an improvement of LV diastolic dysfunction [234]. Three-dimensional echocardiography (3D-TE) has a better accuracy and reproducibility than 2D-TE, as it does not rely on geometric formulas. However, further research is needed to more reliably establish normality values, prognostic significance and general feasibility [235,236].

5.5.1.3 Cardiac magnetic resonance

Cardiac magnetic resonance is the gold standard for quantification of cardiac structure and function in clinical studies. An important application of cardiac magnetic resonance is tissue characterization, using late gadolinium enhancement [237] and T1 mapping [238] for extracellular volume. This allows to detect interstitial myocardial fibrosis, which may precede the development of LVH. Further studies, together with a wider availability and substantially lower costs, are needed to increase the clinical use of cardiac MRI. It is also important to mention that the better accuracy and reproducibility of cardiac MRI to detect LV changes provides an important advantage for research in the cardiac HMOD area [239].

Left atrial and aortic root dimensions. LA dilatation is usually a response to increased LV filling pressure and is independently associated with adverse CV events and greater incidence of AF [240,241]. Together with LVH and age, hypertension is also associated with ascending aortic dilatation, which has been found to lead to a greater risk of CV events and may predict the development of aortic regurgitation [242].

Left ventricular diastolic dysfunction. LV diastolic dysfunction is usually the first manifestation of cardiac damage, even before the development of LVH. LV diastolic dysfunction can be detected as an alteration of transmitral inflow pattern (*E/A* ratio) at Echo-doppler examinations. Initial LV abnormal relaxation may progress to increased LV filling pressure, which may be detected using additional parameters, such as tissue doppler of mitral annulus (e' velocity) and estimated pulmonary pressures (tricuspid regurgitation retrograde velocity) [243]. Echocardiographic LV ejection fraction may not identify early preclinical LV systolic dysfunction and is also characterized by a large variability at repeated measurements [244]. Speckle tracking echocardiography is a valuable tool to detect early subclinical LV systolic dysfunction, particularly with the measurement of global longitudinal strain, which is characterized by high sensitivity and excellent reproducibility, and has been also standardized in absolute values [245].

5.5.1.4 Computed tomography of the heart

Computed tomography may be used in hypertensive patients to obtain noninvasive coronary angiography, mainly to exclude coronary artery disease, when signs and symptoms are atypical, and the results of other cardiological examinations (i.e. exercise ECG, perfusion scintigraphy, stress echocardiography) are ambiguous.

Coronary artery calcium scanning offers the possibility to detect coronary atherosclerosis in its early stages. Coronary artery calcium is identified by noncontrast cardiac-gated multislice computed tomography of the heart, which is a rapid test using low radiation (<1 mSv) that can be performed at low cost by any modern multidetector computed tomography scanner. Coronary artery calcium is increased in individuals with high BP, predicts the risk of new-onset hypertension, and is also a predictor of CV events in patients with and without hypertension [246,247]. Coronary artery calcium scans have been proposed as a tool to refine quantification of CV risk, particularly CAD events, in patients with hypertension, and to better gauge who may benefit from early initiation of BP medications [248,249]. The effect of antihypertensive treatment on this marker of CV risk is not yet known.

5.5.2 HMOD in the arteries

5.5.2.1 Carotid artery IMT and plaques

Carotid intima–media thickness, combines the thickness of the intimal and medial layer of the carotid artery, is quantified by carotid ultrasound, and can be considered a marker for the early stage of atherosclerosis [250]. It is assumed that the IMT value at the carotid bifurcations primarily reflects atherosclerosis and that the IMT value at the level of the common carotid artery primarily reflects hypertension-related hypertrophy [217]. Carotid IMT predicts CV risk [251,252], and a carotid IMT of more than 0.9 mm is considered abnormal [253], although the upper limit of normality varies with age. However, the relative importance of cIMT evaluation in the overall CV risk quantification is still under debate, because in some studies, addition of cIMT did not improve, or only minimally improved, CV risk stratification [254,255]. The debate includes the prognostic value of treatment-induced IMT changes. In a recent meta-analysis of 119 RTCs involving 100 667 patients (mean age 62 years), the progression of cIMT (mean follow-up 3.7 years) [256] was reduced by a combination of antihypertensive, lipid-lowering and

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antidiabetic drugs, as well as by dietary and other interventions. Across all interventions, each 10 μm/year reduction of carotid IMT progression resulted in a significant 9% reduction of the risk of CV outcomes. However, separately analyzed cIMT changes by antihypertensive treatment did not show a significant relationship with CV events, and this was also the case for the separately analyzed cIMT changes with lipid lowering and antidiabetic treatment. The presence of a carotid plaque can be defined by an IMT $\geq$ 1.5 mm, or by a focal increase in thickness of 0.5 mm or 50% of the surrounding carotid IMT value [257]. Carotid plaques have a predictive value for both stroke and myocardial infarction, independent of conventional CV risk factors and risk scores [251,252]. Detection of carotid plaques confer superior prognostic accuracy for future myocardial infarction compared with IMT [258]. It also increases CV risk in patients at all CV risk levels [259]. Carotid imaging is recommended in the presence of carotid bruit, previous TIA or cerebrovascular disease, or as part of the diagnostic work-up of patients with evidence of vascular disease to detect more than mild carotid stenoses (>50% of the vessel lumen). Further information can be found in specific guidelines [260].

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5.5.2.2 Pulse wave velocity

Increase in large artery stiffness is the most important pathophysiological determinant of age-related increase of SBP and reduction of DBP (and thus of ISH or predominant systolic hypertension) and increase in pulse pressure in the old population [261]. The age-related increase of arterial stiffness is accelerated by uncontrolled hypertension [262]. Recent data suggest that increased arterial stiffness may be involved in the early stages of hypertension, with the stiffening preceding its development [263–265]. Arterial stiffness can be measured in superficial arteries (carotid, brachial, radial arteries) by the slope of the relationship between beat-to-beat BP and arterial diameter changes. However, it is now usually measured by carotid–femoral pulse wave velocity (cfPWV) or brachial–ankle PWV (baPWV). cfPWV is the gold standard for measuring large artery stiffness in Europe [260,266], and its reference values are available for healthy European populations and patients at increased CV risk [267]. Currently, reference values for baPWV are available for Asian populations [268,269], with European studies emerging [270]. Arterial stiffness increases progressively with the BP increase [271], and is thus variable and greater in the systolic than in the diastolic phase [272]. This is because of the intravascular pressure-related distension, first of the more distensible elastic tissue and then of the less distensible collagen. Changes in the anatomical structure of the vessel wall, usually less elastin and more collagen and fibrotic tissue, are responsible for large artery stiffening with age and diseases. However, stiffness is also modulated by functional factors that may cause fast increases of stiffness in the absence of BP changes, presumably via contraction of smooth muscle tissue in the vessel wall, because distensibility may differ between contracted and relaxed vascular smooth muscle. This may account for the acute stiffening influence of increases in sympathetic activity on large and medium-size arteries [273,274]. In stiffer arteries, the traumatic effect of pulsatile intra-arterial pressure is greater and favors atherogenesis.

A large body of evidence exists that assessment of large artery stiffness, using cfPWV or baPWV, can be clinically useful in hypertensive patients. Evidence from the Framingham and European studies has shown that increase of arterial stiffness is highly prevalent in the hypertensive population [253,275,276]. cfPWV is higher in MH than in normotension, which means that in patients with a normal office BP, increased PWV may identify those in whom out-of-office BP monitoring should be performed to detect this higher CV risk condition. In two meta-analyses, cfPWV or baPWV [277,278] have shown the ability to more accurately classify CV risk compared with conventional risk-based scores, an advantage of particular relevance in young and middle-aged patients in whom the risk falls into the low or moderate level. Adding cfPWV to conventional Framingham CV risk factors resulted in an NRI for CV mortality of up to 27%, while addition of baPWV to a model incorporating the Framingham risk score improved the NRI by 24.7%. Increased cfPWV [263,264] and baPWV [279] values have been found to predict an increased risk of new-onset hypertension in apparently healthy adolescents [263], young [280] and middle-aged [264] people. Finally, due to its relationship with age, PWV is considered a main element in the assessment of vascular aging, a concept of great current interest and considerable research [281]. All antihypertensive drugs reduce arterial stiffness passively, i.e. by reducing BP and, thus, unloading the stiffer component (collagen) of the arterial wall. The reduction can be maintained over the long-term [282]. A few studies claim that some drugs may reduce stiffness more effectively [283], thus possibly improving arterial structure, but evidence is not conclusive because stiffness must be measured at identical BP levels, which is difficult. There are reports, however, of treatment-induced reductions in stiffness in the absence of BP reductions [284,285]. No RCT so far has proven that reducing arterial stiffness by antihypertensive treatment induces a reduction of CV events. In one recent RCT, i.e. the SPARTE trial, a PWV-based treatment strategy was compared with the classical BP target-based strategy. There was no significant difference in the primary endpoint (CV outcomes) between the two groups for which, however, the study was underpowered. Nevertheless, in the group in which treatment was guided by reduction of PWV, the age-related increase of PWV was significantly lowered [33,286]. Less cfPWV increase has also been reported with a more intense BP reduction in a post hoc SPRINT study [287], in which the effect on PWV was related to less severe outcomes. PWV improvements have also been associated with improved prognosis in patients with resistant hypertension or on dialysis [288].

5.5.2.3 Ankle–brachial index

ABI is the ratio between SBP in ankle and brachial SBP. Measurements are made with the patient supine, using a continuous wave Doppler, a BP sphygmomanometer (preferentially) or an automated oscillometric device [275]. A low ABI (i.e. $\leq$0.9) indicates a LEAD condition. A high ABI ($\geq$1.40) is also abnormal and indicates medial calcification. In addition to their role in diagnosing LEAD, both a low (<1.00) and a high ABI are independently associated with incident CV events. In an

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individual-participant meta-analysis [289], the 10 year risk of CV mortality associated with a low ABI was greater (4.2-fold in men and 3.5-fold in women), compared with a normal ABI. Adding ABI to the Framingham risk score reclassified the risk category in 19% of men and 36% of women. Measurement of ABI is relatively easy and requires only short training. It should be performed in all patients with symptoms or signs of LEAD.

5.5.3 HMOD in the kidney

Hypertension is the second most important cause of CKD after diabetes and can also be the consequence of a primary kidney disease. Deterioration of kidney function can be detected by routine laboratory testing, using widely available equations for estimation of GFR (eGFR) based on serum creatinine [290]. Serum creatinine alone is an insensitive marker of renal impairment, because a major reduction in kidney function can occur before serum creatinine rises. CKD is classified according to eGFR, calculated by the 2009 CKD-Epidemiology Collaboration formula [291,292], and the presence and amount of albuminuria [290]. The albumin : creatinine ratio (ACR) is measured from a spot urine sample (preferably early morning urine) and is the preferred method to quantify urinary albumin excretion. The diagnosis of HMOD in the kidney is based on the finding of reduced kidney function or detection of albuminuria, but in hypertension-induced kidney disease, albuminuria may not appear until after the reduction in GFR [290].

A lower eGFR and a higher amount of albuminuria, indicating loss of kidney function and kidney damage, are both independent and additive predictors of increased CV risk and progression of kidney disease [292,293]. In a study based on more than three million participants, eGFR and ACR improved risk stratification for myocardial infarction, stroke and CV mortality based on SCORE2 and SCORE2 OP [33] with an NRI improvement of approximately 10%.

On the other hand, whether treatment-induced changes in eGFR and ACR are predictive of kidney and CV outcomes is still under discussion. Short-term effects of eGFR and albuminuria by pharmacological intervention, either an increase or a decrease, may be mixed up with long-term reductions of eGFR and albuminuria. Treatment-associated long-term changes of eGFR have shown a relationship with kidney failure and CV events, whereas treatment effects on proteinuria or albuminuria have been inconsistently related with mortality. In the ONTARGET study, change of albuminuria after 2 years was assessed in more than 20 000 patients at high CV risk, and change of albuminuria was related to total mortality, CV events and kidney outcomes in both diabetic and nondiabetic patients [294]. That is, patients with a decrease of albuminuria by 50% had a lower mortality, while an increase of albuminuria by 100% was associated with adverse CV and kidney outcome as well as a higher mortality. BP reduction by antihypertensive treatment often leads to an acute increase (up to 20–30%) in serum creatinine, especially if treatment makes use of RAS-blockers. This is interpreted as having a hemodynamic basis (BP-dependent reduction of GFR) and, thus, not to usually reflect kidney injury. However, the long-term clinical significance of this early treatment-associated reduction of kidney function is still unclear [295,296]. Serum creatinine, eGFR and ACR should be documented in all hypertensive patients, and if CKD is diagnosed, repeated at least annually [290]. One negative urinary dipstick test does not rule out albuminuria, in contrast to a normal ACR [297]. Spectral Doppler ultrasonography enables to evaluate the renal resistive index (RRI), a noninvasive and reproducible measure of renal and systemic arterial compliance or resistance. In healthy patients, RRI has been shown to vary from 0.58 ± 0.05 (mean $\pm$ SD) to 0.64 ± 0.04, and a value slower than 0.7 has been traditionally taken to indicate normal impedence to renal blood flow, although a considerable heterogeneity has been reported [298]. An elevated RRI is associated with subclinical signs of renal organ damage in untreated patients with hypertension and normal renal function but it has also a prognostic role for CV morbidity, mortality and renal outcomes in essential hypertensive patients, in CKD and in various CV diseases, in addition to albuminuria and eGFR, independently of the traditional risk factors [299,300].

5.5.4 HMOD in the brain

Hypertension is a major risk factor, not only for acute cerebrovascular events such as ischemic stroke, intracranial hemorrhage and TIA, but also for chronic and asymptomatic or oligosymptomatic brain damage, which may ultimately lead to dementia. In particular, long-standing arterial hypertension is known to exert a cumulative effect on cerebrovascular damage, including atherosclerosis, white matter lesions, silent brain infarcts, microinfarcts, microbleeds and brain atrophy [301], especially hippocampal atrophy [302].

Hypertension causes pathological alterations in cerebral microvessels that damage microvascular structure, network architecture and function, and contribute to the genesis of cerebral microbleeds and lacunar infarcts. The latter are small infarcts, 2–20 mm in diameter, in the deep cerebral white matter, basal ganglia or pons that are presumed to result from the occlusion of a single, small perforating artery supplying the subcortical areas of the brain. In addition, white matter lesions, i.e. areas of abnormal myelination in the brain, that are best visualized as hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences, develop in hypertension [303,304]. White matter hyperintensities and silent infarcts are associated with an increased risk of stroke and cognitive decline, including dementia [304,305].

In hypertension, aortic stiffening leads to increased propagation of high BP pulsatility to the high flow–low impedance cerebral circulation [306], leading to small artery remodeling and damage. This arteriolar remodeling can be assessed by analyzing retinal arterioles by high-end fundoscopic cameras, but this technology is not widely available. In cross-sectional studies in middle-aged and older adults, the association between stiffening of the aorta, transmission of excessive flow pulsatility into the brain, microvascular structural brain damage and lower scores in various cognitive domains has been shown repeatedly [307,308]. The relationship between transmission of higher pulsatile energy to the brain in individuals of 60 years of age and faster cognitive decline 10 years later has been documented in a longitudinal study [309]. In individuals

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older than 80 years, PWV has been associated with cognitive decline independently of BP levels [310] A recent meta-analysis, including 29 cross-sectional and 9 longitudinal studies, confirmed the negative association between large artery stiffness (measured by PWV) and cognition, specifically executive function, memory and global cognition. This association seemed to be independent of demographic, clinical and assessment characteristics [311]. Increased BP variability (day-to-day measurements) may also play a role [312], as well as orthostatic hypotension in older people [301]. In clinical studies, long-term elevated SBP and pulse pressure in cognitively healthy adults aged 50 years or older was clearly associated with subsequent cognitive decline and dementia [313].

In hypertensive patients, the presence of lacunes, microbleeds or large white matter hyperintensities on MRI is the second most prevalent HMOD [276]. Low availability and high cost do not permit the widespread use of brain MRI for the evaluation of hypertensive patients, but white matter hyperintensity and silent brain infarcts should be sought in all hypertensive patients with neurological disturbances, cognitive decline or memory loss, if possible [301,305]. For screening in clinical routine, short cognitive screening tests such as the Mini Mental State Examination (MMSE) or the newer Montreal Cognitive Assessment (MoCA) are available and might be considered in hypertensive patients >65 years of age [301]. Their simplicity allows the tests to be performed by primary care physician or referral hypertension specialists. A MMSE score below 24, a MoCA score below 26 or subjective complains of memory loss should lead to referral to a neurologist or a geriatrician [301].

5.5.5 HMOD in the eye

The classification of hypertensive retinopathy is based on fundoscopy, which permits the detection of retinal lesions such as hemorrhages, microaneurysms, hard exudates and cotton wool spots (grade 3), papilloedema and/or macula edema (grade 4). These alterations are indicative of severe retinopathy and are specific, reproducible and predictive of all-cause mortality [314]. Retinal damage of grades 1 and 2, such as focal or general arteriolar narrowing and/or arteriovenous nicking, are less specific and reproducible and also have much less predictive value [315]. Hypertension is also a major risk factor for other retinal vascular diseases, including occlusion of retinal veins and arteries and ischemic optic neuropathy [316]. Fundoscopy should be performed only in selected patients, particularly in those with hypertensive emergencies, suspected malignant hypertension or patients with associated diabetes. New techniques to visualize the fundus using smartphone technologies may help to assess hypertensive retinopathy in a larger number of patients [317].

Retinal arterioles may represent a useful indicator of the remodeling of the microcirculation in other vascular beds of hypertensive patients. In recent years, Scanning Laser Doppler and Adaptive Optics have been increasingly used to estimate the wall-to-lumen ratio of retinal arterioles [318]. Retinal wall-to-lumen ratio was found to be directly related to pressure load, other markers of HMOD and small arteries structural alterations measured in different vascular beds with micromyography, which is the gold standard method, albeit invasive, for evaluating microvessels [319]. Although the prognostic value of small renal artery alterations has been documented in hypertension [320], the predictive value of the retinal wall-to-lumen ratio and its change for CV events, needs to be demonstrated (Table 11).

5.6 Using HMOD to help stratify risk in hypertensive patients

Assessment of HMOD should be performed at the time when the diagnosis of hypertension has been confirmed in order to fine-tune the CV and kidney risk stratification. The data may influence the decision to initiate or intensify drug treatment. However, assessment of HMOD is also relevant during FU, as it can help physicians to evaluate the efficacy of therapy. A reduction in a previous HMOD may indicate the success of the therapy while, by contrast, the persistence/increment of HMOD may be a clue to review the prescribed treatment, with lack of adherence being a predominant reason. Likewise, the absence of HMOD at the time of initial evaluation should be monitored in the future, as new development of HMOD usually indicates a higher risk. As a consequence, repetition of HMOD assessment should be a main aspect of the FU.

As reported above, HMOD assessment may play a role in stratifying the risk of patients with hypertension. In this regard, LVH [215,220], baPWV [277] and cfPWV [321], carotid IMT [252,322], carotid plaque [251], CAC [323] and ABI [323] have been shown to predict CV risk on top of traditional CV risk factors. A higher number of measures of HMOD is associated with higher CV risk [251]. In multivariable-adjusted models, the presence of HMOD was associated with a two-fold to three-fold increase in the risk of CVD compared with the referent group in the Framingham study in any BP category above the optimal [276]. Moreover, LVH [223,224], baPWV [277] and cfPWV [321], carotid IMT plus plaque [252], CAC [323] and ABI [289] have been able to significantly reclassify CV risk, when added to traditional CV risk factors/risk scores.

In post hoc analyses, BP treatment-induced regression of some (but not all) manifestations of HMOD has been associated with a reduction in CV risk, thereby providing additional information on the effectiveness of treatment in individual patients. This has been best illustrated for the treatment-induced regression of LVH measured by either ECG or echocardiography [228,324]. A reduced incidence of CV events and slower progression of kidney disease has been reported with the treatment-induced reduction in urinary protein excretion in both diabetic and nondiabetic patients [325,326], but results are discordant [327–330]. There is also evidence that treatment-induced changes in eGFR predict CV events and progression to ESKD [331,332]. A very large recent meta-analysis, including >100 000 participants [256], showed a reduction of CV risk with reduced cIMT progression, in contrast with the conclusion of an older and smaller meta-analyses [333]. Improvement in PWV over a few years is associated with improved prognosis in patients with resistant hypertension [288] or under dialysis [334]. The predictive power of changes of ABI over time has been mainly investigated in CKD patients [335].

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TABLE 11. Criteria to define HMOD

Measurement	Parameter	Abnormality threshold
ECG		
LVH	$S_{V1} + R_{V5}$ (Sokolow–Lyon)	>35 mm
	R wave aVL	≥11 mm
	$S_{V3} + R_{aVL}$ (Cornell voltage)	>28 mm (M), >20 mm (W)
LVH	Cornell voltage (+6 mm in W) × QRS duration (Cornell duration product)	>2440 mm s
ECHO		
LVH	LVM/BSA (g/m^2)	>115 (M), >95 (W)
	LVM/height (g/m$^{2.7}$)	>50 (M), >47 (W)
RWT	LV conc. Remodeling	≥0.43
LV chamber size	LVDDim/height	>3.4 (M), >3.3 (W) cm/m
LV diastolic dysfunction	*e*′ velocity septal	<7 cm/s
	e′ velocity lateral	<10 cm/s
LV filling pressure	*E*/*e*′ average ratio	>14
	LAV/BSA	>34 ml/m^2
	LAV/height^2	>18.5 (M) or >16.5 (W) ml/m^2
LV systolic dysfunction	GLS	<20%
Kidney		
Function	eGFR	<60 ml/min/1.73 m^2
Albuminuria	UACR	>30 mg/g
Renal resistance index	RRI	<0.07
RRI ?		
Large artery stiffness		
Pulse pressure	Brachial PP (>60 years)	≥60 mmHg
Pulse wave velocity	baPWV (in people 60–70 years)	>18 m/s
	cfPWV (in people 50–60 years)	>10 m/s
Carotid atherosclerosis		
	Plaque	IMT ≥1.5 mm, or focal increase in thickness ≥0.5 mm, or 50% of surrounding IMT
	IMT	>0.9 mm
Coronary atherosclerosis		
	CAC	Age-specific and sex-specific reference value
LEAD		
	ABI	<0.9
Eye		
	KWB score	Grade III (hemorrhages, microaneurysms, hard exudates and cotton wool spots) and grade IV (papilloedema and/or macula edema)
Microvascular changes	Wall-to-lumen ratio	no established reference value

ABI, ankle–brachial index; ACR, albumin : creatinine ratio; baPWV, brachial–ankle pulse wave velocity; BSA, body surface area; CAC, coronary artery calcium; cfPWV, carotid–femoral pulse wave velocity; DDim, diastolic dimension; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; IMT, intima–media thickness; KWB, Keith–Wagener–Barker; LAV, left atrial volume; LEAD, lower extremity artery disease; LVH, left ventricular hypertrophy; LVM, left ventricular mass; M, men; RWT, relative wall thickness; w, women.

Guidance on use and repetition of HMOD with time needs to consider several factors, such as the ability of the HMOD marker to be modified by treatment, the reproducibility of the changes, the time necessary to detect them, their prognostic value and the costs. The characteristics of the most frequent HMOD are shown in Fig. 6.

5.7 When to refer a patient to a specialist or for hospital-based care

Although most patients with hypertension are managed in the primary care setting, in some circumstances, a hospital- based evaluation and treatment may be required, keeping in mind that out-of-office or office-based care of hypertensive patients also depends on the healthcare organization of a given country (Table 12).

6. SECONDARY HYPERTENSION

Secondary forms of hypertension account for only a small fraction of the overall hypertension prevalence, which is largely due to primary hypertension. However, their true prevalence is not precisely known, because available data may be confounded by the selection bias of the studies reported in the literature, the number of undiagnosed cases and the varying definition of secondary forms of hypertension. Hence, the classification of OSA, a phenotype more frequently observed in obese patients, as a secondary form of hypertension is questioned by many experts. Nevertheless, despite their limited prevalence, detection and management of secondary forms of hypertension is of utmost importance, because these forms often carry a high or very-high risk of morbidity and mortality and can possibly be cured by timely treatment of their cause [336]. Secondary forms of hypertension require specific diagnostic approaches, which allow to detect their specific causes and to select effective drug treatment or appropriate interventional treatment that control or cure the elevated BP. Secondary forms of hypertension are a frequent cause of severe or true-resistant hypertension, worsening of previously controlled hypertension or increased severity of HMOD, which may appear as disproportionate to the duration of hypertension (Table 13). Although secondary forms of hypertension are particularly frequent in younger patients (<40 years) with an elevated BP, some forms (such as atherosclerotic renovascular disease) are more common at an older age (Fig. 7).

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Marker of HMOD	Sensitivity to changes	Reproducibility and operator independence	Time to changes	Prognostic value of changes
LVH by ECG	Low	High	Moderate (> 6 months)	Yes
LVH by echocardiogram	Moderate	Moderate	Moderate (> 6 months)	Yes
LVH by MRI	High	High	Moderate (> 6 months)	No data
eGFR	Moderate	High	Moderate (> 6 months)	Yes
UACR	High	Moderate	Fast (weeks to months)	Yes
RRI	Low	High	Slow (>12 months)	Yes
Carotid IMT	Very low	Low	Slow (> 12 months)	Limited data
PWV	High	Low	Fast (weeks to months)	Limited data
ABI	Low	Moderate	Slow (> 12 months)	Limited data
Retina Microvasculatur[a]	High	High	Moderate (> 6 months)	No data

[a]Using modern adaptive optics technology.

FIGURE 6 Characteristics of the most frequent markers of HMOD in hypertension.
[a]Using modern adaptive optics technology.

TABLE 12. When to refer a hypertensive patient to a specialist or to hospital

- Patients in whom secondary hypertension is suspected
- Young patients (<40 years) with grade 2 or 3 hypertension in whom secondary hypertension should be excluded
- Patients with sudden onset or aggravation of hypertension when BP was previously normal
- Patients with treatment-resistant hypertension
- Need of more detailed assessment of HMOD, which might influence treatment decision
- Requirement of more in-depth specialist evaluation from the referring doctor
- Hypertensive emergencies (inpatient care will usually be needed)

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TABLE 13. Patient characteristics that should raise the suspicion of secondary hypertension

Younger patients (<40 years) with grade 2 or 3 hypertension or hypertension of any grade in childhood
Sudden onset of hypertension in individuals with previously documented normotension
Acute worsening of BP control in patients with previously well controlled by treatment
True resistant hypertension hypertension
Hypertensive emergency
Severe (grade 3) or malignant hypertension
Severe and/or extensive HMOD, particularly if disproportionate for the duration and severity of the BP elevation
Clinical or biochemical features suggestive of endocrine causes of hypertension
Clinical features suggestive of renovascular hypertension or fibromuscular dysplasia
Clinical features suggestive of obstructive sleep apnea
Severe hypertension in pregnancy (>160/110 mmHg) or acute worsening of BP control in pregnant women with preexisting hypertension

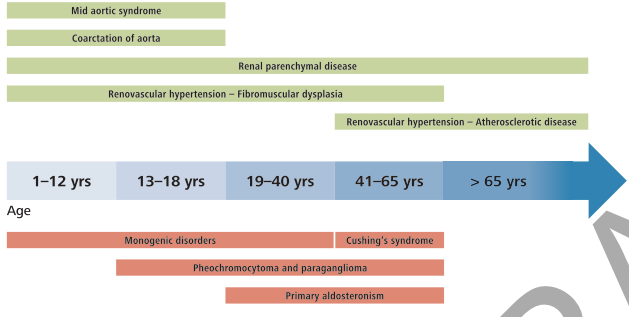


FIGURE 7 Incidence of selected forms of secondary hypertension according to age.

Screening all hypertensive patients for secondary hypertension is not feasible or cost-effective. However, secondary hypertensions frequently show clinical findings that suggest their presence and even their specific nature. More common causes of secondary hypertension are primary aldosteronism, renal parenchymal disease and renovascular disease, while Cushing syndrome, phaeochromocytoma and paraganglioma, or coarctation of the aorta are less frequently observed. The different types of secondary hypertension show different age distributions (Fig. 7).

Diagnostic suspicion (Table 13) should prompt immediate referral to specialized hypertension centers where the appropriate diagnostic tests and subsequent treatments can be performed [212,337–342]. It is beyond the scope of these Guidelines to describe in detail the clinical management of specific causes of secondary hypertension. For most of them, the reader may refer to corresponding ESH position papers [212,339–342]. A summary of important features of selected forms of secondary hypertension is provided in Figs. 8a–e.

6.1 Genetic causes of secondary hypertension

Several rare monogenic forms of hypertension have been described, in which mutations in specific genes, mostly coding for proteins involved in sodium tubular reabsorption or steroid metabolism account for the pathogenesis of hypertension (Table 14). An exception represents familial autosomal dominant hypertension with brachydactyly, in which the pathogenetic mechanism resides inside the vascular smooth muscle cells [343]. Hypertension is usually already present in childhood or early adulthood, though age of onset and severity of hypertension may be modulated by lifestyle, environmental factors and genetic susceptibility. Specific drug treatments addressing the corresponding molecular defects are indicated (for example, amiloride in Liddle's syndrome or dexamethasone in glucocorticoid remediable aldosteronism) [12]. Routine genetic testing by approved genetic laboratories should be done in all phaeochromocytomas and paragangliomas (PPLG) with a yield of genetic mutation at approximately 40%. PPGL patients with a known succinate dehydrogenase subunit B mutation carry a higher malignant potential and should be more closely followed with regular imaging analysis and biochemical screening (Fig. 8).

7. LIFESTYLE INTERVENTIONS

7.1 Relevance of lifestyle changes

The adoption of a heart-healthy lifestyle is a fundamentally important approach to prevent or delay the onset of hypertension, reduce the elevated BP values and lower the associated increase of CV risk [4,345]. Individuals with a healthy lifestyle score have an approximately 4–5 mmHg lower BP, irrespective of the underlying BP genetic risk, than those with an unfavorable lifestyle [346]. Further, healthy lifestyle measures can augment the BP-lowering effect of pharmacological interventions and reduce the number of drugs needed to control BP [347–350]. Each of the lifestyle interventions has greater efficacy at higher starting levels of BP. However, lifestyle changes should never delay the initiation of drug therapy in patients in whom the protective effect of antihypertensive drugs is documented and the related benefits require BP reductions that cannot be obtained by lifestyle-dependent changes only. Although the

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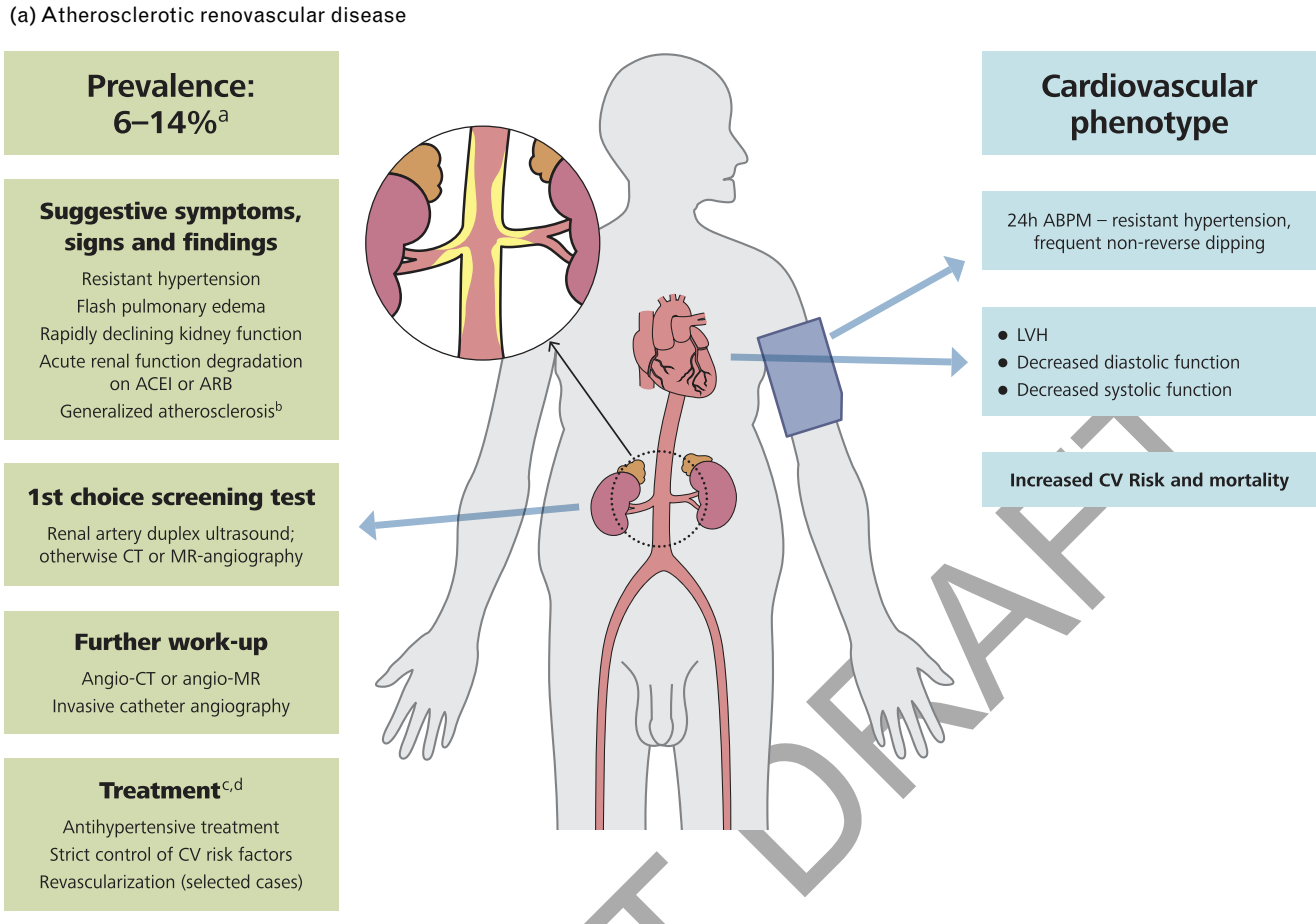


FIGURE 8 A Atherosclerotic renovascular disease (ARVD). (a) The prevalence of ARVD differs considerably between studied populations – in a population-based cohort >65 years of age, ARVD (defined as >60% stenosis) was identified in 6.8%. Among hypertensives, the prevalence of ARVD is probably around 1% in patients with mild hypertension, but may be as high as 14%–24% in patients with severe or resistant hypertension. (b) In view of the frequent association with atherosclerotic lesions in other arterial beds, a cardiovascular work-up should be considered. (c) Medical management of ARVD should aim to reduction of CV risk and protection of kidney function; hypertension control is a prominent goal. With regard to antihypertensive treatment, an ACEI or an ARB are considered as first-line option (contraindicated in bilateral renal artery stenosis or stenosis in a solitary kidney). (d) Observational data showed that renal artery stenting in addition to medical therapy is associated with renal and CV benefits in patients presenting with high-risk ARVD phenotypes – resistant hypertension, recurrent pulmonary oedema, heart failure and deterioration of kidney function.

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evidence is largely limited to observational studies and their meta-analyses, all lifestyle interventions seem to have heart-healthy benefits that may go beyond the benefits associated with their effect on BP. The most important and well established effective lifestyle interventions that have been shown to reduce premature CV morbidity and mortality are losing weight [350], the DASH diet [351,352], salt reduction [353], augmentation of potassium intake [354–356], engaging in regular physical activity and structured exercise [357–360] and a moderation of alcohol consumption [361–363]. In addition, smoking cessation and other lifestyle measures are also important beyond BP. Various other nonpharmacological interventions (e.g. dietary components like polyphenols, coffee and tea, or stress-reducing therapies) have been reported to lower BP, but the extent and/or quality of the supporting clinical trial experience is less robust and persuasive.

The Achilles' heel of treatment strategies based on or inclusive of nonpharmacological interventions is the low persistence of the prescribed measures. This is in part the result of the difficulty of permanently adhering to lifestyles that may interfere with working or home habits and needs. Some lifestyle measures also have a cost, which may not be reimbursed by healthcare providers. After prescribing to their hypertensive patients lifestyle changes that can help or achieve BP control, physicians should establish a FU program that allows to check whether there is adherence to the prescribed measures and whether the therapeutic goal is achieved. This will minimize the risk of the patient continuing with an uncontrolled BP for a prolonged time.

7.2 Weight reduction

Being overweight or obese has been directly associated with hypertension [364,365], whereas weight-loss interventions are well established strategies to lower BP [350,366,367]. A network meta-analysis found reductions of 6.5 mmHg for SBP and 4.6 mmHg for DBP following a low-caloric diet in adults with prehypertension [367]. In patients with hypertension, a low-caloric diet was ranked first among all lifestyle interventions in lowering SBP and DBP [367].

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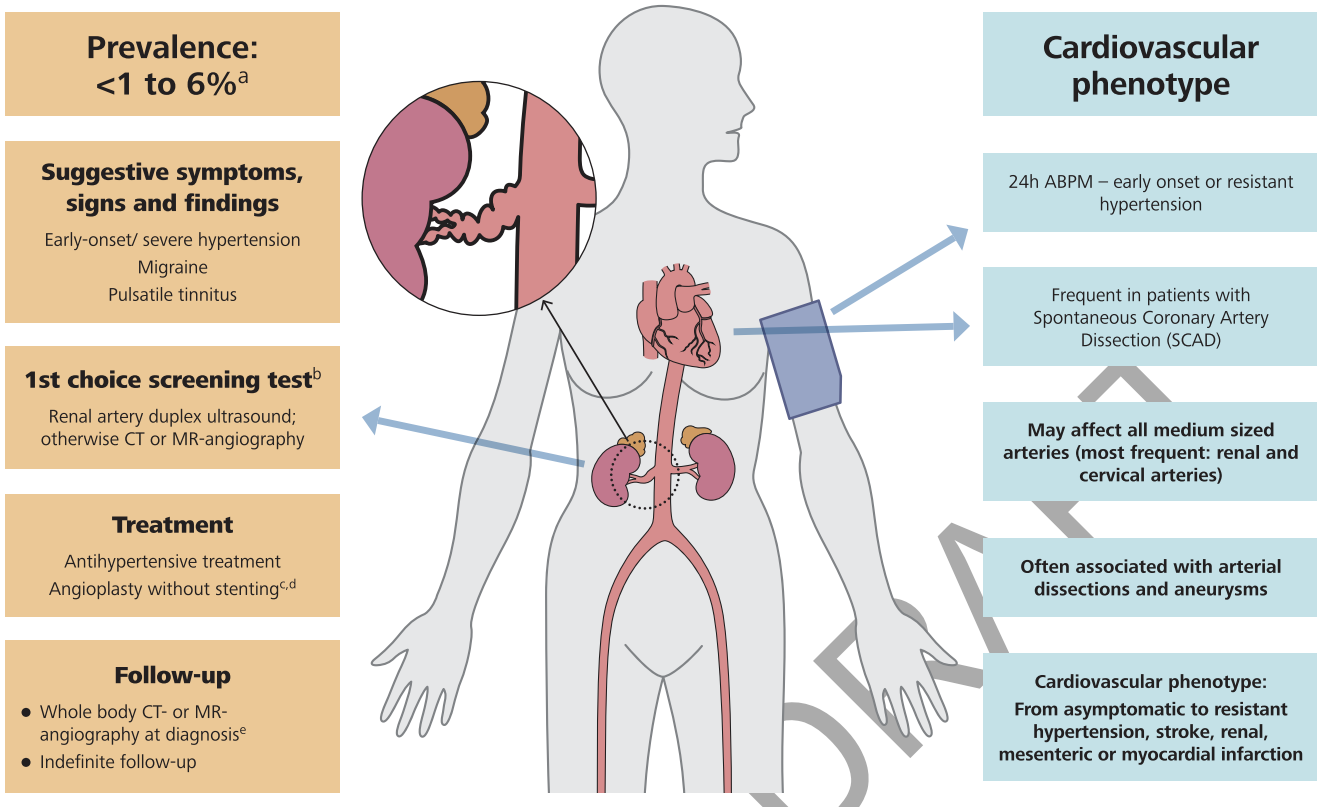


FIGURE 8 B Fibromuscular Dysplasia (FMD). (a) FMD occurs predominantly in young or middle-aged women. However it may be diagnosed at any age, both in women and men. Renal FMD is the second cause of renovascular hypertension after atherosclerotic renal artery stenosis. (b) Two subtypes of FMD have been described: multifocal FMD (80–90% of cases) and focal FMD (10–20% of cases). The characteristic lesion of multifocal FMD is the ''string of beads'', characterized by alternating areas of stenosis and dilatation in the mid and distal portions of the artery. Focal FMD is characterized by focal stenosis of variable length, which may occur in any part of the artery and requires exclusion of atherosclerosis, inflammatory or genetic arteriopathies. (c) In a meta-analysis, the rate of cure of hypertension after angioplasty was 36% (range 14–85%) but may be much higher in younger patients with recent onset hypertension. Angioplasty deserves also to be considered in patients with renal FMD and resistant hypertension. (d) Stent kinking and fracture have been reported in the setting of renal FMD. Accordingly, stenting is usually not recommended in renal FMD and reserved for treatment of flow-limiting per-procedural dissection or in case of renal artery aneurysm. (e) In over 50% of cases, patients with renal FMD have lesions in one or more other arterial beds (multivessel FMD). Patients with FMD also often have arterial dissections, aneurysms or marked arterial tortuosity. For these reasons, it is recommended to perform at least once a life-time from head to pelvis angio CT or if contra-indicated MR-angiography in all patients with FMD.

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Similarly, a meta-analysis of RCTs further concluded that, for each kilogram of body weight loss, both SBP and DBP were reduced by approximately 1 mmHg [350]. Additionally, attenuation of pressogenic factors such as sympathetic activation [368] and a 15% lower all-cause mortality has been found following weight loss interventions, irrespective of age [369]. Modest weight loss, is therefore, a key recommendation and should ideally be achieved through a combination of a low-caloric diet and exercise [367,370]. It should be acknowledged that achievement and maintenance of weight loss through behavioral changes are often challenging, although feasible, over prolonged periods of FU [371]. A rather frequent phenomenon is weight cycling (sequential losses and regains of body weight), which may adversely affect BP, CV risk and the metabolic profile [372]. For those who do not meet their weight loss goals with nonpharmacological interventions, pharmacotherapy could be considered, although evidence on the effectiveness of weight-loss medicines on BP is scant, based on a small number of studies, and these drugs are often associated with unwanted side effects [373]. The GLP-1 receptor agonists reduce body weight and concomitantly lower BP by few mmHg, a favourable therapeutic effect in patients with diabetes and obesity (section 20.1.3). Alternatively, bariatric surgery is an effective, longer lasting strategy for morbidly obese patients to manage BP and CV risk factors and might be considered in case of failure of all of the above measures [374], particularly in patients with severe obesity. Amongst specific predictors associated with weight loss interventions, greater initial weight loss and higher adherence to lifestyle advice were accompanied by greater weight loss success [371]. The type of weight loss programme should always be individually tailored, taking into account setting of realistic goals, tailor-made dietary and exercise regimes and frequent FU to motivate and address challenges in behavior change [371].

7.3 Restriction of sodium intake

There is strong evidence for an association between high sodium consumption and increased BP in the overall population [375,376] and hypertensive patients [377]. Furthermore, the relation between sodium-restricted diets and

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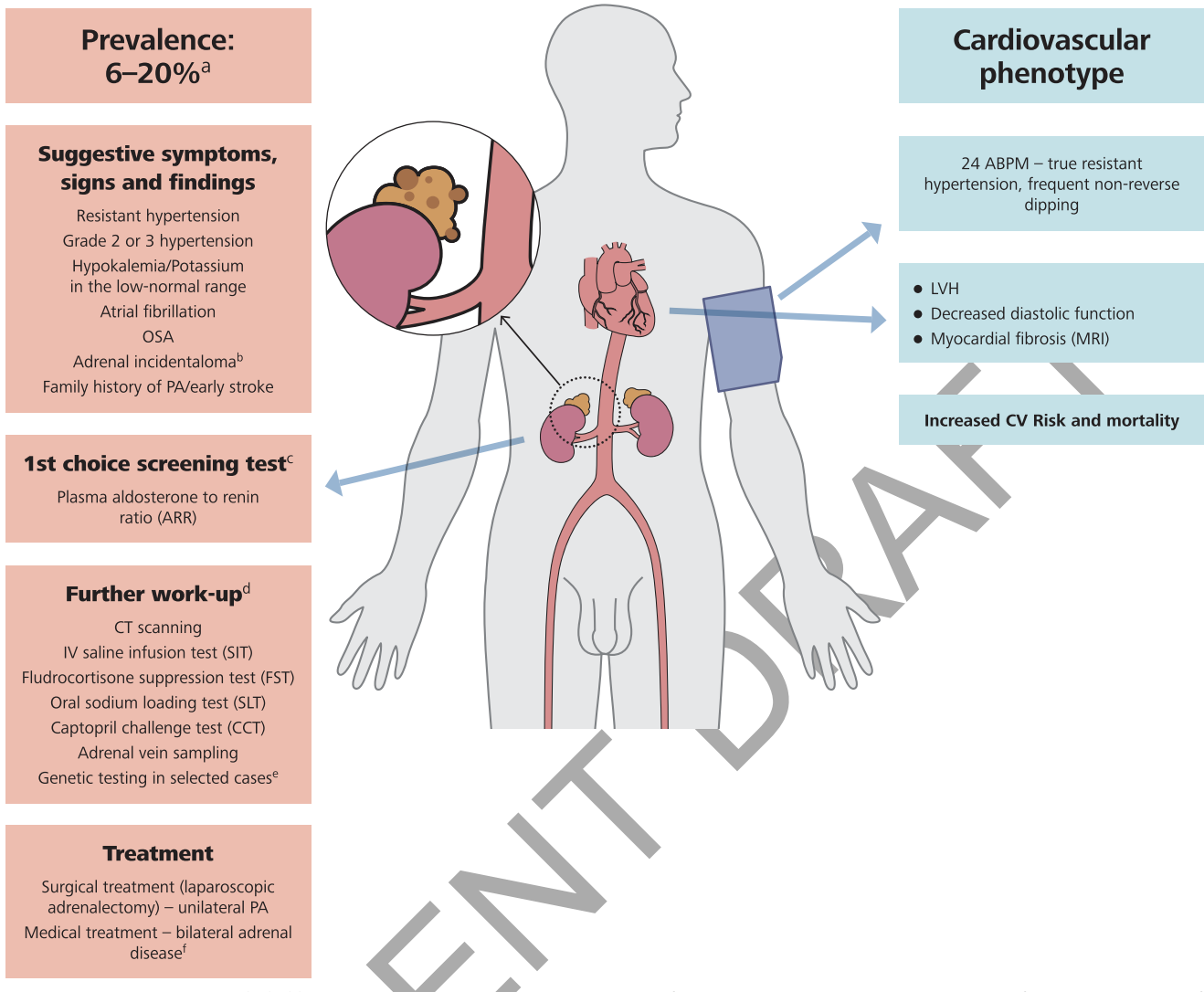


FIGURE 8 C Primary aldosteronism (PA). (a) Depends on the population screened – ranges from 3.2% to 12.7% in primary practice and from 1% to 30% in referral centers; prevalence increases with the severity of hypertension to 20%. (b) PA prevalence in patients with adrenal incidentaloma ranges from 1.6% to 4.3%. (c) ARR requires at least normalization of plasma potassium and interruption of existing treatment with spironolactone and beta-blockers. (d) Overall, seated SIT appears reliable and less complicated than FST and SLT. CCT may be a good alternative in patients at risk of potential fluid overload (patients with kidney failure or HF). (e) Although the majority of primary aldosteronism cases are sporadic, up to 5% of patients may have a familial form of the disease. Genetic testing should be performed in all patients with early onset primary aldosteronism (i.e. <20 years of age), irrespective of the severity of the clinical phenotype, and in patients with a family history of primary aldosteronism. (f) Steroidal MRAs are the treatment of choice for primary aldosteronism in patients with bilateral adrenal disease or unilateral disease that cannot be surgically treated.

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improved BP control has been widely recognized by randomized trials and confirmed by meta-analyses [378,379]. Greater BP reductions have been observed in hypertensive patients and other patient categories (nonwhite people, older populations, patients with diabetes, metabolic syndrome or CKD) [379,380], and restriction of sodium intake has also been reported to lower BP in patients with resistant hypertension [381] and to reduce the number of drugs necessary to achieve hypertension control [382]. A recent network meta-analysis provided evidence for lifestyle interventions restricting sodium intake to <100 mmol (~5.8 g salt per day) resulting in an average of approximately 5/2 mmHg SBP/DBP reduction in patients with hypertension.

Sodium and corresponding salt (NaCl) values are approximately:

Sodium (Na^+) 2.0 g = 87 mmol Na^+ = NaCl (salt) 5.0 g.

Moreover, meta-analysis of RCTs examining sodium intake reduction to as low as 800 mg/day showed a linear decrease in BP [353,379], In addition, a weighted average reduction in dietary sodium intake from about 3.6 g/day to about 2.7 g/day has been found to be associated with an approximately 18–26% reduction in CV disease [383]. However, whether the best

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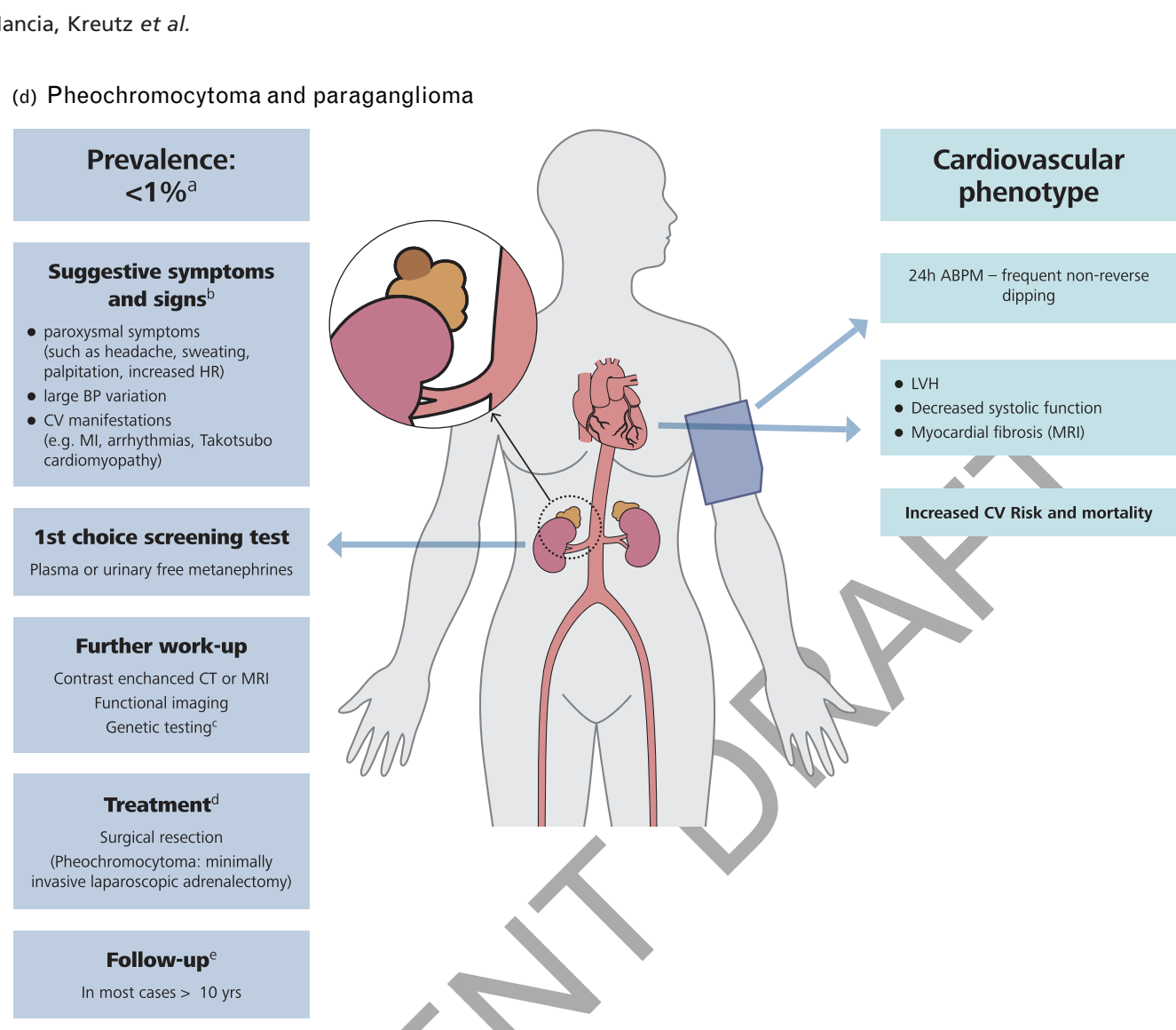


FIGURE 8 D Pheochromocytoma and paraganglioma (PPGL). (a) Varying from 0.2% to 0.6% in hypertensive patients to less than 0.05% in the general population. (b) These symptoms are most commonly reported whereas other (pallor, tremor, nausea, panic/anxiety) occur at a much lower frequency. (c) Routine genetic testing is recommended in all PPGL. The most frequently involved genes include SDHB, SDHD, VHL, RET and NF1. PPGL in patients with a known SDHB mutation do carry higher malignant potential and so require close follow-up with regular imaging and biochemical screening. (d) Presurgical medical preparation using an alpha-1 receptor blocker (doxazosin or phenoxybenzamine) as first choice is always required for preventing life-threatening perioperative cardiovascular complications. (e) All patients operated for a PPGL should be followed up annually for at least 10 years. The first follow-up should be at 2–6 weeks after surgery to verify completeness of surgical resection.

therapeutic strategy should be to pursue unlimited sodium restriction is still a matter of debate [384,385], because there are observational studies showing that below a sodium intake of approximately 3.5 g/day further BP reduction is associated with an increased mortality in both hypertensive patients and the general population [377,386,387]. Furthermore, although no side effects have been reported by epidemiological studies in very low-salt diet populations [354], alterations of BP control mechanisms with low-sodium diets have been observed in experimental settings and studies on hypertensive patients [388,389]. Although some intervention studies are available, a lack of proper long-term randomized trials on the effects of various degrees of sodium restriction on outcomes represents the most important limitation for this medical area. In the studies in which the relationship between dietary sodium and CV outcomes exhibited a J-shaped curve, sodium intake was assessed by sodium excretion in spot urine, and this has been criticized as a measure unable to reflect the more accurate 24 h amount of urinary sodium excretion, from which sodium consumption can be more precisely inferred [390,391]. Larger, longer and more precisely controlled intervention studies than those currently available are needed to shed more light on this issue. Sodium is mainly consumed as salt, which in the diet comes from processed foods or is added to the food during cooking or at the table. For people with a long-established habit of high salt intake, it might be difficult to attain and maintain long-term voluntary salt control, and alternative approaches might be needed. A salt substitute with low-sodium content and an acceptable salty flavor would be an ideal alternative. Evidence supports the use of salt substitutes in adults with prehypertension and hypertension [367,392]. In a random-effects model, participants consuming a salt substitute showed significant SBP and DBP reductions (−4.8 and −1.5 mmHg, respectively) compared with participants consuming normal salt [393]. Of the five studies with mortality outcome data, salt substitute also significantly reduced all-cause mortality (hazard ratio 0.88) [393]. Daily diet modification by this nonpharmacological management may, thus, improve BP control.

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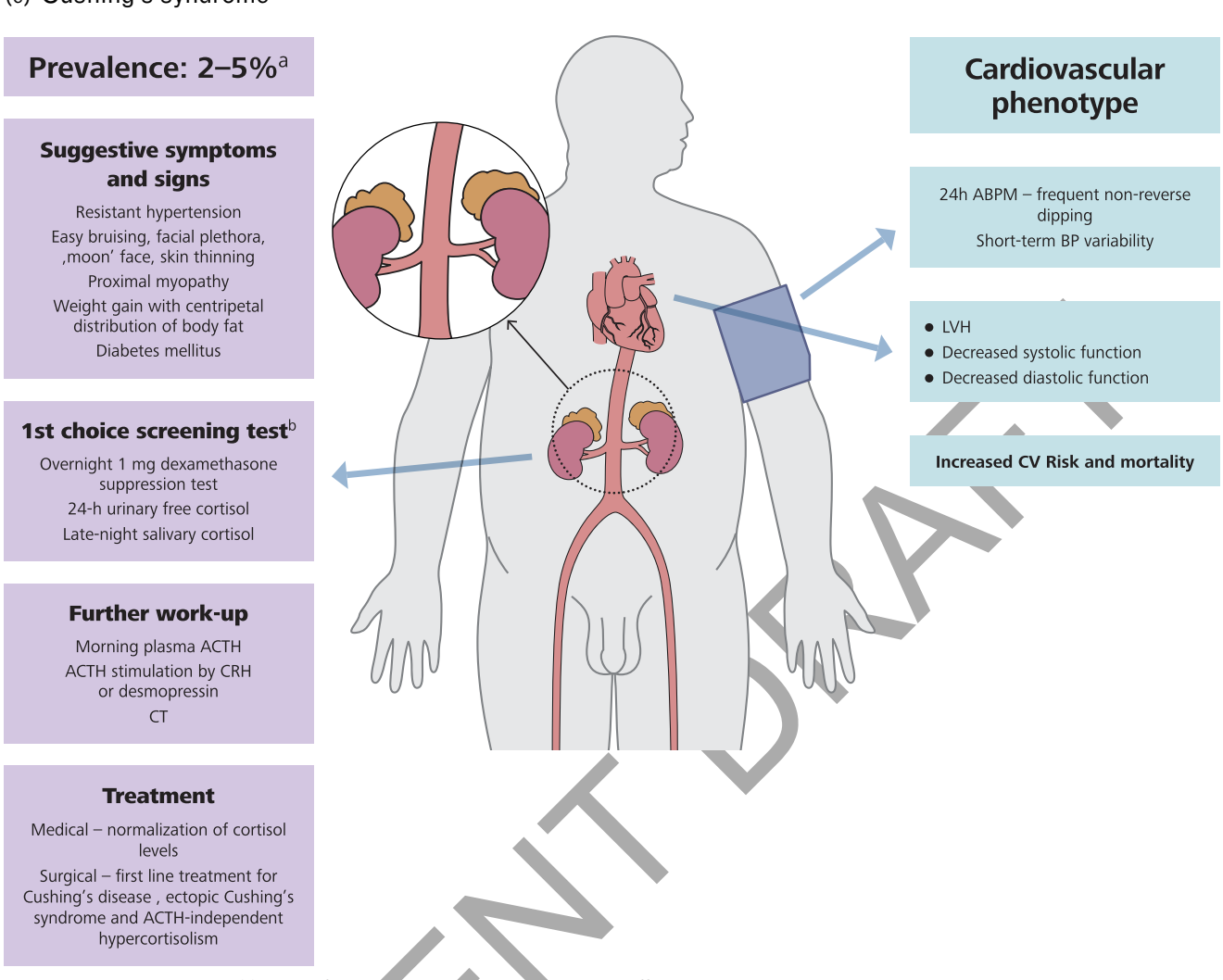


FIGURE 8 E Cushing's syndrome. (a) In specific populations including patients with difficult to control hypertension or type 2 diabetes. The incidence in the general population is 0.7-2.4 per million per year. (b) In case of abnormal initial result of a first screening test, positivity of at least one of the remaining screening tests is required to establish the diagnosis.

7.4 Augmentation of dietary potassium intake

Dietary potassium is associated with BP and hypertension [386], with recent data suggesting a U-shape relation, indicating that an adequate intake of potassium is desirable to achieve a lower BP level but that an excessive potassium intake should be avoided [356]. Potassium supplementations (especially with intakes of 75–125 mmol per day) have been effective in lowering BP [354,355,394], especially in adults with hypertension [395], adults consuming an excess of sodium and Black people. The typical BP-lowering effect of a 60 mmol (1380 mg) administration of potassium chloride has been about 2 and 4–5 mmHg in adults with normotension and hypertension, respectively, although the BP response can be up to twice as much in persons consuming a high-sodium diet [395]. The large recent randomized controlled Salt Substitution and Stroke Study (SSaSS) trial reported that increasing potassium intake as a sodium substitute, i.e. replacing 25% sodium chloride with potassium chloride in salt, reduces the risk of stroke, disease and death in patients with increased CV risk plus low-potassium and high-sodium intake at baseline [392]. A recent meta-analysis [356] provides further support for a population goal of potassium intake recently set by international authorities, such as 90 mmol per day (3500 mg/day). In most trials, potassium supplementation was achieved by administration of potassium chloride pills, but the BP response pattern was similar when dietary modifications were used [394]. Because potassium-rich diets tend to be heart-healthy, they are preferred over the use of pills for potassium supplementation. Good sources of dietary potassium include fruits and vegetables, as well as low-fat dairy products, selected fish and meats, nuts and soy products. Four to five servings of fruits and vegetables will usually provide 1500 to >3000 mg of potassium. This can be achieved by a diet, such as the DASH diet, that is high in potassium content.

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TABLE 14. Rare genetic causes of secondary hypertension [344]

Condition	Phenotype	Mechanism and Treatment
Liddle syndrome	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC	Increased renal tubular ENaC activity; responds to treatment with amiloride
Apparent mineralocorticoid excess	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC	Decreased 11β-hydroxysteroid dehydrogenase isoenzyme 2; responds to spironolactone
Gordon syndrome	Hyperkaliemia, metabolic acidosis, low PRA or PRC, low/normal PAC	Overactivity of the sodium-chloride cotransporter; responds to Thiazide
Geller syndrome	Pregnancy-exacerbated hypertension, low PRA or PRC, low PAC	Agonist effect of progesterone on the mineralocorticoid receptor (which is constitutively active); responds to amiloride, spironolactone activates instead of blocking the receptor
Glococorticoid-remediable aldosteronism (familial hyperaldosteronism type I)	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Chimeric *CYP11B1/CYP11B2* gene; responds to glucocorticoids
Familial hyperaldosteronism type 2	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Increased activity of CLCN2 chloride channel; responds to steroidal MRA
Familial hyperaldosteronism type 3	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Loss of selectivity of KCNJ5 potassium channel; patients who do not respond to steroidal MRA require bilateral adrenalectomy
Familial hyperaldosteronism type 4	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC	Increased activity of CACNA1H calcium channel; responds to steroidal MRA
PASNA syndrome (primary aldosteronism, seizures and neurological abnormalities)	Hypokalemia, metabolic alkalosis, low PRA or PRC, increased PAC; neurological defects coexists	Increased activity of CACNA1D calcium channel; responds to steroidal MRA and CCB
11beta-hydroxylase Deficiency	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC, virilization of female individuals	Reduced activity of 11β-hydroxylase with increase of DOC and androgens; responds to glucocorticoids
17alpha-hydroxylase deficiency	Hypokalemia, metabolic alkalosis, low PRA or PRC, low PAC, pseudohermaphroditism in male individuals	Reduced activity of 17α-hydroxylase with increase of DOC and reduction of androgens; responds to glucocorticoids
Autosomal dominant hypertension with brachydactyly [343]	Brachydactyly type E (BDE), short stature, severe hypertension (salt-independent, age-dependent), high risk of death from stroke before age 50	PDE3A mutations upregulated the cAMP-hydrolytic activity that results in lower cAMP levels in vascular smooth muscle cells

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7.5 Increase levels of daily physical activity and regular exercise

The acute pressor effect of dynamic and isometric exercise does not contraindicate regular exercise on a chronic basis. Large epidemiological studies, which allowed for age and other confounding factors, have yielded consistent evidence of an inverse relation between the incidence of hypertension and habitual levels of physical activity, assessed by means of questionnaires or sometimes an interview [396,397]. For each 10 metabolic equivalent of task (MET)-hours per week increment in leisure-time physical activity (which corresponds to the recommended minimum physical activity level of 150 min per week), the risk of developing hypertension was found to fall by 6% [396]. In addition, the BP-lowering effect of structured exercise has been repeatedly demonstrated in RCTs [347,357,360,398], especially when focused on dynamic aerobic exercise [357,358,399,400] but also, though to a lesser extent, following dynamic resistance training [359,401] and static isometric exercise [402,403,404]. The BP reductions have been documented irrespective of age [399,405], sex [406,407] or ethnicity [399,408]. The average SBP reductions with aerobic exercise are approximately 2–4 and 5–8 mmHg in adult patients with normotension and hypertension, respectively [409]. Regarding the exercise intensity, moderate-intensity aerobic exercise (40–60% heart rate reserve) is recommended to prevent and treat hypertension [358], although many hypertensive patients present with diverse comorbidities, are older or limited in the level of physical activity they can undertake. In this context, it is of note that a Cochrane meta-analysis including 73 trials found moderate-certainty evidence that walking already results in meaningful BP reductions [410]. In patients with hypertension, a daily bout of exercise is preferred, to minimize the problem of postexercise hypotension [411–413]. Finally, a physically active lifestyle and regular exercise have positive effects on many other adverse health outcomes and CV risk factors at all ages and sexes, and across all BP categories [398,401]. BP reductions and cardiometabolic benefits have also been reported with low-intensity physical activity (6 min hourly) in highly sedentary people [414]. In addition to its role in the prevention of hypertension and reduction of an elevated BP, there is also evidence from observational studies that a physically active lifestyle prevents the development of CV disease, irrespective of BP level [415–419]. The reduction of risk is continuous across the full range of physical activity volumes, but the slope of the risk decline is steepest for the least active individuals [415,418].

7.6 Moderation of alcohol intake

Large-scale observational studies report a strong positive linear association between alcohol consumption and BP [420,421]. Data from epidemiological studies on alcohol consumption largely rely on self-reported alcohol intake of participating people as defined by drinks per day. Sex differences in the metabolism of alcohol with a lower first-pass metabolism in female individuals and differences in distribution due to body composition have possibly explained differences in the

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recommended upper limits for daily pure alcohol intake with higher limits for men than for women [4]. This contrasts with the fact that the global attributable impact of alcohol intake to mortality is more than four-fold higher in men than in women [422], thus putting in question the recommendation of higher values in men. Previous observational data suggested a decrease in CVD, particularly CAD, with light drinking compared with abstainers [423,424]. However, this potential cardioprotective effect of low-to-moderate alcohol intake on CAD seems largely because of a healthier life style in these individuals, and the effect is attenuated after full adjustment for the confounding factors [425]. Indeed, recent epidemiological and genetic Mendelian randomization studies indicated a continuous nonlinear positive relationship between alcohol intake and BP [425,426]. The risk for hypertension increases in both men and women, if daily alcohol intake is at least one to two drinks (at least 10–20 g alcohol) per day [427]. An important meta-analysis of 36 RCTs with overall 2865 participants (a smaller fraction of 14%, i.e. 401, were women) revealed that alcohol reduction close to abstinence was associated with a 3.3/2.0 mmHg SBP/DBP reduction [361]. The benefit seems to be consistent across trials but confined to people consuming $\geq$3 drinks/day (equivalent to about $\geq$42 g alcohol intake/day according to the definition in this report). A dose-dependent effect was observed particularly in heavy drinkers, i.e. in people who consume $\geq$6 drinks/day at baseline and reduce their alcohol intake by about 50% experiencing an SBP/DBP reduction of approximately 5.5/4.0 mmHg [361]. Additionally, both trial data and observational literature support the hypertensiogenic effect of binge drinking [428]. In this regard, it is important to mention that together with hypertension, excessive alcohol intake is the most important risk factor for intracranial hemorrhage [429]. Consequently, excessive (binge) drinking should be avoided, and patients with high risk for intracranial bleedings should be adviced accordingly. Unfortunately, recommendations among different guidelines vary regarding the upper limits and the definition of drinks, and the recommendations of sex-specific upper limits for alcohol intake appear questionable. Nevertheless, moderation of alcohol intake and implementation of alcohol-free days during the week in people who consume drinks that contain alcohol are generally recommended to improve BP control and overall health [430].

7.7 Smoking cessation

Tobacco smoking is the single largest preventable cause of death and is known to significantly increase the risk of CVD [431,432]. Compared with nonsmokers, smokers more frequently present with MH, documented by normal office and higher daytime ambulatory BP values [433]. Because smoking a cigarette is accompanied by a sympathetic nervous system activation and a prolonged BP increase (about 30 min) [388], the ups and downs of BP also increase daytime BP variability [433]. In addition, smoking may impair the BP-lowering effect of some antihypertensive drugs, i.e. BBs [434]. Therefore, the history of tobacco use should be carefully established, and smokers should be encouraged and counselled regarding smoking cessation. Attention should also be given to passive exposure to smoking, which has been associated with the risk of CVD and a 24 h BP elevation [435]. Brief advice from a physician may already be advantageous when time is limited [436], though combining behavioral support with pharmacotherapy increases the chance of success compared with brief advice alone [437]. Increasing the intensity of this behavioral support, as measured through the number of contacts, duration of each contact, and programme length, had point estimates associated with modestly increased chances of quitting [437]. In recent decades, water pipe smoking has developed into a major and rapidly growing alternative to traditional tobacco smoking within the global tobacco epidemic [438]. Likewise, e-cigarettes [439] originally marketed as potential aids in smoking cessation, have attracted a lot of consumers, including both smokers and nonsmokers. Recent meta-analyses now highlight that these 'so-called safer' alternatives acutely increase BP [440,441], heart rate and may also be associated with increased risk of CV disease [439,440,442]. Similarly, the few available studies showed no clear difference in the CV disease incidence between waterpipe smoking and traditional tobacco smokers [443]. Although the available indirect evidence regarding the CV effect of e-cigarette and water pipe smoking is currently based mainly on nonrandomized observational studies of small sample sizes, overall moderate quality and short-term follow-up, the evidence to date suggests that they should not be regarded as CV safe products [441]. Health professionals should, therefore, be cautious in recommending the use of e-cigarettes to their patients and the general public.

7.8 Other dietary interventions

Diet is an important modifier of vascular health and BP, and it has been shown that targeting the whole diet has synergistic and cumulative effects on BP beyond individual foods and nutrients. The most well established dietary interventions for the reduction in BP are the DASH diet [367] and the Mediterranean diet [444,445,446], with the DASH eating plan offering the best demonstration of BP-lowering effectiveness [348,367]. The DASH diet promotes the consumption of whole grains, fruits, vegetables and low-fat dairy products. It provides a means to enhance intake of potassium, calcium, magnesium and fiber [352]. High-quality evidence confirms that the DASH diet results in a significant reduction in SBP and DBP, irrespective of the hypertension status [348,367]. Even modest adherence to the DASH diet is associated with a lower risk of all-cause and cause-specific mortality [447]. Greater adherence to a Mediterranean diet has also been found to be associated with a 10% reduction in CV incidence or mortality [448]. A higher adherence to the DASH diet also strengthens the risk-reducing association [447]. Other diets including vegetarian, Paleolithic, low-carbohydrate, low glycemic index, high-protein and low-fat diets have also been shown to reduce BP, though results are inconsistent and the quality of evidence low [449,450]. Coffee has been reported to have a modest short-lasting pressor effect but recent data appear to indicate that its moderate regular consumption

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does not adversely affect BP and the CV system [451], including the absence of an effect of acute coffee consumption on premature atrial contractions [452]. Results from four observational and one quasi-experimental studies have shown that, depending on individual's CYP1A2 genetic profile, a high caffeine intake may actually protect nonsmokers but not smokers from hypertension [453].

7.9 Improve stress management

Stress and anxiety are associated with an increased risk of hypertension and CV events [454,455]. Patients with mental distress may develop a sudden increase in BP, which may normalize when the distress is relieved [455]. Growing evidence also links the exposure to intensely traumatic life events with an increased risk of hypertension [455–458]. Recent meta-analyses report promising results for the ability of mind-body stress reducing interventions to not only reduce stress and mood swings but also SBP and DBP, although the quality of the evidence is low [367,459]. Meditation [460,461] and breathing control through e.g. yoga are considered to be among the better stress-reduction interventions for lowering BP [367], though their effect sizes are smaller compared with the main lifestyle interventions [367].

7.10 Exposure to noise and air pollution

Exposure to environmental noise and air pollution are two major risk factors that exert a negative impact on CV health, particularly in urbanized settings. Both factors are environmental stressors that have been identified as risk factors for increases in BP, incident hypertension and also HMOD, including vascular stiffness [462]. Air pollution is a complex mixture of gaseous and particulate matter components, and noise exposure is largely due to traffic noise. Interestingly, clinical and experimental studies support the two factors may share common mechanistic pathways, leading eventually to vascular inflammation and endothelial dysfunction that mediate the BP increasing effects. Additional studies showed that that cessation of air pollution or noise reduce both BP and the intermediate pathways, supporting a causal link [463]. Thus, reducing traffic noise and air pollution are important general health policy measures in the global and national context and can make an important contribution to improving BP control and CV health. On an individual level, the possibility to escape from detrimental environmental exposures is obviously limited. However, hypertensive patients can reduce exposure to air pollution by modifying the location, timing and type of outdoor activities and may also try to reduce indoor exposure to noise and air pollution.

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Lifestyle interventions

Recommendations and statements	CoR	LoE
In adults with elevated BP who are overweight or obese, weight reduction is recommended to reduce BP and improve CV outcomes.	I	A
Preferred dietary products include vegetables, fruits, beans, nuts, seeds, vegetable oils, and fish and poultry among meat products. Fatty meats, full-fat dairy, sugar, sweetened beverages, and sweets should be limited. Overall, a healthy dietary patterns including more plant-based and less animal-based food is recommended.	I	B
In adults with hypertension consuming a high sodium diet (most Europeans), salt substitutes replacing part of the NaCl with KCl is recommended to reduce BP and the risk for CVD.	I	A
Dietary salt (NaCl) restriction is recommended for adults with elevated BP to reduce BP. Salt (NaCl) restriction to < 5 g (~2g sodium) per day is recommended.	I	B
Increased potassium consumption, preferably via dietary modification, is recommended for adults with elevated BP, except for patients with advanced CKD.	I	B
Daily physical activity and structured exercise is recommended for adults with elevated BP to reduce BP and improve cardiovascular risk profile. It is recommended to strive for at least 150-300 minutes of aerobic exercise a week of moderate intensity, or 75-150 minutes a week of aerobic exercise of vigorous intensity or an equivalent combination. Sedentary time should also be reduced and supplemented with dynamic resistance exercise (2-3 times per week).	I	B
Adult men and women with elevated BP or hypertension who currently consume alcohol (≥3 drinks[a]/day) should be advised that reduction of alcohol intake close to abstinence will lower their BP.	I	B
Alcohol should not be recommended for CVD prevention, as previous studies linking moderate consumption to lower CV risk are likely confounded.	III	B
It is recommended to avoid excessive (binge) drinking to reduce BP, and the risks particularly for haemorrhagic stroke and premature death.	III	B
Smoking cessation, supportive care and referral to smoking cessation programs are recommended for all smokers to avoid ambulatory BP increases, reduce the risk of masked hypertension, and improve CV health outcome.	I	B
Reduced stress via controlled breathing exercises, mindfulness-based exercise and meditation may be considered.	II	C

[a]There are varying definitions for drinks used in the literature; a drink may relate to about 350 ml of regular beer containing 5% alcohol by volume or 150 ml of wine containing 12% alcohol by volume.

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8. BENEFITS OF ANTIHYPERTENSIVE TREATMENT

Although improvement or correction of inappropriate lifestyle patterns can lower BP and reduce total CV risk [464], most patients with hypertension require antihypertensive drug treatment alongside lifestyle interventions. A large number of outcome-based RCTs support preventing CVD by drug treatment [465–467]. Meta-analyses of RCTs have shown that in hypertensive patients, a 7 mmHg average reduction in office SBP substantially reduced major CV events, i.e. stroke, coronary and HF, as well as CV and all-cause mortality. RCTs have also shown a protective effect against asymptomatic cardiac [465,466,468] and kidney damage [467], and accumulating evidence supports a BP-dependent prevention of cognitive decline and dementia [469,470]. These protective effects have been observed irrespective of baseline BP within the hypertensive range, the level of CV risk, the presence of comorbidities (e.g. diabetes, dyslipidemia and CKD), age, sex and ethnicity. Furthermore, the clinical benefits shown by more recent meta-analysis [471] are similar to those provided by meta-analysis of the older RCTs published in 1994 [472], indicating that the benefits of antihypertensive treatment have not been attenuated by the widespread concomitant prescription that are common in contemporary medicine of lipid lowering, antidiabetic and antiplatelet protective therapies to higher risk patients. It should also be mentioned, that the antihypertensive drug-related benefits are likely to be even greater than those described by RCTs, because the analyses of trials are usually done according to the intention-to-treat principle, which means that they include patients irrespective of whether they adhere to their treatment. It is well known that adherence to the assigned drug treatment strategy is poor in clinical practice but far from being optimal also in trials [473,474–476], which reduces protection because adherence is closely associated with the benefits of antihypertensive drug treatment [477,478]. Finally, several comprehensive cost-effectiveness analyses on the use of pharmacological treatment of hypertension have been reported [479–482], and there is a general agreement that treatment of hypertension is highly cost-effective, because prevention of a large number of fatal and nonfatal events (the latter leading to hospitalization, complex medical interventions and frequent disabilities) is accompanied by a marked reduction of healthcare-related costs. This can be effectively reduced by treatments, which are largely based on inexpensive drug classes that are almost always also available as generics. The recommendations that follow are based on outcome evidence from RCTs. However, whenever appropriate, mention is also made of other types of data because in hypertension, outcome-based RCTs have some important limitations, such as that data are largely restricted to middle-aged, older and higher risk patients and treatment duration covers a relatively short period, usually 3–5 years. This means that important recommendations such as treatment of hypertension in young patients and continuation of BP-lowering interventions indefinitively require an extrapolation, the appropriateness of which can be supported by other sources of evidence. Big data, now being collected by national health system registries, health insurance companies, health utilization databases and prolonged observational FU of RCTs, are becoming an important source of long-term information in wider population strata. Evidence from these sources suggests that the benefits of antihypertensive treatment reported by RCTs for a limited number of years are maintained for many years beyond the trial duration.

9. ANTIHYPERTENSIVE DRUG TREATMENT INITIATION

9.1 Should treatment initiation be based on total CV risk?

Recent meta-analyses of RCTs reported that BP reduction was beneficial across almost the entire BP range, whereas when BP-lowering data were stratified according to CV risk, relative risk reductions were similar for the various risk strata [483–485], while absolute risk reductions were greater with higher baseline CV risks. These data have been taken as evidence that BP-lowering treatment should be initiated according to the CV risk level and that target patients should be those at the greatest risk, irrespective of their BP. The present guidelines do not support this conclusion, because evidence is available that, although compared with the low-risk condition, patients at high or very-high CV risk exhibit a greater treatment-induced absolute reduction of CV outcomes, higher CV risk levels are associated with a disproportionately greater residual risk compared with patients at low–moderate risk. This means that at high-risk, treatment fails to exert an adequate protection, presumably because a considerable proportion of the high risk is not reversible by treatment anymore [80]. Moreover, failure to recommend antihypertensive treatment in the low-risk condition, such as in younger patients, does not take into account that under this circumstance, the benefit cannot be quantified only by reduction of CV events or mortality, but it includes the delay or prevention of asymptomatic or subclinical organ damage and, thus, progression to a high and largely irreversible risk years later.

The above data and considerations support earlier in-life treatment of hypertension as well as treatment implementation also when CV risk is still low-to-moderate. Although total CV risk provides clinically important information and should always be quantified, the data also support the decision to start antihypertensive drug treatment based on office BP level according to the values mentioned in the subsequent sections.

9.2 Office BP thresholds for initiation of drug treatment

All guidelines agree that patients with grade 2 or 3 hypertension should be offered antihypertensive drug treatment alongside lifestyle interventions [4,32,486,487]. Guidelines are also consistent in recommending that patients with grade 1 hypertension and a high CV risk should also be treated both via lifestyle modifications and BP-lowering drugs. Offering BP-lowering drugs to patients with grade 1 hypertension and low-to-moderate CV risk (no CVD, diabetes, CKD or HMOD) has been denied in the past and is still somewhat controversial. The uncertainty originates from the fact that most RCTs have mainly recruited patients with at least grade 2 hypertension, often within an age range in which age per se importantly contributes to a high CV-risk level [488]. Furthermore, some RCT-based meta-analyses have not found a significant

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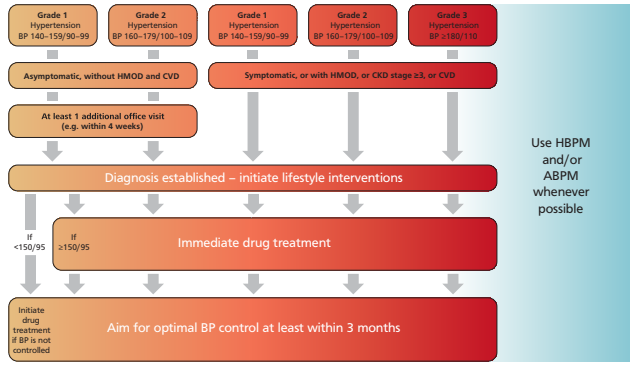


FIGURE 9 Diagnosis by office BP and initial management of hypertension.

treatment-related CV benefit in patients with grade 1 hypertension and low CV risk [485]. However, three more recent meta-analyses [80,471,489], have reported significant treatment-induced reductions of CV events and mortality in patients with grade 1 hypertension. The conclusion of one meta-analysis [26] is weakened by the fact that a substantial number of patients was on antihypertensive treatment, thus having a higher initial BP and thus presumably not always a grade 1 hypertension. Furthermore, several patients had diabetes and were, therefore, at high CV risk. This was not the case for the second meta-analysis [490] (five RCTs including 8974 patients), in which untreated patients with grade 1 hypertension and a true low-risk condition showed a 34% combined stroke and CAD reduction with an about 7 mmHg SBP reduction. It was also not the case for the third meta-analysis [489], which demonstrated a reduction of death and CVD by reducing BP in patients with a baseline BP in the grade 1 hypertension range. These findings have been further supported by the results of the HOPE-3 trial [491], showing a 27% reduction in major CV outcomes when SBP was lowered by 6 mmHg in a subgroup of patients mostly (80%) untreated, at intermediate CV risk and with baseline SBP values >143.5 mmHg (average 154 mmHg). Based on the above data, we recommend that in all hypertensive patients, lifestyle advice should be accompanied by BP-lowering drug treatment, and that this should include patients with grade 1 hypertension, irrespective of the CV risk (Fig. 9). However, in patients with grade 1 hypertension in its lower BP range, no HMOD and a low CV risk, the possibility may be considered to start treatment with lifestyle changes only (Section 7). The duration of a lifestyle-based intervention alone can be of several months (e.g. 6 months) and will depend on the level of BP within the grade 1 range (closer to 140 mmHg SBP), the opportunities for the implementation of lifestyle changes and the perceived adherence to the lifestyle regimen, all related to the likelihood of achieving BP control. If BP control is not achieved within a few months of a lifestyle-based approach, drug treatment will be necessary.

Office BP thresholds for drug treatment initiation

Recommendations and statements	CoR	LoE
In patients 18 to 79 years, the recommended office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP.	I	A
In patients ≥80 years, the recommended office SBP threshold for initiation of drug treatment is 160 mmHg.	I	B
However, in patients ≥80 years a lower SBP threshold in the range 140 – 160 mmHg may be considered.	II	C
The office SBP and DBP thresholds for initiation of drug treatment in frail patients should be individualized.	I	C
In adult patients with a history of CVD, predominantely CAD, drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg).	I	A

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9.3 Should BP-lowering treatment be initiated in patients with office BP <140/90 mmHg?

Previous guidelines [4,492] recommended avoiding antihypertensive treatment in people with high-normal BP and low CV risk. This decision was based on the following findings: (i) in the RCTs and meta-analyses that reported a reduction of CV outcomes by lowering an initial high-normal BP, all or many patients were already under antihypertensive treatment and had thus an original BP higher than that measured in the trials [467]. This has been the case, for example, in the SPRINT trial, in which patients had a baseline SBP slightly below 140 mmHg on a background of almost two antihypertensive drugs per patient [11], (ii) the HOPE-3 trial [491] showed that BP-lowering treatment did not reduce the risk of CV events in people with low-moderate CV risk and SBP values in the high-normal range and (iii) a meta-analysis of 13 RCTs or RCT subgroups of patients at low-moderate CV risk and an untreated baseline BP in the high-normal or normal range showed [467] ($n = 21\,128$ patients) no effect of BP-lowering treatment on any CV outcomes [493]. The present guidelines reconfirm the recommendation not to initiate antihypertensive drug treatment in low-to-moderate risk patients with a BP in the high-normal range. In these patients, intervention should be limited to lifestyle advice, because this reduces their risk of progression to established hypertension and increased CV risk. It is important to note that the recommendation not to offer drug treatment to people with a high-normal and low-moderate CV risk does not take into account the results of a large, recent, individual-participant meta-analysis of RCTs, which has reported that in both primary and secondary CV prevention, an SBP reduction of 5 mmHg reduced outcome risk when baseline SBP spanned almost the entire normality range, including SBP values <120 mmHg [483]. However, interpretation of the data from this meta-analysis is problematic for a variety of reasons [36]. For example, many patients included in this meta-analysis were previously treated with BP-lowering drugs, which means that their true baseline BP was variably higher than recorded. Furthermore, data exhibited subgroup inconsistencies, i.e. benefits, were seen in patients with a baseline SBP <120 mmHg but not in some subgroups of patients with SBP values above 120, 130 or even 140 mmHg. Finally, in this meta-analysis, the benefits of antihypertensive treatment at normal baseline BP were at least in part inferred from comparisons of patients in whom BP differences were obtained by increasing treatment in the lower on-treatment BP group and discontinuing treatment in the higher on-treatment BP Group. Treatment discontinuation might have caused a rebound increase in outcome and magnified or created the outcome difference with the group at lower BP values [494,495].

The decision regarding treatment may be different in patients with a high-normal BP and a very high CV risk. In a meta-analysis of 10 RCTs or RCT subgroups that included individuals with established CVD (mainly myocardial infarction) and an untreated high-normal BP (26 863 patients), a few mmHg SBP reduction was accompanied by a reduced risk of stroke, although not of any other CV event [493]. In another RCT meta-analysis of trials in patients with previous CAD and a baseline mean SBP of 138 mmHg, treatment was associated with a 10% reduction in the risk of major CV events, although not with prolonged survival [471]. Thus, treating people with high-normal BP and established CVD, especially CAD, can be recommended because this has a protective effect, albeit limited to some BP-dependent outcomes and restricted to patients at very high CV risk. It should be considered, however, that the vast majority of these patients will probably already be under BP-lowering drugs, administered in the context of GDMT (e.g. RAS inhibitors or BBs in patients with CAD) for their direct CV protective properties.

9.4 Drug treatment initiation in older people

The present guidelines rely on the definition of older patients as those aged ≥60 or 65 years [488], although further definitions of older persons as those aged ≥80 years are now also used (Section 15.3.2). Evidence that at ≥60 or 65 years of age, antihypertensive drug treatment is beneficial, is unequivocal and greater than that available for younger patients. The BP threshold for drug-based interventions in older patients has for years been an SBP ≥160 mmHg, because this was the BP recruitment criterion for all RCTs in older hypertensive people [5]. Information on the treatment benefits with a lower SBP was of little help, because data included a large number of patients who were already treated at trial initiation. Recently, however, evidence in older patients mostly or entirely untreated at trial initiation has been made available. Thomopoulos *et al.* [488] have shown that, in patients from three major trials aged 60–79 years, BP-lowering treatment was accompanied by a clear reduction of CV death, major CV events and all-cause death [488]. This has been confirmed in two more recent trials. In the HOPE-3 trial [491], the beneficial effects of BP lowering on CV outcomes were observed in patients with grade 1 mostly untreated hypertension, whose mean age was about 66 years. In the STEP trial [496], conducted in patients 60–80 years old, more intense BP lowering reduced the risk of major CV events, and the CV benefits were obtained primarily in people with a baseline SBP >152 mmHg and a Framingham Risk Score ≥15%. Thus, the present guidelines recommend antihypertensive drug treatment to be implemented in patients aged ≥60 or 65 years, when SBP is ≥ 140 mmHg, regardless of the DBP level. In older patients aged 60 to 79 years treatment is recommended also, when a SBP elevation is accompanied by a normal or even low DBP, because outcome-based RCTs have shown that in ISH patients within this age range, antihypertensive treatment is beneficial also if DBP is <90 or 80 mmHg [144,497,498]. This has been recently confirmed by a meta-analysis of five RCTs in 15 636 ISH patients aged 70–84 years (mean 71.5 years) in whom a SBP reduction from 171.3 to 145.2 mmHg was accompanied by a 30% reduction of major CV outcomes compared with placebo patients [143]. Because in ISH-dedicated trials, entry SBP was ≥160 mmHg, candidates to antihypertensive treatment are definitively patients with grade 2 and 3 ISH [497,498]. However, given the considerable number of patients with ISH or a prevalent SBP elevation in most RCTs on patients aged 60 to 79 years with a SBP ≥140 mmHg [499], treatment of patients with grade 1 ISH may be considered. This notion is supported by a recent meta-analysis of 23 RCTs in which antihypertensive treatment was beneficial in patients aged on average 67 years in whom mean baseline SBP and DBP values were ≥140 mmHg and <90 mmHg, respectively [500]. Antihypertensive treatment in ISH is further addressed in Sections 14.6 and 15.3.

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Evidence on the BP threshold for treatment is much more scant for patients aged ≥80 years in whom the beneficial effect of SBP reduction has been documented in only one specifically designed outcome trial, HYVET [501]. In this trial, recruitment was based on a SBP ≥160 mmHg with or without a DBP elevation, which means that at this more advanced age, antihypertensive treatment can be recommended in grade 2 or 3 hypertension. This recommendation applies also to patients aged 80 years or more with ISH, because in this advanced age range, a selective or prevalent SBP elevation involves most patients, as also shown by the HYVET trial. However, although direct information from RCTs is not available, a lower SBP threshold for drug treatment, i.e. ≥150 mmHg SBP (or rarely ≥100 mmHg DBP) may also be considered based on extrapolation from the HYVET data that the treatment-related benefits were seen at SBP values <150/80 mmHg. Furthermore, although BP values were probably underestimated, in a substudy of SPRINT limited to patients aged 75–84 years (average 80 years) treatment-related benefits were seen with SBP reductions from initial values that were well below 160 mmHg [502].

A final important recommendation is that in patients under well tolerated treatment, who reach 80 years of age, treatment should be continued, because there is evidence that in hypertensive octogenarians, discontinuation of chronically used BP-lowering drugs is associated with a rebound increase of outcomes. In the HYVET trial, about two-thirds of the overall 3845 patients were on antihypertensive drugs at randomization to either active treatment or placebo [495]. Accordingly, a substantial number of patients stopped treatment when randomized to the placebo group, and in these patients, the greater risk of outcomes compared with treated patients was particularly consistent and marked. An exception to the recommendation to continue antihypertensive treatment in octogenarians is represented by very old patients with low SBP values (120 mmHg or less) or with severe orthostatic hypotension, especially in the presence of polypharmacy and a high frailty level. In these cases, progressive reduction of drug treatment should be considered, but deprescribing should be implemented cautiously because data on the effectiveness of this procedure are still missing.

The present guidelines strongly support the concept that age should be no barrier to antihypertensive drug treatment, as further emphasized in the section specifically devoted to hypertension in old people. However, they also recognize that evidence on antihypertensive treatment in the old patients has limitations that go beyond the need for more evidence on the most appropriate BP threshold for treatment. One limitation is that in HYVET, the patient age was close to 80 years (mean 83 years) [501] and that, thus, no RCT-based evidence is available on whether treatment is beneficial in hypertensive patients close to or above 90 years of age, an expanding category in Europe. Furthermore, it is widely recognized that evidence is severely limited in physically and mentally frail older patients, and absent in institutionalized patients, because these patients were usually excluded from RCTs on hypertension. Thus, the above recommendations mainly relate to relatively fit and independent older patients. from several observational studies show an inverse relationship between SBP and morbidity/mortality rates in very old frail patients, especially in those under antihypertensive treatment [503–509]. However, in one of these studies, better adherence to antihypertensive drug treatment was associated with a reduced mortality, including in a subgroup of patients in whom a wide number of comorbidities, and a history of multiple previous hospitalizations increased the risk of mortality to up to about 70% in 6 years. This was the case also for use of a statin in people older than 85 years, in whom mortality exceeded 80%. With the limitations of their observational nature, these studies suggest that antihypertensive as well as other CV drug treatments may also be protective in very frail old patients [510,511]. However, RCTs specifically devoted to frail older patients are necessary to obtain solid evidence on antihypertensive-dependent protective effect as well as on the appropriate BP threshold (and target) values for treatment.

Office BP thresholds for drug treatment initiation

Recommendations and statements	CoR	LoE
In patients 18 to 79 years, the recommended office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP.	I	A
In patients ≥80 years, the office SBP threshold for initiation of drug treatment is 160 mmHg.	I	B
However, a lower SBP threshold in the range of 140 – 160 mmHg may be considered.	II	C
The office SBP and DBP thresholds for initiation of drug treatment in frail patients should be individualised.	I	C
In adult patients with a history of CVD, predominantely CAD, drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg).	I	A

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10. OFFICE BP TARGETS FOR TREATMENT

10.1 Office BP targets in the general hypertensive population

Based on RCTs, as well as their meta-analyses and post hoc analyses, the 2018 ESC/ESH guidelines recommended that the first objective of antihypertensive treatment should be to lower BP to <140/90 mmHg in all patients. If drug treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower, with the caveat that in some clinical conditions (e.g. CKD), the evidence for this lower BP target was uncertain. It was additionally recommended that treatment should never target BP values to <120/70 mmHg because of the lack of consistent evidence that this has an incremental protective effect, the risk of introducing harm and the increased risk of side effects, leading to treatment discontinuation and a rebound increase in events. In a large population study from northern Italy, discontinuation of antihypertensive drugs for several months was associated with an almost 40% increase of hospitalization for CAD, stroke and HF compared with patients continuing treatment [512]. With the exception of the STEP trial [497], no further trial on target BP has been made available since the 2018 guidelines, but the issue has been further explored by two Cochrane meta-analyses of RCTs and by a large individual patient-based meta-analysis [483]. The first Cochrane meta-analysis [513] assessed whether targeting BP to <135/85 mmHg is associated with a reduction in mortality and morbidity as compared with standard BP targets, i.e. <140/90 mmHg, in a rather general hypertensive population. The analysis included 11 RCTs involving 38 688 patients with a mean follow-up of 3.7 years. Patients randomized to the lower target achieved a mean SBP/DBP of 122.8/82.0 mmHg versus 135.0/85.0 mmHg in the standard target group. The authors concluded that the benefits of trying to achieve the lower BP target did not outweigh the harms associated with that intervention, because the number of patients needed to treat to the lower target in order to benefit one patient ranged between 167 and 250 while the corresponding number needed to harm was 37 [513]. However, the results of this meta-analysis are open to criticisms because the lower BP target was somewhat arbitrary (no major trial has ever compared targets <140/90 and <135/85 mmHg), and its selection had the purpose of enriching the otherwise small number of trials included in the meta-analysis. Furthermore, the achieved SBP in patients randomized to the lower target was <123 mmHg, which makes the conclusion more against a <120 mmHg than against a <135 mmHg SBP target. Finally, SPRINT [97] was one of the trials included, which means that in a nonmarginal proportion of patients, BP data were obtained by the unattended BP measurement technique, presumably leading to lower BP values than those obtained in all other trials [514]. A similar absence of clinical benefit in the lower SBP target has been reported by the second Cochrane meta-analysis, which was performed in hypertensive patients with a history of CVD [515]. However, the number of trials and patients was smaller than in the first meta-analysis; several major trials on secondary prevention were not included and among the included trials, the risk of performance bias was high and the quality of the studies was graded as low. On the other hand, the results were different in a third meta-analysis, which reported that a 5 mmHg SBP reduction is associated with reduced outcomes in patients with and without previous CVD, whose baseline BP ranged from >170 to <120, which means that protection was found even at a target SBP value <115 mmHg [484]. In addition to the problems discussed in this meta-analysis in Section 9.3, patients with a baseline SBP <120 mmHg represented less than 2% of the overall database and included the SPRINT data, in which BP values were probably underestimated [36].

Thus, information on SBP and DBP targets for drug treatment still substantially rely on the two large meta-analyses of RCTs referred to in the 2018 ESC/ESH guidelines [465,516]. Both meta-analyses concluded that, compared with on-treatment SBP values ≥140 mmHg, fatal CV outcomes, nonfatal CV outcomes and all-cause mortality are reduced at on-treatment SBP values within 130–139 mmHg but that a further incremental benefit can be seen when SBP is reduced to the 120–129 mmHg range. Stratification of RCTs for achieved DBP also showed an incremental reduction in all types of CV outcomes and mortality for values <80 mmHg compared with 80–89 mmHg and ≥90 mmHg. The benefits from intensive BP lowering referred to patients at all levels of risk, including those with and without existing CVD, diabetes and CKD. Two important findings of one of the two meta-analyses were also that, in absolute values, the incremental outcome benefits of BP lowering progressively decreased as the target BP was lowered. Furthermore, permanent treatment discontinuation (because of treatment-related adverse effects) steeply increased in patients targeted to progressively lower BP values, a finding consistent with the much greater incidence of kidney and other major side effects reported at lower BP targets in several major trials [516]. For these reasons, the present guidelines substantially reconfirm the target BP values for treatment of the general hypertensive population recommended by the 2018 guidelines. That is, to have, as a goal, a BP <140/80 mmHg in most hypertensive patients, mindful of the evidence that this already accounts for the major portion of the protective effect of BP-lowering treatment [182]. However, despite the smaller incremental benefit, an effort should be made to reach a BP range of 120–129/70–79 mmHg, but only if treatment is well tolerated to avoid the risk of treatment discontinuation because of adverse events, which might offset, in part or completely, the incremental reduction in CV outcomes. Attention should also be given to the fact that evidence on the advantages of a lower BP target are not available or unequivocal in a number of clinically important subgroups of patients. These issues will be discussed in the sections on special conditions.

10.2 Office versus home and ambulatory BP targets

A crucial gap in hypertension research is that no outcome-based RCT has ever used HBPM or ABPM to guide treatment of hypertension. One attempt to address this issue was made more than 20 years ago by a small RCT in which the number of CV

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events registered during a several-year FU did not differ significantly between treatments based on ABPM versus office BP, although their overall number ($n = 25$) did not make the data conclusive [517]. Another almost simultaneous attempt did not focus on CV events but showed that over 1 year of antihypertensive treatment, 24 h BP reduction was associated with a more effective regression of LVH than office BP reduction, home BP reduction having an intermediate favorable effect [518]. Thus, although HBPM and ABPM have been shown to be prognostically more sensitive and additive to the prognostic value of office BP [128,519], no information exists on (i) whether guiding antihypertensive treatment by HBPM or ABPM has a greater protective effect than guiding by office BP and (ii) which are the optimal HBPM and ABPM targets for treatment. As mentioned in Sections 4.7 and 4.8, currently these targets are indirectly inferred from 24 h mean BP corresponding to the target office BP of <130/80 mmHg, which unfortunately has important limitations. In this context, however, an accepted notion is that the difference between office and HBPM or 24 h mean BP decreases as office BP decreases. This means that the difference between office and out-of-office BP is considerably less pronounced during than in absence of treatment, especially when treatment provides office BP values close to target. At a certain value, office and out-of-office BPs coincide, but this value varies between studies, although for office and 24 h SBP (for which more data are available) is probably around 120 mmHg [520].

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10.3 Timing of BP control and time in therapeutic range

RCTs have usually defined the achieved BP target as the mean BP value during the treatment period. However, it is now clear that this oversimplifies the relationship between BP reduction and outcomes. Post hoc or secondary analyses of several RCTs such as VALUE have shown that in high-risk patients achieving an earlier BP control (within 6 months [521] and or even within 1 month [522]), the risk of outcomes was lower than in those in whom BP control was achieved later. Furthermore, post hoc analyses of large RCTs in high-risk patients or large observational studies have consistently documented that the greater the percentage of visits in which BP is controlled, the lower the risk of outcomes, independently on the mean BP during the overall treatment period [182,184,523]. Similar observations have recently been made in resistant hypertensive patients treated with renal denervation [190] and in type 2 diabetic patients in whom the measurement was, respectively, the number of visits in which BP was within the target BP range and the ratio between the number of visits with BP control and the overall number of available visits [189]. These data emphasize the importance of avoiding a long titration period during which patients remain with an uncontrolled BP, particularly if their CV risk is high, which supports the recommendation to start treatment with two drugs (Section 11). Assuming that an uncontrolled BP at a given visit reflects an uncontrolled BP during the previous between-visit interval, they also strongly emphasize the importance for a physician to pursue a consistent BP control across visits, without considering a high BP at a single visit just an occasional and fortuitous finding. The limitations of outcome data based on average on-treatment BP values suggest that future trials in hypertension should consider a time-based analysis of BP control.

10.4 Residual risk

Although substantially reducing hypertension-related outcomes, effective antihypertensive treatment does not return the CV risk of treated hypertensive patients to the level of normotensive people when matched for age, sex and ethnicity. In other words, even when treatment achieves the target BP value that is believed to maximize CV protection, CV risk is not normalized, the excess risk being referred to as 'residual risk' [524–526]. The magnitude of the residual risk varies between studies, but it has been shown to be consistent up to follow-ups of about 20 years [526,527]. Residual risk can originate from a considerable number of factors, some of which are still hypothetical, while others are supported by evidence and can be considered for therapeutic interventions. The possibility exists that the genetic component of hypertension includes a portion of irreversible risk. It is also possible that the partial risk irreversibility is generated by late treatment, i.e. by interventions made when risk is too high [484] and alterations of CV structure and function are at least in part irreversible. On the other hand, studies performed in the last few decades have provided evidence that in treated hypertensive patients, control of concomitant CV risk factors is poor [528–530], with an obvious adverse impact on total CV risk. Furthermore, in hypertension, CV risk depends on BP aspects that are much more complex than office BP as averaged across a number of treatment years. In individual patients, the optimal office BP target may depart from the average values reported in trials, and residual risk may be generated by failure of apparently effective antihypertensive treatment to reduce the elevated 24 h BP variability that characterizes hypertension and adversely affects the CV risk profile [179]. Coexistence of office BP control with imperfect control of the prognostically important real-life mean BP values and peaks may also be involved (Sections 4.7 and 4.8). In this context, interesting progress has been made in recent years by the observation that in treated hypertensive patients, the risk of CV events depends on the time in which BP is controlled, independently of the mean BP value across the entire treatment period (Section 10.3). In a post hoc analysis of the OnTarget-Transcend study, a greater visit-to-visit BP variability (which reflects the degree of BP inconsistency between different treatment periods [187] was shown to increase the risk of events when added to mean on-treatment BP [188]. Thus, in addition to pursuing a better control of concomitant risk factors, another important practical intervention against residual risk might be to pursue assessment of consistency of BP control during FU, possibly by a widespread use of HBPM.

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10.5 Challenges associated with evidence on BP targets

For guidelines, recommending the BP targets to reach with treatment is a difficult task. First, recommendations on optimal (i.e. most protective) target BP values may vary between different guidelines, and often also within guidelines at a few-year intervals, despite little concomitant increase in available evidence. This is due to the limited consistency of the available data, an example of which is that the incremental benefit of lowering SBP to <130 mmHg shown by some RCTs and meta-analyses does not clearly emerge from other major trials. Second, as mentioned by the present guidelines (sections on special conditions), evidence on optimal BP targets is not always univocal or equally strong for all clinical hypertensive subgroups. An example can be offered by people with LVH, quite a common condition in hypertensive patients. A real-life study from a large Korean population has reported a lower risk of CV outcomes in hypertensive patients with ECG-LVH in whom SBP was reduced to <130 or even <120 mmHg compared with higher on-treatment values [531]. In contrast, in the LIFE Study on ECG-LVH patients, all-cause mortality increased with an on-treatment SBP <130 mmHg [532] compared with patients who had an average on-treatment SBP >130 mmHg. Likewise, in a post hoc analysis of the high-risk hypertensive population of the VALUE Trial [522], cardiac and all-cause mortality was found to be greater in the group that had ECG-LVH and achieved on average a SBP <130 mmHg, at variance from hypertensive patients with no LVH in whom an SBP reduction <130 mmHg was protective [533]. Pathophysiologically, this may be explained by the higher oxygen consumption associated with the increased LVM as well as by the degenerative changes in the microcirculation that accompany a hypertrophic myocardium, both factors making it more susceptible to a reduction of perfusion pressure. In a small old mechanistic study [534], a progressive DBP reduction to about 70 mmHg (nitroprusside infusion, intra-arterial measurement) did not affect coronary blood flow (coronary sinus thermodilution measurement) in hypertensive patients without LVH, whereas in hypertensive patients with LVH, coronary blood flow showed a steep reduction as DBP decreased below 90 mmHg. Finally, posthoc analyses of RCTs, have often shown an increased risk of outcomes in the general trial population or in a usually limited number of patients exposed to intense BP lowering treatment, i.e. a J-shaped relationship between BP values and outcomes. Although the observational nature of a posthoc approach does not allow to establish whether the increased risk seen at lower BP values is caused by vital organ hypoperfusion or by an originally high risk or frailty status [535], this shows that hypertensive patients may not all uniformly respond to the same BP target. Future studies should expand knowledge on the optimal BP target for treatment in different clinical subgroups and try to clarify the factors and mechanisms behind its possible heterogeneity (Fig. 10).

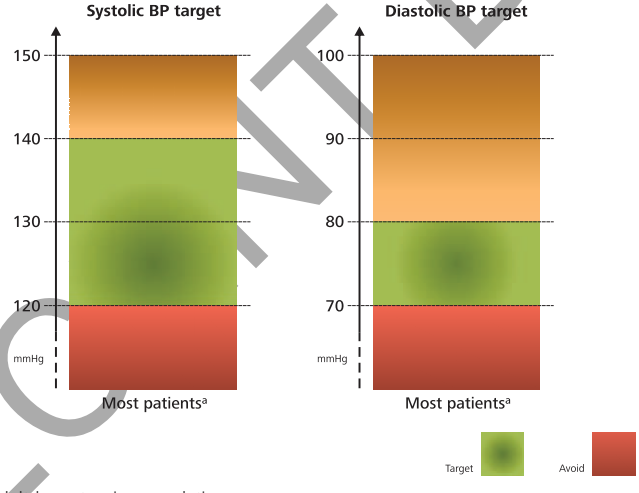


FIGURE 10 Office BP targets in the general adult hypertensive population.
[a]The first objective of antihypertensive treatment should be to lower BP to <140/80 mmHg in most patients, because this accounts for the major portion of the protective effect of BP-lowering.
[a]If drug treatment is well tolerated, treated SBP values should be targeted to 130 mmHg or lower in most patients up to 79 years old.
[a]Despite the smaller incremental benefit, an effort should be made to reach a BP range of 120–129/70–79 mmHg in patients up to 79 years old, but only if treatment is well tolerated. Evidence on the advantages of this lower BP target range is not available or unequivocal in a number of clinically important subgroups of patients (e.g. patients with LVH, CKD, or ISH). These issues are discussed in the sections on special conditions (Sections 17 to 20).
[a]In patients at least 80 years old who are not frail, the first objective of antihypertensive treatment is to lower BP below 150/80 mmHg. However, a SBP target range between 130-139 mmHg may be considered, if well tolerated.
[a]In very frail patients, treatment targets should be individualized.

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Office BP targets for drug treatment

Recommendations and statements	CoR	LoE
Patients 18 to 64 years old		
The goal is to lower office BP to <130/80mmHg	I	A
Patients 65 to 79 years old		
The primary goal of treatment is to lower BP to <140/80mmHg	I	A
However, lowering BP to below 130/80mmHg can be considered if treatment is well tolerated.	I	B
Patients 65 to 79 years old with ISH		
The primary goal of treatment is to lower SBP in the 140 to 150 mmHg range.	I	A
However, a reduction of office SBP in the 130 to 139 mmHg range may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B
Patients ≥80 years old		
Office BP should be lowered to a SBP in the 140 to 150 mmHg range and to a DBP <80mmHg.	I	A
However, reduction of office SBP between 130 to 139 mmHg may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B
Additional safety recommendations		
In frail patients, the treatment target for office SBP and DBP should be individualised.	I	C
Do not aim to target office SBP below 120 mmHg or DBP below 70 mmHg during drug treatment.	III	C
However, in patients with low office DBP, i.e. below 70 mmHg, SBP should be still lowered, albeit cautiously, if on-treatment SBP is still well above target values	II	C
Reduction of treatment of can be consider in patient aged 80 years or older with a low SBP (< 120 mmHg) or in the presence of severe orthostatic hypotension or a high frailty level	III	C

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11. ANTIHYPERTENSIVE DRUGS AND TREATMENT

In the 2018 ESC/ESH guidelines [4], five major drug classes were recommended as first-line agents for the treatment of hypertension i.e. ACEis, ARBs, CCBs, Thiazide/Thiazide-like diuretics and BBs. However, the recommendations included two particular weightings within this group of drug classes. First, the use of an RAS inhibitor (ACEi or ARB), if not contraindicated, was considered as a common component of the general combination treatment strategy, and second, the use of BBs was restricted to special clinical conditions or situations. The selection of these five drug classes was based on the following criteria:

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1. A proven ability to reduce BP as monotherapy.
2. Evidence from RCTs that they reduce morbidity and mortality.
3. A favorable tolerability and safety profile.

Based on RCTs and their meta-analyses [536–538], the 2018 guidelines concluded that all the above drug classes met the required criteria, i.e. they (i) effectively reduce SBP and DBP; (ii) reduce the major specific outcomes associated with hypertension when compared with placebo and (iii) exert an overall similar or only slightly different effect on the combined risk of major CV outcomes and mortality when given as the initial treatment step, albeit with some differences for some cause-specific outcomes (lesser stroke prevention with BBs and ACE-inhibitors, lesser HF prevention with CCBs and greater HF prevention with Thiazide diuretics) [536]. Additional considerations were that (iv) the reduction of events is due essentially to BP lowering per se rather than to specific drug properties, which means that the greater the number of drug options, the greater is the opportunity of tailoring an effective BP-lowering treatment to the individual patient characteristics; (v) the antihypertensive effect of these five drug classes extends to ABPM and HBPM; (vi) their BP-lowering ability and protective effect include use in combination with other drugs as shown in RCTs in which BP-lowering treatment by multiple drugs was associated with a reduction of CV outcomes and (vii) side effects of drug classes are largely related to the doses employed and their between-class differences are minimized by use at lower doses in combination treatment. These considerations and recommendations are shared by the present guidelines, which also share the subordinate position attributed to other antihypertensive drugs (alpha-blockers, centrally acting agents and MRAs), because these drugs have been less widely studied in outcome-based RCTs, or are known to be associated with a higher risk of adverse effects. These drugs can be useful additions to the major antihypertensive armamentarium, in some specific cases, or when BP cannot be controlled by various combinations of the major drug classes.

Moreover, mention is made of new drug classes, such as SGLT2 inhibitors (SGLT2is) and nonsteroidal MRAs, which have become available and exhibit BP-lowering effects. These effects may be less pronounced than those of classical antihypertensive drugs [539], but there is now strong evidence from RCTs that they decrease CV and kidney events in patients with type 2 diabetes and – in the case of SGLT2i – also in patients without diabetes [540–544]. New criteria for drug performance are also discussed, such as the evidence of differences in the persistence and discontinuation rates of treatment between the major drug classes and even between drugs or drug combinations within a given class [545]. This has clinical relevance because antihypertensive treatment discontinuation leads to increased CV outcomes. Precise and correct prescriptions of drugs for documented CV or other medical conditions are among the most important decisions that can be taken by physicians to maintain or improve adherence and persistence to the prescribed drugs (Section 21). A synopsis of the major drug classes and additional drug classed for BP-lowering therapy in hypertension is shown in Fig. 11.

Compelling or possible contraindications for the selection of drug classes are summarized in Table 15.

11.1 Blockers of the renin–angiotensin system (RAS)

11.1.1 Angiotensin-converting-enzyme inhibitors

ACEis are among the most widely used classes of antihypertensive drugs. Because of their earlier availability and, thus, their earlier evaluation against placebo in outcome-based RCTs, knowledge about ACEis is based on a large amount of RCT data, particularly in patients with HF, CAD and at high CV risk [546–548]. In these trials, ACEis have been shown to be associated with major benefits [547,548]. ACEis are associated with an increased risk of a very rare event such as angioneurotic edema, especially in people of Black African origin. They are associated with a cough that affects about 5–10% of treated patients, although with a large variability (1.5–11.0%) between studies and with a greater frequency in women and patients of Asian origin [549,550]. These side effects may affect their long-term persistence [551], although in a study on about half a million

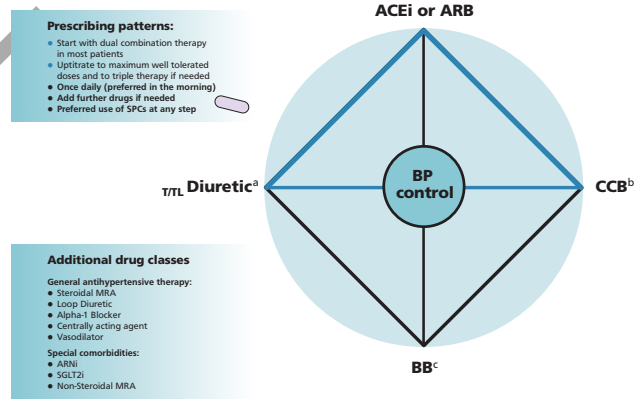


FIGURE 11 Drug classes for BP-lowering therapy.(a) Use of Diuretics: Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2. If eGFR <30 ml/min/1.73 m^2 use Loop Diuretic. (b) Non-DHP CCB should not be combined with BB. (c) BB should be used as guideline directed medical therapy in respective indications or considered in several other conditions (Table 16).

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TABLE 15. Compelling contraindications and conditions requiring cautious use of BP-lowering drugs

Drug class	Contraindications	Cautious use
ACEi	• Pregnancy • Women planning pregnancy • Previous angioneurotic edema • Severe hyperkalemia (e.g. potassium >5.5 mmol/l) • Bilateral renal artery stenosis or stenosis in solitary (functional) kidney	• Women of child-bearing potential without reliable contraception
ARB	• Pregnancy • Women planning pregnancy • Severe hyperkalemia (e.g. potassium >5.5 mmol/l) • Bilateral renal artery stenosis or stenosis in solitary (functional) kidney	• Women of child-bearing potential without reliable contraception
Beta-blocker	• Severe asthma • Any high-grade sino-atrial or atrioventricular block • Bradycardia (e.g. heart rate <60 bpm)	• Asthma • Glucose intolerance • Athletes and physically active patients
DHP-CCB		• Tachyarrhythmia • Heart failure (HFrEF, class III or IV) • Preexisting severe leg edema
Non-DHP-CCB (verapamil, diltiazem)	• Any high-grade sino-atrial or AV block • Severe LV dysfunction (LV EF <40%), HFrEF • Bradycardia (e.g. heart rate <60 bpm) • Co-medications susceptible to significant drug interactions mediated by P-gp or CYP3A4	• Constipation
Thiazide/Thiazide-like diuretics	• Hyponatremia • CKD due to obstructive uropathy • Sulfonamide allergies	• Gout • Glucose intolerance • Pregnancy • Hypercalcemia • Hypokalemia • Cancer patients with bone metastasis
MRA	• Severe hyperkalemia (e.g. potassium >5.5 mmol/l) • eGFR <30 ml/min/1.73 m^2	• Co-medications susceptible to significant drug interactions mediated by P-gp or CYP3A4 for eplerenone

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individuals, the discontinuation rate of people taking ACEis was considerably lower than that of BBs, CCBs and Diuretics and only modestly albeit significantly greater than that of people taking ARBs [512]. With the availability of several compounds, the class of ACEis represents a relatively homogenous class of drugs.

11.1.2 Angiotensin receptor blockers

ARBs have a similar antihypertensive efficacy and protective effect as ACEis [551–553], albeit with a somewhat different mechanism for RAS inhibition and a smaller RCT database. A difference between ACEis and ARBs is their tolerability profile, with ARBs having a rate of side effects similar to placebo. ARBs are associated with the lowest treatment-discontinuation rate when compared with all other antihypertensive therapies [512]. With several compounds' availability, the class of ARBs represents a relatively homogenous class of drugs.

11.1.3 Renin inhibitors

The renin inhibitor aliskiren is a potent, long-acting antihypertensive drug when prescribed alone or in combination with a diuretic or a CCB [554]. Several RCTs on the impact of aliskiren on HMOD or CV outcomes have been conducted, but two of them were interrupted prematurely because of an increased incidence of adverse events, mainly when aliskiren was associated with another RAS blocker [555] Subsequently, aliskiren has almost disappeared from medical practice in European countries.

11.1.4 Combination of RAS inhibitors

ACEis, ARBs or aliskiren should not be combined because no added benefit on CV outcomes has been shown by dual RAS inhibition [556]. Although double RAS blockade has been shown to have a greater antialbuminuric effect and might have favorable effects in HF, the association may cause an excess of adverse events, with an increased risk of kidney function impairment (40%), hyperkalemia (44%) and hypotension (42%) [557] in patients with a high CV risk [556], type 2 diabetes [558] and/or a considerable proportion of patients with a BP elevation.

11.2 Calcium channel blockers

CCBs represent a heterogeneous class of drugs that can be divided into vascular-selective dihydropyridine (DHP) and non-DHP-CCBs. CCBs are widely used for the treatment of hypertension, and they are particularly effective in patients of African descent as well as in the general older population.

11.2.1 Dihydropyridine CCBs

Most RCTs demonstrating their benefits on outcomes have used DHP–CCBs, especially amlodipine [536]. DHP and non-DHP-CCBs differ in the tolerability profile and side effects. DHP-CCBs may be used, if necessary, to control an elevated BP in

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patients with HFrEF, although caution is needed because of their moderate negative inotropic effects. DHP-CCBs have only a limited potential for drug interactions.

11.2.2 Nondihydropyridine CCBs

Diltiazem and verapamil are not vascular-selective CCBs, but they are also efficacious in reducing BP. A smaller number of RCTs have compared non-DHP-CCBs with other drugs, while meta-analyses evaluating DHP and non-DHP-CCBs versus other drugs have not shown substantial differences in effectiveness [536]. Diltiazem and verapamil also belong to the class IV of antiarrhythmic drugs. Accordingly, they can delay atrioventricular conduction and slow heart rate in patients at sinus rhythm. DHP-CCBs are also used for heart rate control as an alternative to BBs in AF. Both drugs exhibit a potential for drug interactions because they inhibit the Cytochrome P450 3A4 enzyme and the drug efflux transporter P-glycoprotein, which can impair the tolerability and safety of other drugs, some statins (e.g. simvastatin, atorvastatin [559] or oral anticoagulants [560,561]) by increasing their plasma levels (Section 17.3.4). Use of non-DHP-CCB is not recommended in HFrEF because of their pronounced negative-inotropic effect.

11.3 Diuretics

11.3.1 Thiazide/Thiazide-like

The effectiveness of Thiazide/Thiazide-like diuretics in preventing CV morbidity and mortality has been shown in RCTs and meta-analyses [536–538,562], with an effect similar to the effect of other major antihypertensive agents. In meta-analyses of RCTs, Thiazide/Thiazide-like appear to be more effective than other major drug classes in preventing HF, but this finding may be influenced by the results of the ALLHAT study [563], in which patients largely under a background diuretic treatment were rolled over to comparison drugs, with a possible emergence of HF symptoms previously under diuretic-based symptomatic control. The thiazide-like diuretics, chlorthalidone and indapamide, are more potent and have a longer duration of action compared with hydrochlorothiazide, but a greater incidence of side effects has been reported for chlortalidone in some studies [564]. A meta-analysis of placebo-controlled studies based on thiazides, chlorthalidone, and indapamide found similar effects for the three types of diuretics on CV outcomes [536]. A greater risk of CV events and HF has been reported with Thiazide diuretics in another meta-analysis [565]. Yet, no major difference between hydrochlorothiazide and chlorthalidone has been observed in a large observational cohort study [LEGEND] using a database spanning from January 2001 to December 2018 [566]. Furthermore, similar results have been obtained by a recent open-label study, DCP, on hypertensive US Veterans older than 65 years [567]. In this study, patients who were already on hydrochlorothiazide were randomized to either chlorthalidone ($n = 6756$) or hydrochlorothiazide continuation ($n = 6767$). Patients on treatment with hydrochlorothiazide 25 or 50 mg were converted to 12.5 or 25 mg chlorthalidone, respectively. No difference in CV outcomes between the two drugs was found, except for patients with a prior stroke in whom there was a greater benefit with chlorthalidone. Despite some limitations (in the last study, very few patients were on hydrochlorothiazide monotherapy at baseline, which means that the results could have been affected by concomitant medications and adherence to their use), the above-mentioned recent observations justify the recommendation of the present guidelines to still consider Thiazide/Thiazide-like diuretics both as suitable antihypertensive agents and as similarly effective in CV prevention. Both Thiazide/Thiazide-like can lower serum potassium and have a side-effect profile that is less favorable than RAS blockers. This may account for their higher rate of treatment discontinuation. Depending on the dose, they may also increase insulin resistance and, hence, the risk of new-onset diabetes. Potassium plays an important role in the metabolic effects of Thiazide/Thiazide-like, and evidence is available that these effects are reduced by the combination of Thiazide/Thiazide-like with a potassium-sparing diuretic [568,569] or with an RAS blocker. A recent placebo-controlled study [570] has demonstrated that chlorthalidone effectively lowers BP and albuminuria in patients with uncontrolled hypertension and CKD stage 4 (eGFR <30 ml/min/1.73 m^2) when added to the therapy of these conditions, which often includes a loop diuretic (60% of the patients) (Section 12).

11.3.2 Loop diuretics

Thiazide/Thiazide-like are considered less effective antihypertensive agents in patients with a reduced GFR (eGFR <30 ml/min/1.73 m^2). Consequently, while loop diuretics (furosemide, bumetanide, torasemide/torsemide) are usually not indicated in the treatment of uncomplicated hypertension, they are recommended in patients with CKD stage 4 and 5 (eGFR below 30 ml/1.73 m^2) and in patients with severe fluid overload/retention, e.g. in patients with HF or nephrotic syndrome. Recently, furosemide and torsemide were found to be equally effective on mortality, independently of ejection fraction in a RCT comprising 2859 HF patients receiving one drug or the other at discharge from hospital [571]. As indicated above, a loop diuretic can be combined with chlorthalidone to improve BP control in patients with advanced CKD stage 4 and uncontrolled or resistant hypertension [570].

11.3.3 Potassium-sparing diuretics

Amiloride is an agent that directly inhibits epithelial sodium channels at the luminal side of the late distal tubule and collecting duct. Hence, it is used as potassium-sparing diuretic in edematous states and for potassium conservation in combination with Thiazide or loop diuretics in hypertension or HF [572]. Amiloride was used for uncontrolled or resistant hypertension in the PATHWAY-3 [568] and PATHWAY-2 [4] studies. In the former study, the mean reduction in home SBP

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during a 24-week treatment did not differ significantly between patients taking amiloride (10–20 mg once daily, −12.2 mmHg SBP) and those taking hydrochlorothiazide (25–50 mg once daily, −12.9 mmHg SBP) However, the effect of the combination of low doses of amiloride (5–10 mg) and hydrochlorothiazide (12.5–25 mg) was associated with greater reductions of BP than those obtained with the higher dose of hydrochlorothiazide alone. Amiloride had no impact on glucose tolerance in a sub-study of PATHWAY-2. Furthermore, a higher dose of amiloride, i.e. 10–20 mg once daily, as assessed during an optional 6–12-week open-label runout phase reduced office SBP by 20.4 mmHg, compared with a reduction of 18.3 mmHg with spironolactone (25 mg once daily). No serious adverse events were recorded. Mean plasma potassium concentrations increased from 4.02 mmol/l on placebo to 4.50 on amiloride ($P < 0.0001$) [573]. Triamterene is another potassium-sparing diuretic acting on the epithelial sodium channel. Its independent effects on BP have not been well studied, but the available evidence demonstrates an additive antihypertensive effect when associated with hydrochlorothiazide [574]. Triamterene is included as a compound of a quadruple combination that is available to treat hypertension in China [575].

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11.4 Mineralocorticoid receptor antagonists

Steroidal MRAs lower BP as do other diuretics. The MRAs spironolactone and eplerenone are established treatments in HFrEF based on outcome-based RCTs, but no outcome trial has been carried out in hypertension. Lack of outcome data and the risk of MRA-induced hyperkalemia and other side effects have restricted the use of MRA in the treatment of hypertension, except in specific conditions such as hyperaldosteronism or resistant hypertension. In resistant hypertension, a meta-analysis of 12 RCTs (1655 patients) [576] assessed the effect of spironolactone on BP compared with other therapies or placebo and showed a significant ability of spironolactone to lower BP, thus confirming the results of PATHWAY-2 [573] (Section 12). Several new nonsteroidal MRAs are under investigation in patients with hypertension, type 2 diabetes or CKD. Among them, finerenone, a nonsteroidal MRA, has been shown to lower BP versus placebo [577] and to reduce cardiac and kidney outcomes in mostly (more than 95%) treated hypertensive patients with diabetic CKD [542–544]. In the Fidelio-DKD study, finerenone lowered SBP (−2.7 mmHg) when administered on top of an RAS blocker [578] mainly in patients who were hypertensive at baseline. A time-varying analysis revealed that 13.8 and 12.6% of the treatment effect of finerenone were attributable to the effect of the change in office SBP on the primary kidney composite outcome and the key secondary CV outcome, respectively [578]. With finerenone, hyperkalemia leading to treatment discontinuation occurred in 1.7% of patients [542] (Section 19).

11.5 Beta-blockers

RCTs and meta-analyses have demonstrated that when compared with placebo, first-generation and second-generation BBs like propranolol, atenolol and metoprolol significantly reduce the risk of stroke, HF and major CV events in hypertensive patients. When compared with other BP-lowering drugs, BBs were almost equivalent in preventing major CV events, except for a less effective prevention of stroke [536–538,579,580]. It is possible that this difference on stroke data between BBs and other antihypertensive drug classes originates from small differences in achieved BP, including central SBP, to which cerebrovascular events may be, especially sensitive. BBs are also associated with increased risk of new-onset diabetes in predisposed individuals (mostly those with the metabolic syndrome). They also exhibit a less favorable side-effect profile than that of RAS blockers, with a higher rate of treatment discontinuation when assessed in real-life conditions [512]. In previous guidelines [4,32,487], BBs were included among the five major antihypertensive drug classes. However, in the general treatment algorithm, they were recommended only when there is a specific indication, e.g. in patients with HF, angina, post-MI, AF or in younger hypertensive women of child-bearing potential or planning pregnancy. BBs do not constitute an homogeneous class but show several pharmacological differences, among which beta1-selectivity and an additional direct vasodilating property are of special interest. Third-generation BBs, such as nebivolol or carvedilol, exhibit direct vasodilating properties. Studies not only with nebivolol but also with bisoprolol, i.e. BBs with higher beta-1 selectivity and limited to nebivolol an added vasodilatation via increased release of nitric oxide, reported a more favorable side effect profile than other BBs, including fewer adverse effects on sexual function [581,582]. RCTs with carvedilol, bisoprolol, metoprolol and nebivolol showed improved outcomes in patients with HFrEF [583]. However, there are no outcome trials with vasodilating BBs in hypertensive patients, and the same applies to bisoprolol. There are also some recent large real-world studies with vasodilator BBs conducted in the USA, with inconsistent results. In one study, there was no statistically significant difference in CV outcomes between 118 133 patients receiving either nebivolol or carvedilol and 267 891 patients receiving atenolol [584]. In other three studies, use of nebivolol led to greater CV protection compared with use of atenolol or metoprolol [585–587].

A recent pragmatic review scrutinized the use of BBs in medical treatments [588]. It was seen that, in addition to their compelling use as GDMT in specific diseases, BBs exhibit favorable effects in about 50 clinical conditions including (i) various cardiac diseases less or not related to hypertension, (ii) other vascular conditions and (iii) non-CV diseases (Table 16). Finally, increased resting heart rate (>80 bpm) is common in hypertension, in which it reflects an increased sympathetic activity [589]. A progressive increase in resting heart rate is accompanied by a progressive increase in the risk of AF, HF and mortality both in the general population and in hypertensive patients [590–592]. Although in hypertension, the advantage of reducing heart rate is limited to post hoc analysis of RCTs [593–595], the available evidence makes treated hypertensive patients with an increased heart rate a clinical phenotype supporting the use of BBs [596].

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TABLE 16. Selected diseases and conditions for the use of BBs in patients with hypertension [588]

Selected indications with guideline directed medical therapy for BBs
Chronic coronary syndromes, antiischemic therapy
Postmyocardial infarction: arrhythmias, angina, known incomplete re-vascularization, HF
Acute coronary syndrome
HFrEF and HFpEF if coronary disease (ischemia), arrhythmias and tachycardia
Atrial fibrillation: prevention, rhythm control, heart rate control
Women with child-bearing potential/planning pregnancy
Hypertension disorders in pregnancy
Selected other conditions in which therapy with BBs can be favourable
Hypertension with elevated resting heart rate >80 bpm
Emergency, urgency and parenteral administration
Perioperative hypertension
Major noncardiac surgery
Excessive pressor response to exercise and stress
Hyperkinetic heart syndrome
Postural orthostatic tachycardia syndrome
Orthostatic hypertension
OSA
Peripheral arterial disease with claudication
COPD
Portal hypertension, cirrhosis-related esophageal varices and recurrent variceal bleeding
Glaucoma
Thyrotoxicosis, hyperthyroidism
Hyperparathyroidism in uremia
Migraine headache
Essential tremor
Performance anxiety and anxiety disorders
Psychiatric disorders (posttraumatic stress)

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11.6 Alpha-1 blockers

Treatment with the alpha-1 blocker doxazosin was equally effective as chlorthalidone in preventing the primary endpoint in ALLHAT [563], which was incident or fatal CAD. However, doxazosin was associated with a marked increase of incident HF, which led to stopping the doxazosin arm early. This was a controversial decision, because the increased incidence of HF in the doxazosin arm could have resulted from a HF misdiagnosis due to doxazosin-related fluid retention as well as discontinuation of diuretic treatment in patients with background HF in order to randomize them to doxazosin. In the ASCOT trial [597], doxazosin was given as a third-line therapy, and it showed no increase in the risk of HF. In the PATHWAY-2 study, it was more effective than placebo but less effective than spironolactone at lowering BP in resistant hypertension [598]. Alpha-1 blockers may also be required in specific conditions (e.g. treatment of benign prostatic hyperplasia). Orthostatic hypotension and fluid retention may be a concern with the use of alpha-1 blockers, especially in the older patients [599]. In a real-life study on older patients, administration of alpha-1 blockers in newly treated old hypertensive patients was followed by a significant increase of hospitalization for hip fracture over the following month, presumably as a result of orthostatic BP reductions and injurious falls [600].

11.7 Centrally acting drugs

In recent decades, centrally active drugs have been less frequently used, principally because of the lack of evidence by outcome RCTs and/or their poorer tolerability relative to the newer major classes of drugs. Thus, older compounds such as reserpine, alpha-methyldopa, clonidine, moxonidine or rilmenidine are no longer recommended for the routine treatment of hypertension and are primarily reserved for add-on therapy in the rare cases of resistant hypertension where other treatment options have failed or for specific conditions such as the use of methyldopa in pregnancy. It is worth noting that a recent study demonstrated a significant BP-lowering effect of clonidine in resistant hypertension that was similar to that of spironolactone [601] (Section 12).

11.8 Vasodilators

Vasodilators are a heterogeneous groups of drugs, which exert a direct relaxing effect on vascular smooth muscle cells, thereby reducing BP via vasodilation and reduction of systemic vascular resistance. Powerful vasodilators, such as hydralazine and minoxidil were occasionally used in the past, but they have been now virtually abandoned because of their association with serious side effects. Side effects include marked baroreflex inactivation with tachycardia and increased activity of the sympathetic nervous system and activation of the RAS system resulting in tachycardia and fluid retention. Hydralazine may be occasionally considered in resistant hypertension that is unresponsive to multiple attempts to control BP, always in combination with BBs and diuretics to limit its side effects. A serious specific side effect for minoxidil is hirsutism. Nitrates and nitroprussiate also relax vascular smooth muscle cells and can lower BP. Intravenous nitroprussiate has a very efficacious and well controllable BP-lowering effect and is, therefore, used to manage hypertension emergencies (Section 16.2).

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11.9 Angiotensin receptor-neprilysin inhibitor (ARNI)

ARNI is a chemical combination of the ARB valsartan and the neprilysin inhibitor sacubitril, which simultaneously blocks the effects of angiotensin II at the AT-1 receptor (by valsartan) and inhibits the degradation of natriuretic peptides, thus promoting peripheral vasodilatation (by sacubitril) [602]. Initial studies including a successful phase 2 RCT were performed in patients with hypertension [603–605], but the manufacturer later switched the focus to the treatment of HF. Currently, in most countries, the drug is only approved for the treatment of HF, where it showed better effects on outcomes than treatment with an ACEi alone in patients with HFrEF. In a recent meta-analysis of 10 studies including 5931 hypertensive patients, sacubitril–valsartan reduced office SBP by 6.5 mmHg and DBP by 3.3 mmHg [602] compared with placebo. 24 h SBP was reduced by 7.0 mmHg and 24 h DBP by 3.2 mmHg. ARNI is not approved for the treatment of hypertension in Europe or in the USA, while it was approved as an antihypertensive agent in China and Japan.

11.10 Antihypertensive drug combinations

11.10.1 Impact on hypertension drug treatment strategy

Guidelines have generated a variety of different strategies to initiate and increase BP-lowering medications in order to control an elevated BP. Before 2018, guidelines largely focused on the stepped care approach, initiating treatment with a variety of different monotherapies and then sequentially adding other drugs, until BP control was achieved. Starting with a two-drug combination was proposed only for patients with marked BP elevations and/or a high/very-high CV risk. Despite this, BP control rates have remained poor in Europe and worldwide. Failure to achieve BP control in most hypertensive patients, despite numerous iterations of guidelines, suggested that, whatever the reasons, the step care treatment strategy was not sufficiently effective and that a different approach was needed. The new strategy elaborated by the 2018 ESC/ESH guidelines was based on the following main considerations:

1. **Efficacy of pharmacological therapies**. Evidence from RCTs investigating BP responses to antihypertensive drugs demonstrates that BP control can be achieved in most patients and that no more than 5–10% of these patients exhibit resistance to the selected treatment regimen [606]. Thus, ineffective drug therapy is unlikely to be the source of the problem.

2. **Physician or treatment inertia.** Evidence suggests that medical inertia, i.e. failure to adequately intensify or up-titrate treatment, contributes to failure or delay of treatment initiation but exerts an important adverse role also on suboptimal BP control with many patients remaining on monotherapy and/or suboptimal drug doses [607,608]. This was found to be the main reason for lack of BP control in major RCTs [609]. ACCOMPLISH achieved BP control in approximately 80% of study participants (the highest BP control achieved in major antihypertensive treatment RCTs from the Western World), but most of the remaining uncontrolled patients had not been up-titrated [610]. As expected, treatment inertia is quantitively much more important in real-world practice where it can be rated as a major factor responsible for poor BP control [608]. Addressing clinical inertia with specific measures is associated with an improvement in BP control [611].

3. **Patient adherence to treatment**. Evidence is accumulating that adherence to treatment is a fundamental factor to consider. Studies using urine or blood assays for the presence or absence of medication have shown that low or partial adherence to treatment is frequent, in particular, among patients with an uncontrolled BP [612]. This was also shown in studies of the general population, in which adherence to treatment based on prescription refilling was less than 50% in half of the patients [475,613]. Poor adherence has been associated with increased risk of developing CV complications in several studies, as reviewed recently [477,478,614].

4. **Insufficient use of combination treatment.** BP is a multiregulated variable depending on many pathophysiological pathways. Therefore, monotherapy is likely to be inadequate or insufficient to control BP in most patients, and combinations of drugs, working through different mechanisms, are necessary to achieve BP targets in most people with hypertension [609,615]. Indeed almost all patients in RCTs have required combinations of drugs to control their BP [616].

5. **Complexity of current treatment strategies**. There is also evidence that adherence to treatment is adversely affected by the complexity of the prescribed treatment regimen [478,617]. Several studies have demonstrated that adherence to treatment is strongly influenced by the number of pills a patient was prescribed for the treatment of hypertension as well as by the dosing frequency; the higher the number of pills, the lower the adherence.

The above considerations suggest that the most effective evidence-based treatment strategy to improve BP control would be one that:

1. encourages the use of combination treatment in most patients, especially in the context of lower BP targets
2. promotes the use of simplified single-pill-based combination therapies to support long-term persistence to treatment
3. recommends initial combination treatment in most hypertensive patients, as evidence is available that compared with monotherapy, initial combination treatment bypasses the problem of inertial monotherapy [608], improves long-term adherence to treatment [618–620], is accompanied by a better short-term and long-term BP control [618,621] and, in observational studies, reduces the incidence of outcomes [613,622–624].

These are the main reasons why the 2018 ESC/ESH guidelines recommended a new simple and pragmatic treatment algorithm applicable to most patients, with the use of SPC therapy as first-line initial therapy. Exceptions are frail and very

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old patients, because of the impairment of the baroreflex and greater risk of hypotension, and very high-risk patients with high-normal BP, in whom the small BP reduction associated with monotherapy may allow to reach the BP target. For the same reason, initial monotherapy may also be considered in grade 1 hypertensive patients at low risk with a BP only modestly elevated above the BP threshold for drug treatment.

11.10.2 Drug combinations

Among the large number of RCTs of antihypertensive therapy, only a few have directly compared two different drug combinations, with systematic use of the two combinations in both arms. In most trials, treatment was initiated using monotherapy in either arm and another drug (and frequently more than one drug) was added, usually in a nonrandomized fashion, according to a prespecified treatment algorithm. In a few trials, such as ALLHAT [563], the design precluded the use of what could be optimal combinations, because multiple monotherapies were evaluated. With this caveat, Table 17 shows that a variety of drug combinations have been used in at least one active arm of placebo-controlled trials and have been associated with significant benefit on major CV events.

In trials comparing different regimens [625] (Table 18), all combinations have been used in a larger or smaller proportion of patients, without major differences in benefits. The only exceptions are two trials in which a large proportion of the patients received either an ARB/diuretic combination or a CCB/ACEi combination, with both regimens being superior to a BB (atenolol)diuretic combination in reducing CV outcomes [597,626]. Three outcome trials directly compared two different combinations, each involving a combination of an RAS blocker (ACEi or ARB) and a CCB with other combinations. In the ACCOMPLISH study [627], the ACEi/CCB combination was superior to the same ACEi in combination with a Thiazide diuretic at preventing major CV outcomes and CKD progression, despite only a small difference in BP between the two arms (SBP/DBP: 0.7/1.7 mmHg). The ACCOMPLISH finding [627] was not confirmed in the COLM and COPE [628] trials, which reported no significant difference in CV events, when an RAS blocker–CCB combination was compared with an RAS blocker–Thiazide diuretic combination [628,629]. However, these two last trials were statistically underpowered, and their results on the outcomes, thus, have limited value.

Based on the results of outcome RCTs, recent meta-analyses and evidence of BP-lowering effectiveness, all five major drug classes can in principle be combined with one another, except for ACEis and ARBs (Section 11.10). However, we recommend that treatment of hypertension should be preferentially based on combinations of an ACEi or an ARB with CCB or a Thiazide/Thiazide-like diuretic. These combinations are now widely available in a single pill and in a range of doses, facilitating flexible prescribing and up-titration from lower to higher doses. They also (i) limit potential adverse effects associated with diuretic or CCB monotherapy, i.e. reduce the risk of hypokalemia due to diuretics, or the prevalence of peripheral edema due to CCBs and (ii) ensure that the RAS is inhibited as part of the treatment strategy, which is important for many patient groups (patients with diabetes, LVH, CKD with or without proteinuria etc.). Other combinations, such as CCB or BB plus a diuretic, also have RCT-based evidence supporting their use, as mentioned by the 2018 ESC/ESH guidelines. In addition, they can be the preferred combinations in a number of conditions. In black patients in sub-Saharan

TABLE 17. Major drug combinations used in trials of antihypertensive treatment in a stepped approach or as a randomized combination

Trial	Comparator	Type of patients	SBP difference (mmHg)	Outcomes (change in relative risk)
ACEi and diuretic combination				
PROGRESS [630]	Placebo	Previous stroke or TIA	−9	−28% strokes (P <0.001)
ADVANCE [631]	Placebo	Diabetes	−5.6	−9% micro/macrovasc. events ($P = 0.04$)
HYVET [501]	Placebo	Hypertensive; ≥80 years	−15	−34% CV events ($P < 0.001$)
ARB and diuretic combination				
SCOPE [632]	Diuretic + placebo	Hypertensive; ≥70 years	−3.2	−28% nonfatal strokes (P = 0.04)
HOPE-3 [633]	Placebo	Patients at intermediate CV risk without CV disease (38% hypertensive patients)	−6	NS overall difference in CV events but -27% in CV events in patients with baseline BP>143.5 mmHg
ARB and CCB				
OSCAR [634]	ARB	Older, high-risk hypertensive patients	−2.4	NS overall difference in CV events -31% events, patients with CV disease (P=0.02)
CCB and diuretic combination				
FEVER [635]	Diuretic + placebo	Hypertensive	−4	−27% CV events ($P < 0.001$)
ACEi and CCB combination				
Syst-Eur [498]	Placebo	Older with ISH	−10	−31% CV events ($P < 0.001$)
Syst-China [144]	Placebo	Older with ISH	−9	−37% CV events ($P < 0.004$)
BB and diuretic combination				
Coope and Warrender [636]	Placebo	Older hypertensive	−18	−42% strokes ($P < 0.03$)
SHEP [637]	Placebo	Older with ISH	−13	−36% strokes ($P < 0.001$)
STOP-Hypertension [638]	Placebo	Older hypertensive	−23	−40% CV events ($P = 0.003$)
STOP-Hypertension 2 [639]	ACEI or conv. antiHT	Hypertensive	0	NS difference in CV events
Combination of two RAS blockers/ACEi + ARB or RAS blocker + renin inhibitor				
ONTARGET [641]	ACE inhibitor or ARB	High-risk patients		More renal events
ALTITUDE [558]	ACE inhibitor or ARB	High-risk diabetic patients		More renal events

Combinations versus placebo or monotherapy

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TABLE 18. Major drug combinations used in trials of antihypertensive treatment in a stepped approach or *as a randomized combination*

Trial	Comparator	Type of patients	SBP diff (mmHg)	Outcomes (change in relative risk)
ACE inhibitor and diuretic combination				
CAPPP [641]	BB + diuretic	Hypertensive	+3	+5% CV events (NS)
ACCOMPLISH [642]	ACE inhibitor + CCB	Hypertensive with risk factors	+1	+21% CV events ($P<0.001$)
ARB and diuretic combination				
LIFE [643]	BB + diuretic	Hypertensive with LVH	−1	−26% stroke ($P<0.001$)
Calcium channel blocker and diuretic combination				
ELSA [644]	BB + diuretic	Hypertensive	0	NS difference in CV events
CONVINCE [645]	BB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
VALUE [522]	ARB + diuretic	High-risk hypertensive	−2.2	−3% CV events (P=NS)
COPE [646]	CCB + BB	Hypertensive	+0.7	NS difference in CV events or stroke
CREOLE [647]	ACEI+CA ACEI+D	Black Hypertensives uncontrolled	−0.14 −3.14	No outcome data; CCB+D and ACE+CCB superior to ACEI+D in BP control
ACE inhibitor and CCB combination				
NORDIL [648]	BB + diuretic	Hypertensive	+3	NS difference in CV events
INVEST [649]	BB + diuretic	Hypertensive with CAD	0	NS difference in CV events
ASCOT [597]	BB + diuretic	Hypertensive with risk factors	−3	−16% CV events ($P<0.001$)
ACCOMPLISH [642]	ACE inhibitor + diuretic	Hypertensive with risk factors	−1	−21% CV events ($P<0.001$)
Beta-blocker and diuretic combination				
CAPPP [641]	ACE inhibitor + diuretic	Hypertensive	−3	−5% CV events (P=NS)
LIFE [643]	ARB + diuretic	Hypertensive with LVH	+1	+26% stroke ($P<0.001$)
ALLHAT [650]	ACE inhibitor + BB	Hypertensive with risk factors	−2	NS difference in CV events
ALLHAT [650]	CCB + BB	Hypertensive with risk factors	−1	NS difference in CV events
CONVINCE [645]	CCB + diuretic	Hypertensive with risk factors	0	NS difference in CV events
NORDIL [640]	ACE inhibitor + CCB	Hypertensive	−3	NS difference in CV events
INVEST [649]	ACE inhibitor + CCB	Hypertensive with CAD	0	NS difference in CV events
ASCOT [597]	ACE inhibitor + CCB	Hypertensive with risk factors	+3	+16% CV events ($P<0.001$)
Beta-blocker and CCB combination				
COPE [629]	ARB+CCB	Hypertensive	+0.8	NS difference in CV events or stroke
ARB and CCB combination				
COPE [629]	CCB + diuretic	Hypertensive	−0.7	NS difference in CV events or stroke
COPE [629]	CCB + BB	Hypertensive	−0.8	NS difference in CV events or stroke
COLM [630]	ARB + diuretic	Older hypertensive	0	NS difference in CV events

Combinations versus other combinations.

Africa, amlodipine plus either hydrochlorothiazide or perindopril was more effective than perindopril plus hydrochlorothiazide at lowering BP [648].

11.10.3 Rationale for initial two-drug combination therapy

As discussed above and with the emphasis in the present guidelines on achieving a BP target of <130/80 mmHg in most patients, the majority of patients will require combination therapy. Although no RCT has ever compared major CV outcomes between initial combination therapy and monotherapy, multiple arguments support combination of two antihypertensive drugs as the initial treatment step. One, initial combination therapy is invariably more effective at BP lowering than monotherapy, and indeed even low-dose combination therapy is usually more effective than maximal dose monotherapy. Furthermore, the combination of medications targeting multiple mechanisms (i) reduces the heterogeneity of the BP response to initial treatment and (ii) provides a steeper dose–response effect than that observed with escalating doses of monotherapy and (iii) is safe and well tolerated, with no or only a small increase in the risk of hypotensive episodes, even when given to patients with grade 1 hypertension. Two, initial two-drug combination is associated with a faster BP reduction compared with monotherapy, and observational evidence suggests that the time taken to achieve BP control is an important determinant of clinical outcomes, especially in high-risk patients, with a shorter time to control associated with lower risk [651]. Three, evidence from the more general hypertensive population shows that compared with patients on initial monotherapy, those who start treatment with a two-drug combination reach more frequent BP control after 1 year [621], probably because initial combination treatment prevents therapeutic inertia [608,618], and initial two-drug combination is associated with a better long-term adherence and persistence [620] to the prescribed treatment regimen. Studies from large treated cohorts of patients under antihypertensive treatment have also shown that initial combination treatment resulted in a lower risk of CV events compared with initial monotherapy followed by the traditional stepped-care approach [608,623,624,652]. In one study, it was possible to analyze more than 2200 patients who experienced during the follow-up (1 year) a hospitalization for CV disease, while also showing a shift from initial combination treatment to monotherapy or vice versa. The results of this within-patient comparison (which removed a major limitation of observational studies, i.e. confrontation of external and possibly different patient groups) showed that the risk of hospitalization was much reduced when patients were on combination treatment compared to when they were on single-drug therapy [653].

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General recommendations for antihypertensive drug treatment

Recommendations and statements	CoR	LoE
BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction.	I	A
Five major drug classes including, ACEis, ARBs, BBs, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced BP and CV events in RCTs. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies.	I	A
Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or Thiazide/Thiazide-like diuretic. Other combinations of the five major drug classes can be used.	I	A
Initiation with monotherapy can be considered in patients with: • grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) • high-normal BP and very high CV risk, • frailty and/or and advance age.	I	C
If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker + CCB + Thiazide/Thiazide-like diuretic.	I	A
If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension.	I	A
The use of single pill combinations (SPCs) should be preferred at any treatment step, i.e. during initiation of therapy with a two-drug combination and at any other step of treatment.	I	B
BBs should be used at initiation of therapy or at any treatment step as GDMT, examples: • Heart failure with reduced ejection fraction HFrEF • Anti-ischemic therapy in chronic coronary syndromes • Heart rate control in atrial fibrillation	I	A
BBs can be considered in the presence of several other conditions in which their use can be favorable as summarized in Table xx.	I	C
The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI.	III	A

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11.10.4 Up-titration of treatment to three-drug combination

Evidence from RCTs shows that two-drug combination therapy will control BP in approximately half to two-thirds of patients [654]. For patients whose BP is not controlled by two-drug combination therapy, an option may be to use a different two-drug combination, or as suggested by the ISH guidelines [32], to use the same two-drug combination at higher doses of the combination components. A third logical option, however, is treatment with three-drug combination therapy, usually an RAS blocker, a CCB and a Thiazide/Thiazide-like diuretic. A three-drug combination can control BP in up to 90% of patients, which is a rate of BP control that is much greater than the current rate of BP control across Europe in treated hypertensive patients. There is also evidence that an SPC of three drugs achieves better BP control than usual care [655]. The present guidelines do not recommend to start treatment with a three-drug combination because of the risk of a BP reduction that is too fast and/or excessive, particularly in older patients.

11.10.5 Rationale for single-pill combination therapy

The 2013 and 2018 ESH/ESC guidelines [3,4] favored the use of two antihypertensive drugs as an SPC, because reducing the number of pills to be taken daily improves adherence to treatment and increases the rate of BP control. This recommendation is endorsed by the present guidelines. Use of SPCs is further supported by data from recent studies using various methods to assess adherence to treatment, including quantification of antihypertensive drugs in urine and blood, estimates such as prescription refills and calculation of the percentage of days covered by the treatments, which, although indirectly, enable to measure adherence on a prolonged basis, thereby accounting for its time-variable nature [478,617,622,652]. These studies have unequivocally shown a direct inverse relationship between the number of pills and the likelihood of adherence. This approach is now facilitated by the availability of several SPCs with a range of dosages, which eliminates the often-stated disadvantage of SPC therapy, i.e. the inability to increase the dose of one drug independently of the other. It is also convenient that the most widely available SPCs mirror the major drug class combinations recommended by the present guidelines. The major advantage of an SPC as the usual therapeutic approach for hypertension is that patients can progress from one, two or three drug treatments, remaining on a simple treatment regimen with a single pill throughout, thus increasing the likelihood of adherence to therapy while progressing to BP control. Such an approach can markedly increase the percentage of patients achieving high adherence to treatment (e.g. >80% of the treatment time covered by prescription) while markedly reducing patients characterized by low adherence to treatment (e.g. <20% of treatment time covered by prescription) with a clear reflection independently on age, sex, co-treatment and clinical status, with a clear reflection on patients' protection [652]. It showed the potential to double BP control rates in treated patients from the present low level also with an improvement of outcomes [656]. SPCs of a BB plus a diuretic or a CCB have been available since many years, while at the time of the 2018 ESC/ESH Hypertension Guidelines, additional SPCs were almost exclusively limited to a RAS blocker (ACEi or ARB) plus a CCB or a diuretic. In the 5 years from the 2018 Guidelines, a large number of new two-drug SPCs have been developed and tested for their ability to improve adherence to treatment and reduce CV outcomes. Available two-drug SPCs now extend to most ACEIs or ARBs in combination with a long-acting CCB or a diuretic belonging to the Thiazide (usually hydrochlorothiazide) or Thiazide-like (indapamide or chlorthalidone) class. Moreover, two-drug SPCs are now available for a RAS blocker (ACEi or ARB) with a BB, including SPC containing nebivolol with additional vasodilatory action, and a CCB with a diuretic (e.g. amlodipine plus indapamide or nifedipine plus a Thiazide). The availability of three-drug SPCs has also grown and, although almost invariably based on a diuretic, a RAS blocker and a CCB, it now extends to different compounds within each of the three drug classes involved. This enables to tailor SPC treatment to different clinical requirements [652,656–658].

11.10.6 The quadpill concept

Another innovative therapeutic approach to increase BP control while improving tolerability is to use combinations of low or even ultralow doses of the recommended antihypertensive drugs. With this approach, the ability to effectively reduce an elevated BP appears to be maintained while most side effects are avoided. A proof-of-concept study and a systematic review of quarter-dose BP-lowering drugs was reported in 2017 [659,660]. The systematic review included 36 trials ($n = 4721$ participants) of one drug at quarter-dose and 6 trials ($n = 312$) of two drugs at quarter-dose against placebo. The pooled placebo-corrected SBP/DBP-lowering effects were, respectively, 5/2 mmHg and 7/5 mmHg with no reported side effects. The BP-lowering effect was even greater when quarter-doses of four drugs, i.e. quadpill, were used. These preliminary data have been supported by a phase 3 study by the same authors, in which 591 patients were randomized to the quadpill or to full-dose monotherapy with an ARB. BP changes were assessed at 12 weeks and 12 months. The BP control rate was greater in the quadpill group at both time points. Studies in broader populations are needed, and more information is required on a number of issues such as the strategy to adopt when side effects occur or hypotension develops using the quadpill approach.

11.10.7 The polypill concept

Polypills consist of SPCs of one or two antihypertensive agents and a statin with or without low-dose acetyl salicylic acid (aspirin) [661]. Different doses of antihypertensive agents, usually including an ACEi, are available. The rationale is that (i) hypertensive patients often also have dyslipidemia and an elevated CV risk and (ii) treatment simplification, i.e. a single pill rather than multiple pills daily, improves adherence to treatment, which is low in hypertension [478,613,662–664]. Bioequivalence studies suggest that, when combined in the polypill, different agents maintain their expected effect [665], including the BP-lowering efficacy. Furthermore, studies performed in the setting of secondary CV prevention,

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particularly in patients with a previous myocardial infarction, have shown that use of the polypill is accompanied by better adherence to treatment compared with separately administered medications [661]. This is true for treatment simplification in general. Based on this evidence, the use of the polypill has been recommended for the management of myocardial infarction [665]. However, present data also document that the polypill reduces the risk of CV outcomes. This was initially reported by large observational studies in patients with established atherosclerotic CVD [661] and has more recently been proven by the results of large outcome-based randomized trials in patients with and also without previous CV events [666,667]. In an individual-participant meta-analysis of three primary prevention trials, a combination of two antihypertensive agents and a statin at low doses reduced the risk of CV outcomes by 38%. A polypill including low-dose aspirin was associated with a nearly 50% outcome reduction. The benefits were seen across various subgroups (different lipid and BP levels, diabetic patients, smoking, obesity) with the smallest effect in patients <55 years of age [668]. In a fourth randomized control trial in patients with a recent myocardial infarction, the polypill (aspirin, ACE-inhibitor and statin) treatment strategy reduced the risk of the primary outcome (CV death, myocardial infarction, ischemic stroke and urgent revascularization) by 24% compared with usual care, again across subgroups with different clinical characteristics and with the additional evidence of an improved adherence to treatment in the polypill group. Adverse events were similar between groups and the most common adverse event in the polypill group was dizziness [667]. The above evidence supports use of currently available polypills in hypertensive dyslipidemic patients at elevated CV risk. Polypills without low-dose aspirin may be used in primary prevention, while use of those with aspirin should be restricted to secondary prevention. The previously issued recommendation to check the efficacy of the combination components in separate tablets before switching to the polypill appears impractical [4,669]. Potential inconveniences may be the limited dose flexibility of the polypill components as well as the limited potential of the available polypills to reach the lower LDL-cholesterol and BP targets at present recommended by guidelines. This may require the separate administration of additional drugs in a number of patients, with partial loss of the polypill advantages.

11.10.8 Choice of drug combinations for initiation of treatment

Reflecting on the evidence discussed above and recognizing the need to avoid or minimize the factors contributing to poor BP control in treated hypertensive patients, the following few simple and pragmatic recommendations for the treatment of hypertension can be listed (Figs. 11 and 12):

1. In most patients, treatment should be initiated with an SPC of two drugs to improve the speed, efficiency and predictability of BP control.
2. Although several two-drug combinations can be used, the preferred two-drug combinations should be an RAS blocker with a CCB or a Thiazide/Thiazide-like diuretic.
3. A BB can be used at any step of combination with any drug from the other major drug classes as GDMT or in several other conditions (Table 16).
4. Initial monotherapy is recommended for very-high-risk patients with a high-normal BP as well as (for cautionary reasons) for very old and frail patients. It may also be considered in low-risk patients with stage 1 hypertension whose SBP is more modestly elevated (<150 mmHg).

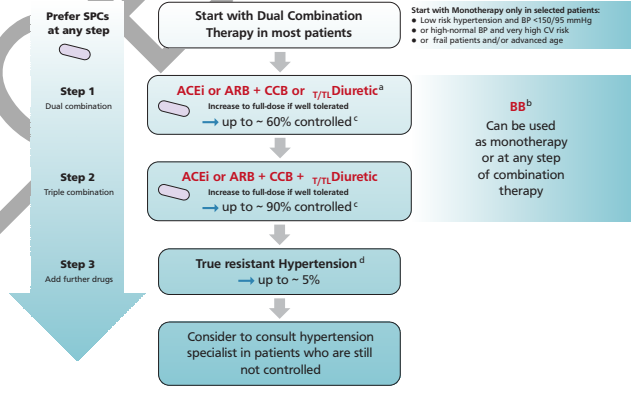


FIGURE 12 General BP lowering strategy in patients with Hypertension.
[a]Use of Diuretics:
–Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2
–If eGFR <30 ml/min/1.73 m^2 use Loop Diuretic
[b]BB should be used als guideline directed medical therapy in respective indications or considered in several other conditions (Table 16)
[c]Controlled below 140/90 mmHg
[d] When SBP is ≥140mmHg or DBP is ≥90 mmHg provided that:
–maximum recommended and tolerated doses of a three-drug combination comprising a RAS blocker (either an ACEi or an ARB), a CCB and a Thiazide/Thiazide-like diuretic were used
–adequate BP control has been confirmed by ABPM or by HBPM if ABPM is not feasible
–various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension have been excluded (Section 12).

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5. An SPC comprising an RAS blocker + CCB + Thiazide/Thiazide-like diuretic, should be used if two-drug combinations do not achieve BP control (at the maximum tolerated doses) and a BB is not indicated.
6. Regardless the initial treatment choice, ultimately most patients should be on combination treatment, using SPC whenever possible.

11.10.9 Tolerability and side effects of drugs

All antihypertensive drugs can elicit side effects, which can be modest or, in some instances, serious, leading to treatment discontinuation. Side effects play a major role for treatment nonadherence and discontinuation [670] and can be either related to BP lowering per se or because of class-specific effects [671,672]. Nevertheless, the recommended major antihypertensive drug classes show by and large a good tolerability, which is one of the criteria that supports the recommendation for their use, in addition to their BP-lowering effect and proven outcome reduction. Side effects vary not only between different classes but also within a drug class, e.g. between different BBs and between DHP and non-DHP-CCBs. Fortunately, the potential for pharmacokinetic drug–drug interactions that may influence plasma concentration of drugs is marginal for any of the major BP-lowering drug classes, thereby providing the basis for their safe use in combination therapy. It should also be mentioned that there are clinically favorable interactions between major antihypertensive drugs, a most important one being their additive BP-lowering effect. Furthermore, there are interactions that increase drug tolerability, i.e. reduced incidence or intensity of ankle edema by adding an RAS blocker to a CCB or reduced hypokalemia by adding an RAS blocker to a Thiazide/Thiazide-like diuretic [670].

11.10.10 Prescribing of antihypertensive drugs

11.10.10.1 Standard drug administration

The primary goal of antihypertensive treatment is to provide BP control over the 24- h period (short-term) and to maintain this control over time (long-term). To achieve this goal, clinicians must consider (1) the half-lives and dose of the used drugs, as well as their interactions with the concomitantly used drugs (pharmacokinetics), (2) the mechanism of action of the drugs (pharmacodynamics) and (3) patient characteristics that might influence absorption, metabolism or elimination of the drug [673]. It is generally accepted that use of multiple daily doses during the day may achieve BP control at the expense of reduced patient adherence to treatment [478,613,662,664,674]. For this reason, drugs that have a duration of action that covers the 24 h period with a single daily administration should be preferred. This is not fulfilled by all agents [675] within major antihypertensive drug classes. This shortcoming has been accounted for by giving a drug at higher doses, which can also prolong the effect of short-acting agents albeit with the risk of inducing hypotension at the time of the peak effect. To allow once-daily drug administration, extended release formulations have also been developed. Different durations of action of antihypertensive drugs given once daily [675] may also affect short-term or long-term BP variability [179] and perhaps outcomes, but the extent of these influences is still unclear.

Most of the available evidence on the outcome benefit of BP-lowering therapy has come from RCTs using morning dosing of the drugs. However, recent evidence that night-time hypertension is not rare as well as that a nondipping profile may have adverse prognostic consequences [676] has favored the hypothesis that bedtime administration of antihypertensive drugs should be preferred to more effectively reduce night-time BP and CV outcome risk [676,677]. The limitations of the supporting data have been discussed by some critical articles [676,677] and by a systematic review of eight studies on the effects of morning versus bedtime dosing of antihypertensive agents. Reaching a conclusion was considered problematic because of major methodological limitations and bias [678]. In this regard, the recent TIME pragmatic trial [675] has provided important data. In TIME, 21 104 participants from the United Kingdom were randomized in a 1 : 1 ratio to take their usual BP medications in the morning or in the evening. The average age of participants was 65 years and 58% were men. The median follow-up was 5.2 years, but some patients were followed up for more than 9 years [675]. Overall, no safety concerns were detected in the study. The reported nonadherence to therapy was significantly higher with evening versus morning dosing (39.0 versus 22.5%, $P < 0.0001$). However, there was no significant difference in the primary outcome (hospitalization for major CV events and vascular death) between the evening-dosing and the morning-dosing groups. Thus, data do not support preferential use of antihypertensive drugs at bedtime, which is, however, also not harmful. Based on TIME, patients have a choice as to when to take their medication, while physicians may consider bedtime dosing in patients with documented high night-time BP [679]. In general, the present guidelines recommend taking BP in the morning, as adherence to antihypertensive medication is worse at bedtime [675,679,680].

11.10.10.2 Partial treatment reduction or complete withdrawal

Complete withdrawal of antihypertensive drug therapy, because of side effects or other reasons, is accompanied by a more or less rapid return of BP to the pretreatment elevated values [681]. With centrally acting agents, especially clonidine, an abrupt rebound BP increase may occur, whereas abrupt withdrawal of BBs in patients with CAD may result in angina or other symptoms or complications of CAD, e.g. arrhythmias. Headache, joint pain, palpitations, edema and a general feeling of being unwell have also been reported [681]. A marked increase in CV risk after antihypertensive treatment withdrawal has been documented in many studies [494,682,683], although no adverse consequences have also occasionally been reported [681,684]. Some studies observed no or little BP increases after treatment withdrawal in a sizeable fraction (up to 25%) of the hypertensive population, but the interpretation of this finding is uncertain and possibly related to an erroneous

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TABLE 19. Withdrawal of BP-lowering drugs

Drug class	Effects of abrupt withdrawal
CCBs	• Risk of angina
BBs	• Risk of angina and other complications in CAD patients
Centrally acting agents	• Sympathetic overactivity (nervousness, tachycardia, headache, agitation and nausea for 36–72 h after drug cessation) • Rapid rebound BP increase even above pretreatment levels • Angina and other complications in CAD patients
Diuretics	• Fluid retention, aedema, HF decompensation

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hypertension diagnosis or withdrawal of hypertensiogenic risk factors such as overweight [681] during the treatment period. The possibility that a long-term effective antihypertensive treatment reverses the structural changes of hypertension and favors prolonged BP normality after treatment cannot be excluded. To date, little or no evidence exists on the BP and outcome effects of partial deprescribing of BP-lowering drugs (Table 19).

11.10.10.3 Antihypertensive drugs and cancer risk

Whether hypertension per se or treatment with antihypertensive drugs may influence the risk of cancer has been a matter of debate for many years [685–687]. More recently, two case–control studies suggested that the use of hydrochlorothiazide is associated with an increased risk of developing squamous cell carcinoma in the skin and lip [688,689]. This was not the case with other diuretics or antihypertensive drugs. However, although it cannot be denied that most diuretics (including hydrochlorothiazide) are potentially photosensitizing drugs [690] and that this can be a basis for an adverse influence on skin cancer, the studies had methodological limitations [686] and were confirmed by some, but not by all, subsequent studies carried out in other countries or ethnicities [691]. The issue is confusing also because a recent study from the UK Clinical Research Database again also reported an increased risk of skin squamous cell carcinoma in users of hydrochlorothiazide. However, the increased risk was seen only in women, and no biological rationale was offered for this finding [692]. Finally, a large propensity-matched cohort study in Germany found that hydrochlorothiazide was associated with not only a small increase of skin cancer risk but also with an overall lower risk for any cancer compared with other diuretics [693]. Further well designed observational studies are needed to provide a more solid evidence on the association between hydrochlorothiazide and skin cancer risk. In the meantime, important evidence to quote is that in a recent individual participant data meta-analysis of 33 RCTs, involving 260 447 participants and 15 012 cancer cases, no significant association between Thiazides (including hydrochlorothiazide) and skin cancer was observed. Furthermore, no significant association with any cancer was found for ACEis, ARBs and BBs. Only for CCBs, a small but significant effect size was found for all cancer risk (hazard ratio 1.06, 95% CI 1.01–1.11). Although the relatively short duration of the trials (slightly more than 4 years) represents a limitation, this supports the recommendation not to consider cancer risk a barrier to any drug management of hypertension including hydrochlorothiazide, which is a frequent component of SPCs [694] and has a documented protective effect.

11.10.11 Concomitant medications

11.10.11.1 LDL-cholesterol lowering

Hypertension and dyslipidemia are highly prevalent in the general population and often coexist, contributing to CV risk in an additive way [529]. Lipoproteins in plasma are classified according to size, and differ with respect to lipid content and apolipoprotein expression [695]. Several different lipid- and lipoprotein measures (including total cholesterol, non-HDL cholesterol, LDL cholesterol and triglycerides) have been associated with the risk of CVD in a log-linear fashion. Current evidence suggests that all ApoB-containing lipoprotein with a diameter <70 nm may cross the endothelial barrier and contribute to the formation of atherosclerosis. This explains why different lipid measures are used in different contexts, such as non-HDL cholesterol in the SCORE2 and SCORE2-OP models to estimate CV risk, whereas treatment targets are generally guided by levels of LDL-cholesterol. These guidelines support the concept of risk-based lipid-lowering treatment suggested by the 2021 ESC guidelines on CVD prevention [33]. Apparently healthy adults should undergo a CV risk assessment using the SCORE2 or SCORE2-OP tools [33]. In low-risk patients, no specific treatment is needed except for general lifestyle advice. For high-risk or very-high risk primary preventive patients, it is recommended to initially aim for a LDL-cholesterol level below 2.6 mmol/l (100 mg/dl). Depending on 10-year and lifetime risk, comorbidities, frailty and patient preference, the ultimate goal may be an LDL-cholesterol level below 1.8 mmol/l (70 mg/dl) in high-risk patients, and below 1.4 mmol/l (55 mg/dl) in very high-risk patients [33].

The ASCOT trial [507] demonstrated that in people with hypertension and moderately elevated CV risk, treatment with 10 mg/day of atorvastatin reduced the risk of composite CV outcome by 36%. Numerous RCTs and multiple meta-analyses have shown that statin treatment is associated with a reduction of CV outcomes that is proportional to the LDL-cholesterol reduction [696]. In recent years, evidence from RCTs on ezetimibe and PCSK9-inhibitors have accumulated, adding to the overall body of evidence supporting the causal role of LDL-cholesterol reduction for CV protection [697]. Importantly, the relative benefit of lipid-lowering treatment in patients at moderately elevated risk seems to be independent of BP level [698,699], although the absolute benefit is more pronounced in people with hypertension because of elevated CV risk [700].

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Based on the results of the ASCOT and HOPE-3 trials [507,698], among others, people with hypertension and elevated CV risk should be treated with a moderate dose of a statin, whereas hypertensive patients classified as having a high or very high CV risk, thus fulfilling the criteria for intensive LDL-cholesterol-lowering treatment the required lower LDL-cholesterol goals for CV prevention should be attained by uptitrating statins to the maximally tolerated dose [695]. It is of note that most side effects, including muscle symptoms, are nonspecific and not related to statin treatment per se [701]. According to the recent guidelines on dyslipidemia ezetimibe should be added if LDL-cholesterol control is not achieved (preferably as SPC to improve adherence to treatment) [321,702] and PCSK9 inhibitors or siRNA may be considered in very high-risk patients to attain the LDL-C target.

In isolated triglyceridemia, statin therapy should be the initial drug class of choice to reduce CV risk, and may be considered if triglyceride levels are $\geq$2.3 mmol/l (200 mg/dl), especially in diabetic patients. Treatment with fenofibrate has been suggested to provide additional benefit, proportional to its effect on non-HDL-cholesterol [695,697]. The role of n3 polyunsaturated fatty acids (PUFA) is uncertain because of the conflicting results of two major trials published in recent years [703,704].

On the antihypertensive treatment side, BBs and diuretics may be regarded as less preferable in difficult-to-treat dyslipidemia because of their modest dyslipidemic effects, more evident in combination treatment. However, their ability to reduce CV risk through BP lowering greatly outweighs their metabolic downsides, and they should be used to control BP if necessary.

Recommendations for LDL-cholesterol-lowering therapy in hypertension

Recommendations and statements	CoR	LoE
The decision to initiate LDL-cholestrol lowering treatment, as well as treatment goals, should be based on an estimation of total CV risk, with priority given to high-risk patients.	I	A
Statin treatment is recommended in patients with hypertension and elevated CV risk.	I	A
Statin treatment at maximum tolerated dose is recommended as the first-line drug class to achieve LDL-cholesterol targets in patients with hypertension and high CV risk.	I	A
Ezetimibe may be added to maximum tolerated statin dose to attain LDL-cholesterol targets.	I	A
PCSK9-inhibitors and siRNA targeting PCSK9 may be considered in selected high-risk patients not attaining target LDL-cholesterol levels with statin/ezetimibe combination therapy.	II	A
Use of a polypill containing two BP lowering drugs and a statin for LDL-cholestrol lowering can be considered in hypertensive patients for primary prevention.	II	A

11.10.11.2 Antiplatelet therapy

Common complications of hypertension are related to atherothrombotic diseases, i.e. CAD, ischemic stroke, and LEAD [705]. The decision to recommend antiplatelet therapy in hypertension should be based on the individual CV risk, similarly to normotensive patients, i.e. according to their belonging to the primary prevention versus the secondary prevention setting, and to the bleeding risk. In secondary prevention, use of antiplatelet therapy [usually low-dose acetylsalicylic acid (aspirin)] is required, because in patients with established CVD, low-dose aspirin is associated with clinically important reductions of major CV events although with an increase of bleeding risk, especially from the gastrointestinal tract [706]. In

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primary prevention, a Cochrane systematic review [707] comprising 61 015 patients included in six trials (four trials in primary prevention, $n = 41\,695$ patients; and two trials in secondary prevention, $n = 19\,320$ patients) investigated the effects of antiplatelet agents and anticoagulants in hypertension. Four studies compared low-dose aspirin versus placebo and found no evidence of a difference in all-cause or CV mortality. However, aspirin treatment reduced the risk of all nonfatal CV events, albeit increasing the risk of major bleedings. The authors conclude that there is currently no evidence that antiplatelet therapy has a protective effect on hypertensive patients in the setting of primary prevention. The same conclusion had been reached more than 25 years ago in the HOT trial in which, however, some protective effect of low-dose aspirin was shown in a subgroup of patients with no previous CV events but with a high CV risk due to advanced kidney disease [708].

The benefits and harms of the newer drugs, i.e. clopidogrel, prasugrel and ticagrelor, have not been sufficiently studied in clinical trials on patients with hypertension.

Recommendations of antiplatelet therapy in hypertension

Recommendations and statements	CoR	LoE
Low-dose aspirin is not recommended for primary prevention in patients with hypertension.	III	A
Antiplatelet therapy is recommended for secondary prevention in hypertensive patients.	I	A
Use of a polypill containing low-dose aspirin can be considered in hypertensive patients for secondary prevention.	II	A

12. TRUE-RESISTANT HYPERTENSION

12.1 Definition, prevalence, pathophysiology and cardiovascular risk

In the 2018 Guidelines, hypertension was defined as resistant to treatment when appropriate lifestyle measures and treatment with optimal or best tolerated doses of three or more drugs (a Thiazide/Thiazide-like diuretic, an RAS-blocker and a CCB) fail to lower office BP to <140/90 mmHg. The inadequate BP control should be confirmed by out-of-office BP measurement showing an uncontrolled 24 h BP (≥130 mmHg SBP or ≥80 mmHg DBP) values. Evidence of adherence to therapy and exclusion of secondary causes of hypertension are required to define resistant hypertension, otherwise resistant hypertension is only apparent and termed as pseudoresistant hypertension (Fig. 13).

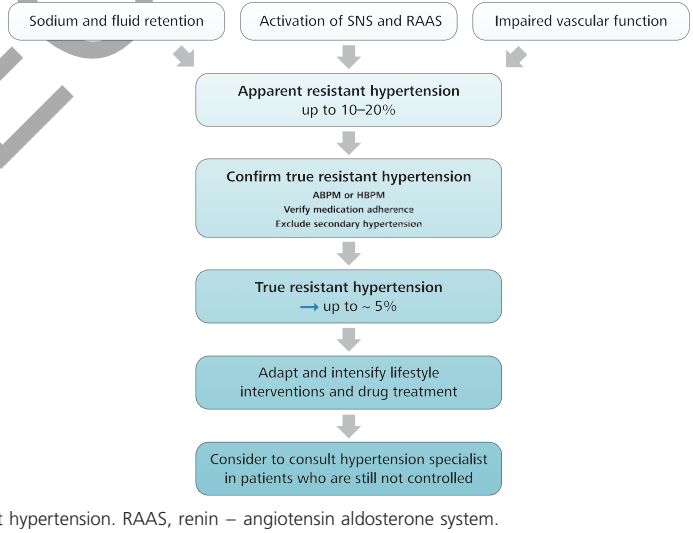


FIGURE 13 Characteristics of true resistant hypertension. RAAS, renin – angiotensin aldosterone system.

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The prevalence of resistant hypertension has been difficult to quantify because of its dependence on a number of factors: (i) the clinical setting (e.g. general population, tertiary referral center, clinical trial), (ii) the classes and optimal doses of the antihypertensive drugs used, (iii) the exclusion or retention of patients not adhering to treatment, (iv) the method of BP measurement and (v) the definition of the target BP value representing BP control [606,709,710]. Resistant hypertension can be very common in patients with advanced CKD [711]. Obviously, it is more common using the <130/80 mmHg than the <140/90 mmHg office BP values to define BP control [712]. It has a lower prevalence after removal of patients with normal out-of-office BP values, and the percentage of patients removed for this reason has been found to vary from about 14% to about 37% in meta-analyses of observational studies, randomized trials, surveys and registries [710,713,714]. After applying the strict criteria outlined above, a reasonable estimate of the resistant hypertension prevalence is that it might involve about 5% of the overall hypertensive population. These patients are referred to as having a true-resistant hypertension phenotype. Contributing demographic and clinical factors are obesity (or large weight gains), excessive alcohol consumption, high sodium intake, advanced HMOD and atherosclerotic disease as well as older age, male sex, Black African origin, low income, depression, high BP values at hypertension diagnosis and a 10-year CV risk score >20% [715–718]. The pathophysiology of true-resistant hypertension involves an interplay between multiple neurohumoral factors such as increased levels of aldosterone [598,719,720], endothelin-1 [721], vasopressin [722] and increased sympathetic activity [723]. These factors contribute to volume and sodium overload, increase in peripheral vascular resistance, arterial stiffness and more advanced HMOD, including cardiorenal damage [724–726]. Patients with resistant hypertension are at higher risk of HMOD [727], CKD [728] and premature CV events [729,730] (Fig. 13).

12.2 Diagnostic work-up

The diagnostic work-up should rule out pseudoresistant hypertension and, once true-resistant hypertension is identified, characterize the patient's clinical status by history, physical examination and laboratory and imaging analysis for the assessment of risk factors and HMOD (Section 5.5). Exclusion of pseudoresistant hypertension requires (i) the demonstration of an elevated ABPM; (ii) the exclusion of an origin of the BP elevation from inaccurate BP measurement, e.g. the spurious BP increase associated with marked brachial artery calcification, especially in older patients or in patients with advanced CKD; (iii) the exclusion of a secondary cause of hypertension (Section 6) or (iv) the exclusion of poor adherence to the prescribed treatment regimen (Section 21). The prevalence of secondary hypertension, especially primary aldosteronism [731] and atherosclerotic renal artery stenosis (particularly in older patients or patients with CKD) can be as high as 10–20% of patients with resistant hypertension [719]. Search for OSA (by sleep history and specific tests) should not be omitted because of the frequent involvement of this condition in resistant hypertension, including night-time hypertension [732–736].

Poor adherence to antihypertensive drug treatment is common in hypertension [652], and in resistant hypertension, this is even more the case [617], because adherence is inversely related to treatment complexity and the number of prescribed daily tablets [478,613,617,662,664,674]. Precise information on adherence can be difficult to obtain. Careful inquiry about a patient's medical habits, if necessary with the help of the patient's relatives, is the first step. Help can also be sought from some objective measures of adherence, which is unfortunately not easy to do [617]. Confirmation of adherence to antihypertensive medications may be provided by drug screening of urine or blood whenever available [617,664] or by pharmacodynamic markers of exposure to medications [bradycardia on BBs, increase blood levels of uric acid on diuretics, increase in plasma renin concentration on diuretics or RAS blockers, increases in urine N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) concentration on ACEi [737] and specific drug-related side effects] [617]. History should include accurate information on use of drugs or substances potentially interfering with BP control either by impairing the efficacy of antihypertensive drugs or by increasing BP (Table 20). Careful evaluation of the drugs taken by patients is made easier by use of standardized questionnaires [738] or drug–drug interaction-checking applications or web-tools.

12.3 Optimizing lifestyle changes and ongoing drug therapy

Effective treatment of resistant hypertension should combine (i) lifestyle changes (particularly reduction of sodium and alcohol intake, implementation of regular physical activity and weight loss in overweight or obese patients) (ii) discontinuation of interfering substances, (iii) rationalization of current treatment and (iv) the sequential addition of antihypertensive drugs to the existing triple therapy.

Replacing current drugs with a more rational and possibly simpler treatment regimen is based on use of combination therapies that are appropriate to a patient's age, ethnicity, compelling indications for certain drug classes, comorbidities and risk of drug–drug interactions. Drugs should be used at the maximal tolerated doses and SPCs should be preferred when available to reduce pill burden and improve adherence to treatment [618,739]. Because volume retention of multifactorial origin is frequent, reducing sodium intake (<2 g/day) or NaCl intake (<5 g/day) and increasing the intensity of diuretic therapy, particularly in older patients, patients of Black African origin or CKD patients, should be implemented. If eGFR is ≥30 ml/min, BP control may be improved by increasing the dose of the existing Thiazide diuretic or by switching to a possibly more potent and longer acting Thiazide-like diuretic (indapamide or chlorthalidone). If eGFR is <30 ml/min, a loop diuretic (furosemide, bumetanide and torsemide) should replace Thiazide/Thiazide-like diuretics, although even under this circumstance, Thiazides may retain their natriuretic and antihypertensive effects. In the CLICK trial [569], patients with stage

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TABLE 20. Medications and other substances that may increase BP

Medication/substance	Proposed mechanism	Comments
NSAIDs	Inhibition of COX-1 and 2 decreasing PG I2 and E2 synthesis with subsequent reduction in urinary Na excretion and an increased systemic vascular resistance.	Mild, dose-dependent increase in BP. Increased risk with age, preexisting hypertension, salt-sensitive patients, patients with renovascular hypertension.
Paracetamol (acetaminophen)	Presumably via inhibition of cyclooxygenases and reduced production of prostaglandins.	Increased relative risk of 1.34 of hypertension with almost daily paracetamol use.
Estrogens and progestins	Increased renin synthesis (by estrogens) leading to RAS activation and subsequent Na and water retention.	Mild, sustained increase in BP (6/3 mmHg increase with high doses of estrogen (>50 μg of estrogen and 1–4 μg progestin) but can be severe, common in premenopausal women, cause hypertension in 5% of women.
Glucocorticoids	Enhanced Na reabsorption and fluid retention via stimulation of mineralocorticoid receptors. Increased systemic vascular resistance due to upregulation of AT1 receptors on vascular smooth muscle cells.	Dose-dependent, low doses have less effect on BP, more common in older patients, or with a family history of primary hypertension.
Calcineurin inhibitors	Reduced NO production, ET-1 overproduction, systemic and renal vasoconstriction, renal Na retention.	Dose-dependent, mild-to-moderate increase in BP. Severe hypertension has been reported. Increased risk with preexisting hypertension, elevated creatinine levels and maintenance therapy with corticosteroids. See Section 20.8.2
Antidepressants SNRIs	Increased noradrenaline release causing adrenergic activation and increased SNS activity.	Dose-dependent, mild (2/1 mmHg) increase in BP.
Nasal decongestants	Vasoconstriction due to stimulation of alpha-1 receptors on vascular smooth muscles.	Dose-dependent, sustained increase in BP.
Erythropoietin-stimulating agents	Increased thromboxane, reduced prostacyclin levels and activation of the local RAS. Increased ET-1 production, decreased NO synthesis with subsequent vasoconstriction.	Dose-dependent, mild increase in BP, increased risk with preexisting hypertension, or when the initial hematocrit level is low. See Section 20.8.2
Stimulants - Modafinil - Amphetamines - Methylphenidate	 Block noradrenaline or dopamine reuptake. Promote release of catecholamines	Caffeine may cause persistent BP effects with regular consumption. Genetic polymorphisms may affect BP response.
VEGF inhibitors	Decreased NO production via VEGFR-2 antagonism and stimulation of ET-1 receptors promoting vasoconstriction.	A class effect. The incidence of hypertension is dose-related, risk is increased by preexisting hypertension, old age and overweight. See Section 20.8.2.
Substances of abuse - MDMA - PCP - Methamphetamine - Cocaine - Alcohol	Increased release and inhibited reuptake of monoamine neurotransmitters with subsequent SNS activation. Increased CNS catecholamine release with decreased neuronal uptake. Cocaine induces an increase in arterial wall stiffness and atherosclerosis. Alcohol increases SNS and RAS activity.	Cocaine induces acute but not chronic increase in BP. Alcohol causes a dose-dependent, sustained increase in BP independent from obesity or salt intake.
Herbal products - Licorice - Ephedra - St. John's wort - Yohimbine - Ginseng (high doses) - Ma huang	Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism. Ephedra activates the alpha-1 receptor increasing SNS activity.	Licorice: Dose-dependent, sustained increase in BP characterized by hypokalemia, metabolic alkalosis and suppressed plasma renin activity and aldosterone levels Yohimbine causes acute, dose-dependent increase in BP.
Diet pills - Sibutramine - Phenylpropanolamine	Increased levels of norepinephrine with subsequent activation of noradrenergic transmission	Mild increase in BP.

SNRI, serotonin-noradrenaline reuptake inhibitors.

4 CKD (eGFR 15–29 ml/min/1.73 m^2) and poorly controlled hypertension, showed an about roughly 10 mmHg 24-h SBP reduction with chlortalidone versus placebo, and the BP-lowering effect was particularly evident in patients already on loop diuretics [740]. Furosemide and bumetanide should be administered twice daily, because of their short duration of action, whereas longer acting agents, such as torsemide, can be administered once daily [741]. The dose or intake frequency of the loop diuretic may be increased in patients with severe CKD and/or albuminuria [741]. Careful monitoring of kidney function, serum electrolyte levels and fluid status is required to detect dehydration, hypokalemia, hyponatremia, hypovolemia or worsening of kidney function. After optimizing the ongoing therapy, a stepwise addition of other antihypertensive drugs should be considered if BP is still not at goal.

12.4 Fourth and subsequent lines of antihypertensive therapy

In patients with resistant hypertension, the fourth line treatment should include the MRA spironolactone, based on the evidence of its efficacy in the PATHWAY-2 trial [598] as well as in meta-analyses [576], including those in patients with HFrEF (Fig. 14). A secondary analysis of the TOPCAT trial has shown beneficial effects of spironolactone also in patients with

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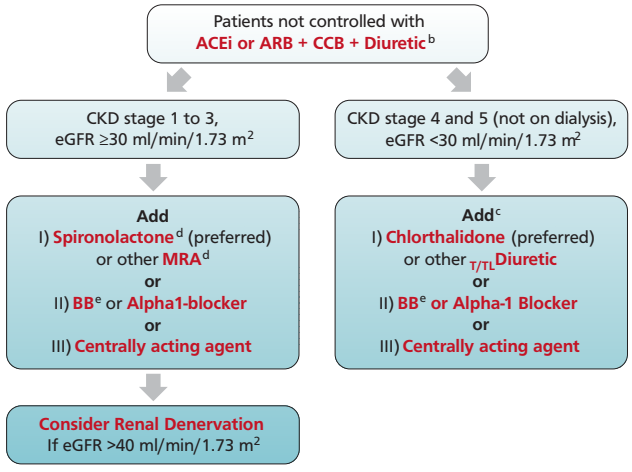


FIGURE 14 BP-lowering strategy in true resistant hypertension. (a) When SBP is ≥140mmHg or DBP is ≥90 mmHg provided that: maximum recommended and tolerated doses of a three-drug combination comprising a RAS blocker (either an ACEi or an ARB), a CCB and a T/TL Diuretic were used. adequate BP control has been confirmed by ABPM or by HBPM if ABPM is not feasible. various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension have been excluded (Section 12). (b) Use of Diuretics: Use T/TL Diuretic if eGFR >45 ml/min/1.73 m^2. Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2. Use loop Diuretic if eGFR <30 ml/min/1.73 m^2. (c) MRA contraindicated. (d) Caution if eGFR <45 ml/min/1.73 m^2 or serum potassium >4.5 mmol/l. (e) Should be used earlier at any step as guideline directed medical therapy in respective indications or considered in several other conditions (Table 16).

HFpEF [742], a condition in which difficult-to-control hypertension is frequent [192]. In the 2018 guidelines, it was recommended that spironolactone (25–50 mg/day) should be used with caution in patients with an eGFR <45 ml/min and a plasma potassium concentration >4.5 mmol/l, as these were exclusion criteria in the PATHWAY-2 trial. Thus, the efficacy and safety of spironolactone in patients with more advanced CKD or higher potassium levels at baseline have not yet been established. The spironolactone-associated risk of hyperkalemia is greater in patients with CKD, particularly if the drug is added to a treatment regimen that usually already includes an RAS blocker [743], making it necessary to closely monitor plasma potassium and eGFR after treatment initiation and, depending on individual risk and the CKD stage, at least annually or at three to 6 month intervals thereafter. The use of newer potassium binders such as patiromer [744] or sodium zirconium cyclosilicate [745] can reduce the risk of hyperkalemia, without increasing sodium overload (in the case of patiromer) or decreasing antihypertensive drug absorption as observed with sodium polystyrene sulfonate. Not all patients will be able to tolerate spironolactone because of its antiandrogenic side effects resulting in breast tenderness, gynecomastia and sexual impotence in men, and menstrual irregularities in women. The other steroidal MRA, eplerenone, has lesser potential to interfere with progesterone or androgen receptors and can, thus, be used alternatively to lower BP, but it is less potent than spironolactone [746]. Furthermore, in many countries eplerenone is only approved in patients with HF, and both eplerenone and spironolactone are not approved for use in hypertension in some European countries. A suboptimal tolerability profile as well as restrictions of its use, may partly explain the low prescription rate and the low persistence on treatment of spironolactone in real-life settings. Only 9.0% of patients with apparent resistant hypertension were treated with an MRA in a survey carried out in the USA [714], and only about 30% of patients were prescribed spironolactone at enrolment in the RADIANCE TRIO trial testing the efficacy of renal denervation in patients with resistant hypertension [739]. Alternative drugs can be amiloride, to be used at high dosages (10–20 mg per day), which was as effective as spironolactone (25–50 mg per day) in reducing BP in an open-label extension period of the PATHWAY2 trial [573]. However, this can lead to an increased pill burden as the marketed dose of amiloride is only 5 mg, and the drug is not available as a single agent but only in combinations (usually 5 mg) in many countries. Finally, new more selective nonsteroidal MRAs such as finerenone (approved for the treatment in diabetic kidney disease), esaxerenone (approved for the treatment of hypertension in Japan), and ocedurenone (KBP-5074, in development for resistant hypertension in CKD) might provide future alternatives to spironolactone for patients with resistant hypertension [746]. Ocedurenone (0.25–0.50 mg/day) reduced BP in patients with resistant hypertension and stage 3b/4 CKD with a higher incidence of hyperkalemia at the highest dose [747]. Finally, the use of selective aldosterone synthase inhibitors such as baxdrostat has been shown to effectively lower BP in patients with resistant hypertension in a phase 2 trial [720] and may, thus, develop into an additional treatment. This approach will avoid the noxious overall effects of aldosterone by reducing its synthesis instead of blocking its effects on mineralocorticoid receptors. Spironolactone as well as all above discussed alternatives should be used with caution in patients with reduced eGFR and baseline potassium levels >4.5 mmol/l.

When spironolactone and other MRAs are not tolerated or contraindicated (i.e. in CKD stage 4, eGFR <30 ml/min), bisoprolol (5–10 mg/day), doxazosin extended release (4–8 mg/day) or a centrally acting agent such as the alpha-adrenergic receptor agonists (clonidine, 0.1–0.3 mg twice a day) [601] can be used as alternatives [748]. However, bisoprolol and doxazosin reduced BP less effectively than spironolactone in the PATHWAY-2 trial [598], while clonidine has shown BP-lowering effects similar to spironolactone in a head-to-head comparison open-label RCT in patients with resistant hypertension [601]. Depending on approval and availability, the dual endothelin antagonist aprocitentan may

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also be used, because this drug had a sustained BP-lowering effect in patients with resistant hypertension as compared with placebo [721]. However, dose-dependent increase in the incidence of mild-to-moderate edema and fluid retention was also observed and may impair tolerability and safety [721]. Direct vasodilators, such as hydralazine or minoxidil, should be used parsimoniously because they may cause severe fluid retention and reflex sympathetic activation with tachycardia. Recent RCTs have shown that endovascular RDN can be associated with a significant, albeit not marked, office and ambulatory BP reduction in patients with uncontrolled hypertension [739,749–751]. In a large registry of renal denervated patients, the BP reduction was long-lasting and devoid of significant safety problems [190,752]. RDN can thus be proposed as an adjunctive therapy to patients with resistant hypertension provided eGFR >40 ml/min/1.73 m^2, in whom BP control cannot be achieved or serious side effects cannot be avoided with antihypertensive medications [739,753] (Section 13.1).

It is important to emphasize that in resistant hypertension, dedicated trials such as the PATHWAY-2 [572] and ReHOT [601] were short-term efficacy studies showing the effect on BP lowering after 12 weeks of treatment. Both studies included a relatively small number of patients (314 and 187, respectively) and in a relatively large fraction of patients, BP was still not controlled after treatment with spironolactone (about 40% in PATHWAY-2 based on HBPM measurements and about two-thirds of patients in ReHOT based on office BP) [754]. Finally, and most importantly, outcome RCTs in resistant hypertension are lacking. A recent real-world-evidence study in the United States included a total of 80 598 patients with resistant hypertension and compared the effectiveness of newly prescribed MRA treatment (6626 patients, 98% of whom were spironolactone users) with newly prescribed BB treatment (73 972 patients) as fourth line drugs [748]. In propensity score matched analysis, a 23% nonsignificant (95% CI 0.50–1.19) reduction in favor of spironolactone for the combined primary outcome of stroke and myocardial infarction was found. The risk of hyperkalemia and worsening of kidney function was significantly greater for spironolactone. An earlier similar and smaller observational study in a UK primary care database involved 8639 patients with resistant hypertension receiving new prescriptions of MRAs ($n = 350$), BBs ($n = 2869$) and alpha-1 blockers ($n = 5420$) [755]. The risk of the primary outcome (combined all-cause mortality, stroke and myocardial infarction) indicated a nonsignificant risk difference in favor of BBs compared with spironolactone and a significant risk difference (−32%) in favor of alpha1-blockers [755]. Taken together. these observational studies show a substantially lower use of MRAs (spironolactone) in clinical practice, while data supporting a benefit for CV outcomes or mortality with use of spironolactone remain lacking. RCTs to identify the most protective medical therapy in resistant hypertension are needed.

Treatment of resistant hypertension includes the patients' frequent comorbidities, for which additional treatment options may apply. Hence, for patients with OSA, continuous CPAP may be of moderate benefit [756,757], especially when this condition is severe (AHI >30 events/h), baseline BP is high and adherence to CPAP is good [758]. In obese patients, GLP1 receptor agonists can reduce body weight [759], modestly lower BP [760,761] and improve CV prognosis in patients with type 2 diabetes or with established CVD [762]. Bariatric surgery can lower BP, CV risk factors and risk of CV events in severely obese patients [763] and may, thus, reduce the burden of antihypertensive medication when these patients have resistant hypertension [764]. In patients eligible for treatment with SGLT2is their use may add a moderate BP-lowering effect to the background antihypertensive therapy for resistant hypertensive patients [765]. Finally, compared with valsartan alone, the sacubitril–valsartan combination did not lower hospitalization for HF and death in patients with HFpEF [766], but did reduce significantly the NYHA class of the patients. Furthermore, in a post hoc analysis of the same study, its use reduced BP in patients with resistant hypertension, despite treatment with at least four antihypertensive drugs, including an MRA [767]. This confirmed the BP-lowering effect of this compound reported in a phase 2 trial in hypertension [605].

Given the association with multiple comorbidities and the need for multiple and complex drug therapeutic regimens, we recommend to address patients with resistant hypertension to a hypertension specialist or, if necessary, to a hypertension specialist center. A dedicated tertiary BP clinic can be useful to perform the necessary diagnostic steps, optimize the multidrug treatment regimen, reduce the likelihood of drug-related adverse effects and increase adherence to treatment. Patients should receive a dedicated program of follow-up.

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True-resistant hypertension

Recommendations and statements	CoR	LoE
It is recommended that hypertension is defined as true resistant hypertension when SBP is ≥ 140mmHg or DBP is ≥ 90 mmHg provided that: -maximum recommended and tolerated doses of a three-drug combination comprising a RAS blocker (either an ACEi or an ARB), a CCB and a Thiazide/Thiazide-like diuretic were used -adequate BP control has been confirmed by ABPM[a] -various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension have been excluded.	I	C
If confirmation of true resistant hypertension by ABPM is not feasible, HBPM may be used.		
It is recommended to manage resistant hypertension as a high-risk condition, because it is frequently associated with HMOD and increased CV risk.	I	B
In patients with resistant hypertension, BP should be reduced below 140/90 mmHg and below 130/80 mmHg, if well tolerated.	I	B
In resistant hypertension, it is recommended to reinforce lifestyle measures.	I	B
Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or BB or Alpha-1 blockers or Centrally acting agents (clonidine), or amiloride (if available).	II	B
Thiazide/Thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥ 30 ml/min/1.73 m^2.	I	B
Loop diuretics may be considered in patients with an estimated eGFR < 45 ml/min/1.73 m^2 and should be used if eGFR falls below 30 ml/min/1.73 m^2.	I	B
Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 ml/min/1.73 m^2.	II	B
RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2	II	B
Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ABPM and assessment of HMOD, particularly kidney function and serum potassium levels. Regular use of HBPM and monitoring of drug adherence are desirable.	I	C

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13. DEVICE-BASED TREATMENT OF HYPERTENSION

13.1 Renal denervation (RDN)

Increased activity of the SNS (Fig. 3) is one of the important factors in the pathophysiology of hypertension, especially in obesity, OSA and CKD [19]. Efferent sympathetic nerves to the kidneys increase renin release via beta$_1$-adrenergic receptor activation at the level of the juxta-glomerular cells, decrease renal perfusion and GFR, increase tubular reabsorption of sodium and induce a rightward shift of the BP-natriuresis curve. Conversely, increased afferent sensory nerve signaling to the central nervous system in response to kidney ischemia, injury or inflammatory, fibrotic processes and other alterations of the tissue environment leads to reflex sympathetic activation, with peripheral vasoconstriction, increased BP and aggravation of HMOD [768–771]. The rationale of RDN is to modulate the overactive signaling between the kidneys and the central SNS, which may be at least partly responsible for the sympathetic hyperactivity of resistant hypertension [723]. The introduction of endovascular catheter-based RDN devices has allowed to obtain RDN in a minimally invasive fashion [772]. RDN has been shown to reduce whole-body and renal sympathetic activity in humans [773–775], although not in all studies [752]. However, a recent meta-analysis of available studies has reported a limited relationship between the RDN-dependent reduction of sympathetic activity as measured by microneurography and the BP reduction [776]. This is compatible with the possibility that more than just a neural factor is responsible for the RDN-dependent therapeutic effects.

13.1.1 Clinical Evidence of the BP-lowering effect of RDN

Proof-of-concept human studies applying radiofrequency energy, high focused ultrasound energy and perivascular injection of alcohol found substantial decreases in BP in patients with uncontrolled, treatment-resistant hypertension [772,777,778]. However, when in 2014, the sham-controlled SYMPLICITY-3 HTN trial failed to show a significant BP reduction after RDN compared to sham treatment, clinical investigations of RDN almost stopped [779]. Lack of significant BP reduction in the SYMPLICITY-3-HTN study was later attributed to energy delivery at the proximal (instead of distal) location of the innervated renal artery, incomplete noncircumferential denervation, high rates of drug changes during the run-in and treatment phase and lack of adherence to drug treatment [780]. As a result, clinical consensus conferences in Europe and the US recommended to (i) use optimized techniques, ensuring complete circumferential ablation of renal nerves, (ii) apply strict criteria for patients inclusion and during the run-in phase and (iii) objectively measure medication adherence individually [781].

To categorize the scientific quality of published randomized controlled trials (RCTs), the following quality criteria were applied: (i) sham-controlled, multicenter trial, (ii) adequate blinding of patients and outcome assessors, (iii) ambulatory BP change as the primary outcome, (iv) study completion as planned and (v) use of advanced RDN systems [777]. Of the 18 RCTs already published or ongoing, 9 RCTs fulfilled all these criteria [777]. The REQUIRE trial, which included patients with uncontrolled resistant hypertension, failed to fulfill all quality criteria because of incomplete medication blinding of treating physicians and coordinators combined with a lack of objective measurements of medication adherence [782]. Two RCTs with perivascular injection of alcohol are not yet published [777]. Thus, at present, an RDN should be based on the procedures that applied RF energy to main, accessory, and distal arteries or high focused ultrasound energy to main and accessory arteries.

13.1.2 Off-medications studies

Patients with uncontrolled office and 24-h ABPM in the absence of antihypertensive drugs, with suitable renal artery anatomy, and eGFR $\geq$40 to 45 ml/min/1.73 m^2 were investigated in four of the nine RCTs. In the SPYRAL HTN-Off MED Proof-of-Concept Study, radiofrequency-based RDN decreased 24 h SBP (primary objective) by 5.0 mmHg ($P = 0.041$) compared with the sham procedure [783]. In the SPYRAL HTN-Off Med Pivotal Study comprising 331 patients off any antihypertensive medication, 24 h SBP reduction was in favor of radiofrequency-based RDN [group difference −3.9 mmHg ($P < 0.001$)] [750]. In the RADIANCE HTN SOLO trial, ultrasound RDN decreased daytime SBP by 6.3 mmHg ($P = 0.001$) versus a sham procedure [749]. In the pivotal RADIANCE-II trial randomizing 224 patients with uncontrolled BP in the absence of antihypertensive drugs, the daytime SBP reduction (primary objective) was greater with ultrasound RDN than with the sham intervention [between-group difference of 6.3 mmHg ($P < 0.001$)] [748]. Thus, multiple evidence exists that RDN using radiofrequency and ultrasound energy reduces BP significantly in hypertensive patients in the absence of antihypertensive medication.

13.1.3 On-medications studies

In the SPYRAL HTN-ON Med study in 80 patients with uncontrolled office BP and 24 h ABPM on one to three antihypertensive drugs, radiofrequency-RDN was associated with a greater BP reduction than sham procedure at 6 months (between-group difference of −7.0 mmHg, $P = 0.0059$), while antihypertensive therapy was unchanged [784]. In the SPYRAL-HTN ON Med Extension trial [785], including 337 patients with uncontrolled office BP and 24 h ABPM on one to three antihypertensive drugs (including those of the SPYRAL HTN-ON Med study), no significant 24 h ABPM reduction (primary objective) was observed, compared to the sham group. However, the medication number increased more in the sham than RDN group and changes in office BP (key secondary endpoint) were significantly greater following RDN versus sham (difference −4.9 mmHg, $P = 0\,0015$). In the RADIANCE HTN-TRIO Study, 136 patients with uncontrolled hypertension resistant to more than three antihypertensive medications were switched to a single pill, triple antihypertensive drug

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combination during 4 weeks run-in and prior to the RDN intervention. Ultrasound RDN reduced daytime SBP to a greater extent than the sham procedure at 2 months (between-group difference of −4.5 mmHg, $P = 0.022$) [738]. The triple therapy remained unchanged and adherence to treatment was stable (about 80% in both groups).

Published meta-analyses including RCTs of high, medium and even low scientific quality showed variable results, albeit data from RCTs showed consistent 24 h BP reduction ranging from 3.9 to 7.0 mmHg SBP and from −3.7 to −6.9 mmHg DBP after RDN. Remaining gaps in knowledge concern a more precise definition of the prevailing magnitude of BP reduction after RDN, an issue that might be fruitfully addressed by individual patient-level meta-analysis [772,777], although pooled analysis of trials conducted by ultrasound RDN showed a rather consistent BP-lowering effect [786]. Head-to-head comparisons of RDN to properly conducted intensified pharmacotherapy studies are also needed. The Prague-15 study, reporting similar effects between RDN and optimized pharmacotherapy mainly by adding spironolactone, was inconclusive, since after 6 months, 25% of the RDN group were also prescribed spironolactone, and in the pharmacotherapy group, only 61% were still on spironolactone [787]. Finally, no solid predictor of future BP reduction after RDN has yet been identified, with the exception of pretreatment BP [772,777]. The latter finding is not specific for RDN, as it has been almost invariably observed in virtually all trials on the BP-lowering effect of antihypertensive drugs. Nevertheless, the lack of a diagnostic measure that predicts the BP response to a device-based treatment such as RDN represents a relevant limitation.

13.1.4 Safety

The main concerns regarding the safety of RDN is potential damage to the arterial endothelium, intima and media by the applied energy, renal artery dissection, contrast-induced nephropathy in the short-term, occurrence of de-novo renal artery stenosis and eGFR loss in the long-term [772,777]. No safety signals emerged in any of the sham-controlled RCTs in which there were similar rates of major adverse events in the RDN and control groups [738,748–750,780,781,783–785,788]. This conclusion is limited to the studied population with an eGFR >40 ml/min/1.73 m^2. A meta-analysis of 50 trials comprising 10 249 patient-years of data estimated a 0.20 annual incidence of renal artery stenting following RDN, which is similar to the reported natural incidence of renal artery stenosis in hypertension [787,789]. RCTs systematically using noninvasive renal artery imaging 1 year after the procedure confirmed vascular safety of RDN. Likewise, a meta-analysis of 48 studies with 2381 patients showed no significant change in eGFR after a follow-up of 9.1 months [790]. No acute kidney injury or time-dependent decrease in kidney function was reported. In the Global Simplicity Registry, the observed eGFR decrease being within the expected time-dependent eGFR decline, with the limitation that so far, the follow-up is limited to 3 years [751]. Since with current-generation RDN devices, femoral arterial access is needed, access-site vascular complications, e.g. hematoma, pseudoaneurysm, fistula, bleeding among others may occur [772,777].

13.1.5 Durability

Long-term data are available from sham-controlled RCTs, although unblinding of both patients and physicians generally took place after 6 and 12 months, respectively, and antihypertensive medications were added, changed or stopped by primary care physicians. Based on the analysis of patients enrolled in the Global Simplicity Registry ($n = 2652$ patients) [791], the BP decrease documented after RDN appears to be clearly maintained up to 36 months after RDN. Similarly, in the RADIANCE HTN-SOLO FU, the RDN-related BP reduction was found to be maintained over a FU of 3 years although, because of the high rate of cross-over to RDN, no formal comparison with the sham group was provided [792,793]. Similar limitations involve the 3-year durability of the BP effects of RDN reported by the SPYRAL HTN-ON MED trial [794] as well as the long-term increase of the antihypertensive effect of RDN reported by the SYMPLICITY HTN-3 trial [795,796], because of the different magnitude of the long-term BP differences, depending on inclusion or exclusion of patients who crossed over to RDN in the comparison group [797]. It should be mentioned that the durability of the BP reduction associated with RDN argues against a functional reinnervation of the kidneys in hypertensive patients after RDN, even though nerve regrowth has been reported in experimental animal models. However, the functionality of regrown nerves is uncertain in these models and long-term human data yet need to be explored. Notably, in patients after renal transplantation no clinically meaningful reinnervation was observed in long-term studies.

13.1.6 Application

Endovascular RDN with radiofrequency energy or high focused ultrasound energy represents a treatment option, that is additive or alternative to increasing medication in patients with uncontrolled resistant hypertension confirmed by ABPM after excluding secondary causes of hypertension [772,777]. Patients who are repeatedly nonadherent (if this reflects the unwillingness of the patient to take drugs) or intolerant to multiple antihypertensive drugs, may be considered for RDN after information about the potential lack of effect and benefits, and also the risks associated with the procedure [772,777]. These patients may be on fewer than three drugs at the time of their selection for RDN. To date, no prospective multicenter, blinded, randomized, prospective outcome trial exists for RDN. Unfortunately, this also applies to all drug treatment strategies for resistant hypertension. This means that whether, and to what extent, BP reduction in resistant hypertensive patients translates into CV protection is unknown, and the value of BP reduction as a protective marker is necessarily extrapolated from the large body of evidence obtained by RCTs in nonresistant hypertensive individuals. Based on the outcome reductions calculated for SBP reductions in a large meta-analysis of RCTs [80,798] the Global Simplicity Registry concluded that RDN might reduce the relative risk of stroke by 43%, while the absolute risk of major adverse CV events might decline from 11.7% in the control group to 8.6% in the RDN group [798]. Likewise, in 3077 patients of the Registry, the

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conclusion was reached that a 10% increase of time at BP target (120–140 mmHg SBP) during the first 6 months after RDN might reduce by 15% the risk of major CV events in the following 6–36-month period [190]. As mentioned above, these conclusions suffer from the limitations that the BP reduction–outcome relationship reported in the meta-analysis did not concern patients with resistant hypertension [80].

RDN should be performed only in experienced and specialized centers that have established a multidisciplinary team with a structured pathway for evaluating hypertensive patients [772,777]. Understanding the patients' perspective, exploring their preference and expectation is crucial prior to RDN. Benefits and risks of RDN need to be addressed in a shared-decision making process [772,777]. In this regard, roughly 1/3 of hypertensive patients were prone to prefer RDN instead of pharmacotherapy to have the elevated BP controlled [799]. This applied particularly to younger patients, male patients, those with experience of side effects, and those who admitted to be nonadherent [799].

Use of renal denervation

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients an eGFR >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2.	II	B
Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient's information.	I	C
Renal denervation should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

13.2 Carotid baroreceptor stimulation

Stretch-sensitive baroreceptors located in the carotid sinus and the aortic arch are involved in short-term and long-term BP regulation. Carotid baroreceptor external stimulation via a pacemaker-like device or baroreflex neuromodulation by endovascular deployment of a self-expanding nitinol implant in the carotid artery has been investigated for treatment of resistant hypertension [800]. Carotid baroreceptor stimulation was associated with a reduction of sympathetic nerve activity in studies on hypertensive patients [801,802], and a sympathoinhibitory effect was also shown when the stimulation was applied to HF patients [802]. The first-generation bilateral electrical stimulation device (Rheos, CVRx) was tested in a double-blind, randomized, sham-controlled pivotal trial, which included 265 patients with resistant hypertension [803]. At 6 months, the office BP fall was significantly larger in the treatment group compared with the sham group. However, the study failed to meet two of the five co-primary endpoints, and safety was not established. Therefore, the Rheos device did not receive approval from the Food and Drug Administration for use in patients with resistant hypertension [803]. A second-generation unilateral stimulation device has been developed to reduce the complexity, complications and costs of the procedure (Barostim). However, no RCT is currently available with this new device in patients with resistant hypertension. The endovascular baroreflex amplification therapy is achieved via implantation of a dedicated stent, which aims at passively increasing wall stretch by increasing the vessel-effective radius while preserving pulsatility [804]. In a small, noncontrolled, open-label, first-in-human CALM-FIM study, 30 patients underwent implantation of the MobiusHD system (Vascular Dynamics). At 6 months, there were significant reductions in both office and ambulatory BP compared with baseline, which appeared to be maintained through 36 months [805]. Several RCTs investigating this approach are ongoing.

13.3. Other device-based treatments

The creation of a fixed-diameter iliac arteriovenous anastomosis with a catheter-based device (ROX coupler; ROX Medical) was investigated in resistant hypertension to lower peripheral vascular resistance [800]. The creation of such a shunt significantly decreased BP in the prospective, open-label, randomized, controlled ROX CONTROL HTN trial [806]. However,

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33% of all patients undergoing implantation of the arteriovenous coupler developed late ipsilateral venous stenosis requiring treatment. Because of a potential HF risk following treatment with the coupler, the development of this device has been stopped.

The Moderato system (BackBeat Cardiac Neuromodulation Therapy, Orchestra BioMed) is a dual-chamber, rate-responsive, implantable pulse generator that variably shortens and lengthens the atrioventricular interval [800]. By shortening the atrioventricular coupling interval, left ventricular filling can be reduced, and BP falls. The device intermittently and asymmetrically introduces short sequences of one to three beats of longer atrioventricular delay with the aim of preventing a compensatory baroreflex-mediated activation of the SNS [807]. Following the initial proof-of-concept study (MODERATO I) [807], which included 35 patients with uncontrolled hypertension despite ≥2 antihypertensive medications, the results of the MODERATO II study [808], a prospective, multicenter, randomized, double-blind study were reported. In this trial, 68 patients with uncontrolled hypertension despite treatment with at least one antihypertensive medication and an indication for the implantation or replacement of a dual-chamber pacemaker underwent the Moderato device implantation. In the treatment group, 24 h SBP immediately dropped after the device activation, and the BP-lowering effect was maintained through 6 months of FU. Although the primary efficacy endpoint (difference of 24 h SBP change between groups) was met, and treatment appeared to be safe through 6 months, the long-term consequences of cardiac neuromodulation therapy need to be investigated in larger trials. Device-based therapies such as carotid baroreceptor stimulation, arteriovenous anastomoses and cardiac neuromodulation therapy (via a dedicated pacemaker) are not recommended for antihypertensive treatment.

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14. SPECIFIC HYPERTENSION PHENOTYPES

14.1 Sustained hypertension and true normotension

Use of out-of-office BP measurements by HBPM and/or ABPM allows identifying BP phenotypes that were unknown when BP measurements were limited to office BP. One phenotype is termed sustained hypertension and consists of an elevation of both office and out-of-office BP. Another is true normotension, which is characterized by office and out-of-office BP normality. These phenotypes may refer not only to untreated but also to treated individuals, where they indicate extended office and out-of-office BP control or no control of all these BP values. Available studies have defined out-office BP normality or elevation by either HBPM or ABPM and, at present, only the PAMELA study (a study based on a population sample from northern Italy) provides office BP, ABPM and HBPM in each individual, although with a restricted protocol for home BP measurements [142]. This study allowed defining the sustained hypertension and true normotension phenotypes based on all three BP values and found that, compared to true normotension, sustained hypertension is associated with a clearcut increase in the prevalence and incidence of CV mortality. Outcome differences have also been reported between patients with one versus two or three elevated BP values [157], suggesting a clinical relevance for even more complex BP-based phenotypes.

14.2 White-coat hypertension

WCH refers to the untreated condition in which BP is elevated in the office but is normal when measured by ABPM, HBPM or both [4]. The term white-coat effect is used to describe the difference between an elevated office BP and a lower home or ambulatory BP, which is believed to mainly reflect the pressor response to an alerting reaction elicited by office BP measurements by a physician or a nurse [809,810]. However, other factors are probably also involved, as shown by the poor correlation between the office and out-of-office BP difference and the white-coat effect measured directly with beat-to-beat BP recording [811,812]. Although the prevalence varies between studies, WCH can account for about 30% of people attending hypertension clinics [62] and up to 30–40% among patients with an elevated office BP. It is more common with increasing age (>50% in the very old patients), in women and in nonsmokers. Its prevalence is lower when office BP is based on repeated measurements or when the attending physician or nurse are not involved in the BP measurement [95]. A significant white-coat effect can be seen at all grades of hypertension (including resistant hypertension), while the prevalence of WCH is the greatest in grade 1 hypertension.

There has been much debate in the literature about whether WCH should be considered an innocent condition. HMOD is less prevalent in WCH than in sustained hypertension, and several studies have shown that this is the case also for the risk of CV events [62]. However, compared with true normotensives, patients with WCH have increased adrenergic activity [813], a greater prevalence of metabolic risk factors and a more frequent asymptomatic HMOD [814]. In the PAMELA population, cardiac and renal asymptomatic HMOD was detected in about one of three patients with WCH compared to one of ten individuals with normal office and out-of-office BP [216]. Furthermore, compared to normotensive individuals, white-coat hypertensive individuals have shown a greater long-term risk of new-onset diabetes, progression to sustained hypertension and CV mortality [216,815–819]. The increased CV risk and mortality have been reported with (i) diagnostic use of both HBPM and ABPM, (ii) in the absence of HMOD at baseline and (iii) in ISH, older patients and other conditions [820–823]. In addition to the above-mentioned factors (dysmetabolic risk profile, more common HMOD and increased risk of new-onset diabetes), this can probably also be accounted for by a greater prevalence of nocturnal hypertension and by 24 h BP values that, albeit normal by definition, are a few mmHg higher than in nonwhite-coat hypertensive individuals [819]. Due to its limited reproducibility, the diagnosis of WCH should be confirmed by repeated office and out-of-office BP measurements.

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Ideally, out-of-office BP measurements should include both ABPM and HBPM because the two values can give discrepant results, i.e. one value can be normal and the other elevated or vice versa, and the CV risk appears to be lower (and close to sustained normotension) in white-coat hypertensive individuals in whom ABPM and HBPM are both normal [819]. Thorough assessment of CV risk factors and HMOD are recommended. Treatment should consider lifestyle changes to reduce CV risk and a closer FU compared with true normotensive individuals. Antihypertensive drug treatment effectively lowers office BP, while the effect on out-of-office BP is small and variable [824,825]. Whether or not patients with WCH should receive antihypertensive drugs is still unresolved, because, although WCH patients have been a considerable proportion of virtually all RCTs proving the benefits of antihypertensive treatment [826], no specific outcome-based trial has been performed. Drug treatment may be considered in patients with HMOD and a high CV risk.

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White-coat hypertension (WCH)

Recommendations and statements	CoR	LoE
Out-of-office BP measurement by ABPM and/or HBPM should be done when WCH is suspected, particularly in people with grade 1 hypertension.	I	B
In patients with WCH, assessment of CV risk factors and HMOD is recommended.	I	B
Out-of-office BP measurements should be done by ABPM and/or HBPM and repeated during follow up to timely identify sustained hypertension or new HMOD.	I	B
In patients with WCH, lifestyle interventions to reduce CV risk and close follow are recommended.	I	B
Whether BP lowering drug treatment should be used is still unresolved, but it can be considered in patients with HMOD and high CV risk.	IIb	C

14.3 Masked hypertension

MH refers to untreated patients in whom the BP is normal in the office but elevated when measured by HBPM or ABPM [827]. About 10–20% of patients attending hypertension clinics have MH [62], with out-of-clinic BP measured either with ABPM or HBPM. A noticeable prevalence has been found in population-based studies, especially in Asian and African American patients [827,828]. The prevalence of MH also varies when different ABPM periods (daytime, 24 h or night-time) are used to define the out-of-office hypertension status. The optimal approach for the detection of MH has not been established. Screening all individuals with nonelevated office BP for MH is impractical. An office BP in the high-normal BP range is associated with a higher likelihood of MH. The prevalence is greater in younger people, men, smokers and those with higher levels of physical activity, alcohol consumption, anxiety and job stress [829,830]. Obesity, diabetes, low HDL-cholesterol, CKD, family history of hypertension, are also associated with an increased prevalence of MH [829]. An exaggerated BP response to exercise and to the orthostatic posture have also been found to be predictors of MH [831]. A CV risk-based approach, limiting the use of out-of-clinic BP measurement to those individuals with multiple risk factors for MH, has been proposed [827]. MH has been associated with HMOD such as impaired kidney function, LVH, carotid intima–media thickness and large artery stiffness [820,831–833]. People with MH have an increased risk of developing metabolic abnormalities and diabetes as well as sustained hypertension [817,834] and have increased sympathetic activity [835,836]. Meta-analyses and recent studies have shown that the risk of CV events is substantially greater in MH compared with normotension, and intermediate risk or even close to the risk of sustained hypertension [827,837–839]. Both ABPM-based and HBPM-based MH has been found to be independently associated with CV events and mortality [827,837,838]. An increase in risk of CV and kidney events has also been observed in diabetic patients with MH, especially when the BP elevation occurs during the night [840]. A systematic review and meta-analysis has shown a slight to fair reproducibility of MH which was better for ABPM than for HBPM [841], while a limited reproducibility has been reported in other studies [62]. Thus, the diagnosis of MH requires confirmation with at least a second set of office and out-of-office BP measurements. No RCT has ever been performed on MH, which means that the effects of antihypertensive treatment are unknown. Given the adverse prognostic importance of out-of-office BP elevations, it seems appropriate to recommend that in patients with confirmed MH, stringent lifestyle modifications and a closer follow-up are implemented. Antihypertensive drug treatment may be considered if CV risk is particularly elevated, and with HMOD.

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Masked hypertension (MH)

Recommendations and statements	CoR	LoE
Out-of-office BP measurement by ABPM and/or HBPM should be done in people with high normal blood pressure to identify MH.	I	B
In patients with MH, lifestyle interventions and close follow up are recommended to reduce CV risk and to timely identify sustained hypertension and new HMOD.	I	C
Whether BP lowering drug treatment should be used in MH is still unresolved, but it can be considered in patients with HMOD and high CV risk.	IIb	C

14.4 White-coat uncontrolled hypertension (WUCH) and masked uncontrolled hypertension (MUCH)

Originally referred to untreated patients, WCH and MH now also include patients on antihypertensive treatment, defined as (i) WUCH (white-coat uncontrolled hypertension), i.e. BP control by treatment during the 24 h but not in the office and (ii) MUCH (masked uncontrolled hypertension), i.e. BP control by treatment in the office but not outside the office. Although patients with WUCH have shown greater large artery stiffness than those with controlled BP [842], several studies have shown that their CV risk does not differ significantly from that of the treated population in which both office and out-of-office BP achieved control. Consistent results were provided by two large studies in which WUCH was assessed with HBPM [132,843]. In the IDACO study, analyses were stratified by the presence or absence of antihypertensive therapy and found that WCH was associated with an increased CV risk only in untreated patients [132]. Data provided by large meta-analyses have confirmed that patients with WUCH do not have an increased CV risk compared to those in whom both office and out-of-office BP are controlled [816]. Patients taking antihypertensive medication have been found to have a higher prevalence of MUCH compared with untreated individuals. In the large IDACO database, the prevalence of MH (ABPM elevation) was about 1.7 times higher for individuals taking versus those not taking antihypertensive medications (31.9 versus 19.2%). Similar results have been obtained in African Americans by the Jackson Heart Study [844], while in participants with controlled office BP of the SPRINT study, MUCH was present in 62 and 56% in the intensive and standard groups, respectively [845]. MUCH has been found to be associated with a worse metabolic profile [846], HMOD [847] and unfavorable clinical outcomes, regardless of the out-of-office BP monitoring technique [837,838]. In a meta-analysis of observational studies, MUCH patients had rates of CV events higher than those in patients with both office and out-of-office BP control, and similar to those of patients with treated uncontrolled office and out-of-office hypertension [848], regardless whether ABPM or HBPM was used for MUCH identification. A limitation of all available studies is that MUCH and WUCH identification was based on a single set of office and out-of-office BP measurements, because post hoc analyses of clinical trials have shown that both phenotypes are extremely inconsistent, irrespective of the type of antihypertensive treatment [172,849]. In the analysis of the ELSA data, only about 5% of the WUCH or MUCH patients exhibited the same condition throughout the 4 years of the trial [172]. Thus, occasional rather than consistent phenotypes may have been addressed in outcome analyses. As observed for MH, MUCH is more frequent with smoking habits, alcohol consumption, overweight, BP response to physical activity, psychological stress and some comorbidities [829,850]. The role of medication nonadherence is equivocal [851]. There is evidence that patients with MUCH have higher level of sympathetic activity assessed in daily life conditions than those in whom both office and out-of-office BPs are controlled by treatment [850,852]. This may be responsible at least in part for the higher CV risk found in MUCH. It is recommended to identify WUCH and MUCH with repeated office and out-of-office BP measurements. Considering the limitations of the available evidence, it seems wise to advise treatment uptitration in both WUCH and MUCH if treatment is well tolerated, so as not to keep the patient above the recommended target BP values generally recommended for antihypertensive treatment, without solid supporting evidence.

White-coat uncontrolled hypertension (WUCH) and masked uncontrolled hypertension (MUCH)

Recommendations and statements	CoR	LoE
The recommendations for WCH and MH apply to WUCH and MUCH, respectively, except that WUCH and MUCH refer to treated people.	I	C
Considering the limitations of available evidence on WUCH and MUCH, uptitration of drug treatment can be done in both conditions to ideally control both BP phenotypes if well tolerated.	IIb	C

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14.5 Isolated systolic hypertension of the young

ISHY, defined as an SBP ≥140 mmHg and a DBP <90 mmHg, is present not only in older persons but also in young and very young individuals (ISHY), more commonly in male individuals [121]. ISHY may be present also in children and adolescents and is often associated with overweight and obesity. There is debate in the literature about the clinical significance of ISHY, i.e. whether this condition associates with worse outcomes and needs antihypertensive treatment. The reason is due to the different pathogenetic backgrounds of this BP phenotype. Mechanistic research has documented that in these people, an isolated SBP elevation may be associated with or caused by multiple factors that can operate in isolation or interact. Increased cardiac output, heart rate and stroke volume are the predominant hemodynamic abnormalities in ISHY [121,853] and may explain why peripheral pulse pressure is higher and ISHY is more common in athletes than sedentary people [854]. However, some studies showed that about 20% of ISHY patients had a normal stroke volume and an increased pulse wave velocity, indicating that ISHY may be associated with premature aortic stiffening [853]. In the NHANES [855] as well as in other studies [121], obesity, male sex, high salt intake and smoking, were associated with higher odds of ISHY. In contrast, some investigations have identified subgroups (more commonly tall men, nonsmokers and people active in sports), in which ISHY was associated with no risk factors, and there was coexistence of pulse pressure amplification with a normal central BP. This low-risk condition has been termed spurious systolic hypertension [856,857]. In a large multiethnic population, individuals with ISHY had central SBP and pulse wave velocity values lower than in individuals with isolated diastolic or systolic–diastolic hypertension and similar to those of individuals with a high-normal BP [858]. These conflicting data suggest that ISHY is a very heterogeneous condition that may include individuals with very different genetic and pathophysiological backgrounds as well as clinical characteristics. Central BP measurement can help to identify ISHY patients at lower risk [121,856,857] and a good prognosis, as shown in longitudinal studies with long-term FU [859,860]. However, different results were reported in two more recent studies in which ISHY has been associated with increased CV risk, limited to men in one study [861] and to women in two other reports [861,862]. It should be noted that between-sex comparison is difficult in ISHY, because all studies have shown a clear predominance of this phenotype and a higher event rate in men. Clinical evaluation of an individual with ISHY should consider the possible presence of WCH because one of the strongest determinants of high pulse pressure in this condition is a pronounced white-coat effect [863]. This means that all individuals with ISHY should be assessed with out-of-office BP measurement. If ISHY is confirmed, assessment of central BP, other central hemodynamic parameters and arterial distensibility may provide additional useful information, although with the limitation that central BP lacks documented cut-off values that differentiate normal from high values (Section 4.6). Other problems are the current limitation of available prognostic data and the uncertain prognostic superiority of central versus brachial BP in the younger population. Young individuals with ISHY should receive recommendations on lifestyle modifications, particularly cessation of smoking, sodium (NaCl) restriction and hypocaloric diet in the presence of overweight [121]. In addition, they require a close FU because those with high central BP are prone to develop sustained systolic–diastolic hypertension over time [864]. In individuals who present with high out-of-office BP, high central BP and other risk factors, pharmacological treatment should be considered.

Isolated systolic hypertension in the young (ISHY)

Recommendations and statements	CoR	LoE
Due to the frequent presence of a pronounced white-coat effect, out-of-office BP measurement is recommended.	I	C
Central BP measurement can be considered to identify ISHY individuals at low CV risk to detect spurious hypertension, if available.	II	C
Close follow-up and lifestyle interventions are recommended.	I	C
In individuals with high out-of-office BP or high central BP, particularly with other CV risk factors or HMOD, BP lowering drug treatment can be considered.	II	C

14.6 Isolated systolic hypertension in older persons

In older people, several functional and structural abnormalities including endothelial dysfunction, vascular remodeling and fibrosis cause an increase in stiffness of large elastic arteries. The increased size of the forward pressure wave together with the earlier arterial wave reflection from the peripheral to the large arteries lead to an increase of SBP and pulse pressure [865]. As a consequence, aging is accompanied by a steady increase in SBP while a plateau of DBP occurs at the

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age of 50–60 years, followed by a decrease [866,867]. The increased arterial load due to the high SBP promotes vascular atherosclerosis and LVH, ultimately leading to CAD, cerebrovascular disease and HF. ISH, defined as SBP ≥140 mmHg and DBP <90 mmHg, becomes the most common form of hypertension after 50 years of age and is present in most patients with hypertension who are >70 years of age [868]. ISH is also more common in women and overweight people. A large body of evidence has shown that SBP has a greater impact on outcomes than DBP after 50 years of age [869,870] and that ISH, either assessed with office BP [865,871] or by ABPM [872], is associated with a high risk of CV outcomes and mortality. The risk of CV outcomes and mortality is increased also in patients with grade I ISH, i.e. with SBP values between 140 and 159 mmHg [873] and is greater in the ISH subgroup with orthostatic hypertension [874].

Diagnosis of ISH is particularly challenging in old individuals because of the high BP variability that characterizes this condition and the frequent occurrence of a pronounced white-coat effect at office BP measurement [865]. Thus, BP assessment with repeated office visits or out-of-office BP measurement is recommended. The use of central BP measurement may also be of help because it allows the identification of those ISH individuals in whom the aortic SBP elevation is much less pronounced than that seen with peripheral BP measurement. RCTs have demonstrated the benefit of treating ISH [498,637,875] even in the oldest segment of the population [501]. An individual-patient meta-analysis of older patients with ISH showed that active treatment reduced all-cause mortality by 13%, CV mortality by 18%, and all CV outcomes by 26% [876]. This meta-analysis also showed that DBP was inversely associated with total mortality, highlighting the role of pulse pressure as a risk factor. The benefit of treatment was larger in men, in patients aged ≥70 years and in those with previous CV complications. The above studies also showed that early versus late initiation of treatment after the detection of ISH led to a persistently greater CV protection at all ages. Based on the data in aggregate, CCBs and Thiazide-like diuretics emerged as the drugs of choice for the management of ISH, whereas ACEis/ARBs showed less efficacy, suggesting that they should be used as first-line agents when there are compelling indications such as HF, coronary artery disease, CKD, metabolic syndrome and diabetes [865,871]. Because the rate of BP control with monotherapy is low in patients with ISH, the general recommendation to start with dual combination therapy applies also in older patients with ISH, if they are not frail.

Target SBP and DBP values in older patients with hypertension have been an issue of intense debate. In dedicated RCTs, documenting the protective effect of antihypertensive treatment in ISH, on-treatment SBP remained in the 140–150 mmHg range [144,497,498]. This has been confirmed by a recent RCT meta-analysis [143], which supports the primary recommendation to have, as target SBP, values between 150 and 140 mmHg. However, in a large number of trials on older patients in whom a treatment that reduced CV outcomes by lowering SBP below 140 mmHg, the number of patients with ISH or a prevalent SBP elevation was considerable [499]. Furthermore, in a recent meta-analysis that included 23 RCTs in each of which a mean baseline SBP was ≥140 mmHg and mean baseline DBP < 90 mmHg, antihypertensive treatment that lowered SBP <140 mmHg was associated with asignificant outcome reduction [501]. This justifies the additional recommendation to try to reduce SBP in the 140–130 mmHg range, provided that this is well tolerated and DBP is not too low (see below). SBP values <140 mmHg have been found to be safe in the ISH patients of the VALISH trial [877], while in dedicated ISH trials, little information has been provided on the relationship between on-treatment DBP and outcomes.

Nevertheless, in ISH patients, a marked decrease in DBP should be avoided, because the risk reduction obtained by lowering SBP may be jeopardized by the increased risk arising from an excessive decrease of DBP, as recently suggested by the SPRINT study [878]. Intensified BP treatment may be particularly harmful in patients with severe stenosis of large arteries. To prevent organ hypoperfusion, DBP should not be reduced below 70 mmHg by drug treatment, although compliance with this recommendation is often difficult as a large number of ISH patients already have a DBP <70 mmHg [879], and a considerable number exhibits values within the 70–80 mmHg range. In population studies largely based on untreated patients, a very low DBP in ISH patients has been associated with a very high prevalence of CVD [879], although the causative factor may not only be poor vital organ perfusion but also a marked arterial stiffness, of which the very high pulse pressure value is a reflection. Treating ISH with low DBP remains a challenging task because of the difficulty to decrease SBP without reducing DBP at the same time, and to apply rigid safety diastolic boundaries, which may limit the achievement of SBP control, with its proven protective effect. Physicians should thus aim at achieving a balance between the best achievable SBP reduction with DBP values that do not raise suspicion of reduced organ perfusion and affect treatment tolerability. In older patients, ISH is a condition in which antihypertensive treatment individualization, based on patient characteristics, risk profile, and level of both SBP and DBP, is particularly important. However, aiming at SBP control remains the primary goal to improve outcome and if well tolerated, this goal should be pursued also in patients with a low DBP. In the SHEP trial in patients with ISH, a treatment-induced reduction of SBP was accompanied by a clear reduction of major CV events, despite a DBP reduction that brought its average value to 68 mmHg [497].

14.7 Isolated diastolic hypertension

Isolated diastolic hypertension (IDH) is a hypertension phenotype characterized by an SBP <140 mmHg and a DBP >90 mmHg. In the general adult population, IDH prevalence has been reported to be between 2.5 and 7.8% [880,881], with a peak between 30 and 39 years, a decrease in the fifth and sixth decades (<15%) and almost no case above 70 years of age [882]. IDH has a greater prevalence in men than in women [880]. Some reports have shown that awareness and treatment of hypertension are very low among IDH patients [880,883]. In the PEACE study, only 10.3% of untreated patients knew that they had IDH, and 86.1% of patients with IDH did not receive treatment [880]. IDH is more frequent among people with

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overweight and obesity, particularly central obesity, and is linked with other components of the metabolic syndrome [880]. When compared with other hypertension phenotypes, IDH patients are generally younger, of male sex, consume more alcohol and tobacco, and are more frequently diabetic patients [880,884]. Some longitudinal studies have shown that IDH patients have higher odds than normotensive individuals of developing systodiastolic hypertension [885,886], and large longitudinal studies on Asian, American or European people have shown that over long follow-ups (up to 31 years), IDH is associated with a greater CV risk compared with normotensive individuals [860,862,887–889], although with some inconsistent findings about sex differences (greater risk in men), differences between IDH, ISH or systodiastolic hypertension or increase in risk when IDH is diagnosed by the lower ACC/AHA criterion, i.e. by SBP <130 mmHg and DBP ≥80 mmHg [885,887–891]. Longitudinal studies have almost invariably reported that the IDH-related risk is age-dependent, i.e. it is seen in patients aged <60 or even <50 years but not above these ages. This has been observed by a cohort-based study on 107 599 patients, which showed that while the relationship between CV events and SBP was age-independent, the relationship between CV events and DBP was significant only in patients <50 years of age [892]. Confirmation is provided by a meta-analysis of 15 cohort studies including 489 814 participants [893] as well as by the results of the IDACO study in which diagnosis of IDH was made by ABPM [894]. In conclusion, available data suggest that IDH is a CV risk factor mainly among younger adults. Unfortunately, this does not satisfactorily clarify whether younger adults with IDH need antihypertensive treatment because, although in early antihypertensive treatment trials, enrolment of hypertensive patients was mainly based on DBP levels, treatment reduced both DBP and SBP, and no differentiation was possible between the effects of one versus the other BP reduction [895]. Thus, there is no evidence on the protective effect of antihypertensive medications in the IDH phenotype. At any rate, based on the available epidemiological data and the high risk of transition of IDH to ISH or systodiastolic hypertension, periodic BP evaluations and initiation of lifestyle interventions should be implemented in all IHD patients. Because the evidence of an association of IDH with adverse CV outcomes is more evident in younger than in older patients antihypertensive drug treatment may be considered in patients aged <50 years. In contrast, in older patients with IDH, the low IDH prevalence and the uncertain association with CV events may support treatment limitations to lifestyle interventions and close FU. Antihypertensive treatment may be generally considered in patients with high CV risk.

Isolated diastolic hypertension (IDH)

Recommendations and statements	CoR	LoE
Periodic BP evaluation and lifestyle interventions are recommended for all patients with IDH.	I	C
Despite the absence of dedicated RCTs in IDH, it is recommended that the BP lowering drug treatment should follow the general treatment strategy.	II	C

14.8 Night-time hypertension and dipping

Night-time hypertension is defined as an average BP ≥120/70 mmHg recorded during the night hours with ABPM. In recent years, dedicated home BP devices have emerged as a new method for obtaining BP values during sleep, and they could be a practical alternative to ABPM [896,897]. Evidence in favor of this approach has been obtained with either upper arm or wrist devices measuring BP three times during sleep. Despite the limited number of values, there is evidence that there may be a good agreement between BP measured at night with ABPM and home devices (mean SBP and DBP differences +1.4 and −0.2 mmHg, respectively) [149]. In several original studies and meta-analyses, night-time BP proved to be more predictive of adverse outcomes, including CV events and mortality, than daytime [898] or even 24 h BP [899]. Patients with nocturnal hypertension are more likely to develop cardiac and carotid structural changes than people with nocturnal normotension [900]. Two large studies have shown that having nocturnal hypertension in people with normal office BP and normal daytime BP, a condition called isolated nocturnal hypertension, is associated with higher risk of HMOD and adverse outcomes [897,900,901]. Isolated nocturnal hypertension has been found to be present in 9.2–12.9% of adults [902,903] and to be more prevalent in men with high-normal BP and a high CV risk profile, African Americans, older individuals, obese and diabetic patients, patients with CKD and individuals with WCH [904]. A steady increase in asleep BP and a decline in the nocturnal BP fall occur with aging [905]. An increase of CV risk occurs not only with nocturnal hypertension but also with a reduced magnitude of the nocturnal BP fall, regardless the absolute night-time BP values. The night-to-day ratio is a significant predictor of outcome, and allows subdivision of patients into dippers (night-day ratio ≤ 0.9 or ≥10% of the daytime average BP) and nondippers (night−day ratio ≥0.9 or ≤10%), with the latter group exhibiting an increased CV risk [62]. Moreover, in patients in whom there is no night-time BP reduction or even a higher night-time than daytime average BP

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(reverse dippers), the increase in risk is particularly marked [62,157,905]. In patients aged 70 years or older, a U-shaped relationship between the night-to-day ratio and CV has been observed [905]. In this age group, not only nondipping or reverse-dipping but also extreme-dipping (>20% nocturnal BP fall) were found to be associated with increased risk of CV events. In contrast, in younger patients, the nocturnal BP reduction/adverse outcome association appeared to be linear. It is important to know that reproducibility of night-time BP patterns is low in both untreated and treated hypertensive patients [173,906], which suggests that night-time phenotype typization should be based on repeated ABPM readings rather than only on single recordings. Several different mechanisms can lead to nocturnal hypertension, including increased sympathetic nervous system activity, autonomic dysfunction, impaired baroreflex sensitivity, salt sensitivity, increased plasma volume, RAS hyperactivity, OSA and other sleep disturbances, increased stress and renal dysfunction [739,907]. Selective treatment of nocturnal hypertension is not available, and no solid evidence exists on the effects of enhancing nocturnal BP reduction on outcomes in nondippers or reverse-dippers. Several therapeutic strategies have been proposed to achieve this goal, in particular, the chronotherapeutic approach with bedtime administration of antihypertensive medications, salt restriction, treatment of sleep disturbances (e.g. sleep apnea), renal denervation [739,909] and specific drug classes. However, criticism has been raised about the quality of some of these studies and attention has been directed to possible inconveniences of a nightime BP that is too low, as well as to the possibility of a lower adherence to treatment of bedtime drug administration rather than the more usual morning drug administration (which is always adopted in trials) [676,677]. In a recent, large, prospective, open-label and blinded-endpoint RCT, bedtime drug administration did not lead to any difference in CV outcomes compared with morning drug administration (which was associated with a better adherence to treatment), although with bedtime administration, there was a greater morning and, thus, possibly a greater night-time BP reduction [675]. Based on available evidence, morning or evening intake of the prescribed monotherapy or SPC of drugs should be left to the patient preference. In the not infrequent case of a treatment based on multiple drug tablets, patients may prefer to split drug intake into morning and bedtime doses, which may favor a smoother BP profile over the 24 h [908], and some drugs, i.e. diuretics, are not suitable for bedtime dosing.

Night-time hypertension and BP phenotypes

Recommendations and statements	CoR	LoE
It is recommended to assess night-time BP using ABPM because it is more predictive for outcomes than daytime BP, and because nocturnal hypertension, non-dipping and reverse dipping are associated with increased CV risk	I	B
For the identification of night-time BP phenotypes, repeating ABPM is necessary, because of poor reproducibility.	I	B
Elevated night-time BP may be reduced by antihypertensive treatment.	II	C
In the general hypertensive population morning dosing or bedtime dosing results in similar outcome.	I	B

14.9 Orthostatic hypertension and hypotension

BP should also be measured in the standing position at the first visit, and regularly at each visit in patients who are older, under antihypertensive treatment, have diabetes, or with specific causes or factors that may favor an orthostatic BP fall. At least two BP measurements should be taken 1 and 3 min after standing. Orthostatic hypotension is defined as a decline in SBP of at least 20 mmHg or in DBP of at least 10 mmHg within 3 min of standing, and is associated with an increased risk of mortality and CV events [909,910] as well as with a greater incidence of marked BP reductions, with, thus, a greater risk of injurious falls, particularly, when patients are treated with vasodilators . However, it is important to remember that an exaggerated BP increase or a BP elevation on standing is also associated with an increased risk of adverse outcomes both in young [909,911,912] and older [874,913] individuals. An important role for the genesis of this condition can be played by unhealthy lifestyle behaviors, including smoking, heavy coffee drinking and alcohol intake [836,912]. Measuring the BP response to standing may facilitate the identification of people with MH [836]. A neurohumoral overshoot seems to be the driving mechanism of orthostatic hypertension in young adults whereas vascular stiffness seems to be the main pathogenetic factor in older patients [914]. There is no generally accepted definition of orthostatic hypertension in the literature. According to some authorities, an exaggerated pressor response is a sustained SBP increase of at least 20 mmHg when changing from the supine to the standing position. Another definition is an exaggerated pressor response associated with an SBP of at least 140 mmHg while standing [782].

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14.10 Baroreflex failure and efferent autonomic failure

Arterial baroreceptors sense changes in vascular stretch resulting from BP fluctuations. The information is conveyed through afferent nerves to the brainstem and elicits counter-regulatory adjustments in sympathetic and parasympathetic efferent activity, thereby stabilizing BP. Given the importance of the baroreflex in BP control, damage to the afferent portion, the integrating brainstem centers and/or the efferent portion of the baroreflex results in severe BP abnormalities. Despite anatomical preservation of the aortic baroreflex arch, baroreflex failure occurs following bilateral damage to carotid baroreceptors or baroreflex afferent nerves [915–917]. Damage to the efferent portion of the baroreflex is usually part of autonomic failure [917]. Both conditions differ dramatically in their clinical presentation and in either case BP and more general management is not supported by trials with hard clinical endpoints.

Clinically, baroreflex failure is characterized by extreme BP variability with dramatic hypertensive surges, hypotensive episodes and orthostatic hypotension in some but not all patients [915–917]. Causes of baroreflex failure include neck dissection or radiation therapy, bilateral resection of carotid body paragangliomas, familial dysautonomia (hereditary sensory and autonomic neuropathy type 3), and, very rarely, brainstem lesions [915–918]. The diagnosis of baroreflex failure should be confirmed by pharmacological baroreflex testing. Because hypertensive episodes in patients with baroreflex failure are mediated through unrestrained sympathetic activation, which are exacerbated by psychological and physiological stress, long-acting central sympatholytic agents are the mainstay of therapy [917]. Vasodilators and diuretics can dramatically lower BP in patients with baroreflex failure and should be avoided whenever possible. Hypotensive episodes are usually managed using nonpharmacological means. Bradycardia through unrestrained cardiac parasympathetic activation may require pacemaker implantation [919].

The clinical presentation of autonomic failure is characterized by a variety of manifestations of loss of autonomic BP control, including posture-related BP abnormalities with orthostatic hypotension and, in many patients, supine hypertension [920]. Causes of autonomic failure should be differentiated to identify potentially treatable conditions, such as autoimmune-mediated autonomic ganglionopathies [921]. In most cases of severe orthostatic hypotension due to autonomic failure, symptomatic therapies are required. Nonpharmacological therapies, such as venous compression garments, increased salt ingestion, and sufficient water drinking should be tried first [922]. Drugs that could worsen orthostatic hypotension should be discontinued whenever possible. Pharmacological therapies, such as alpha-adrenoreceptor agonists, may be required in patients who remain symptomatic on nonpharmacological therapy [923]. All current antihypotensive drugs, particularly longer acting mineralocorticoids will worsen supine hypertension. Supine hypertension increases urine excretion during the night and worsens orthostatic hypotension the next morning, but data on CV risk in this condition is limited. Sleeping with the whole bed tilted head-up is recommended to lower BP during the night and to decrease orthostatic symptoms the next morning [924]. Antihypertensive therapies, given before sleep, can be considered in selected patients. However, their potential long-term benefits on CV risk have to be weighed against the risk of falls and the prognosis of the condition causing autonomic failure [924].

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Baroreflex failure and autonomic failure

Recommendations	Class	Level
The diagnosis of (afferent) baroreflex failure should be considered in patients with highly volatile hypertension that is exacerbated by psychological and physiological stress, particularly in those with predisposing conditions (e.g., following neck dissection or radiation therapy).	I	C
The diagnosis of (afferent) baroreflex failure should be confirmed by baroreflex testing preferably in specialized centers	I	C
Long-acting sympatholytic drugs can be prescribed to attenuate hypertensive episodes in patients with (afferent) baroreflex failure.	II	C
In patients with (efferent) autonomic failure, the underlying causes should be sought for to identify potentially treatable conditions and to gauge prognosis.	I	C
For patients with (efferent) autonomic failure and symptomatic orthostatic hypotension, non-pharmacological treatments such as increased sodium ingestion, sufficient water ingestion, and venous compression garments should be instituted first. Medications worsening orthostatic hypotension (e.g., diuretics, alpha-1 blockers, vasodilators) should be discontinued whenever possible.	I	C
Anti-hypotensive medications (e.g., alpha-adrenoreceptor agonists) may be considered for patients with (efferent) autonomic failure who remain symptomatic on non-pharmacological treatments, however, the treatment can worsen hypertension in the supine position.	II	C
In patients with (efferent) autonomic failure and hypertension in the supine position, sleeping with the head of the bed tilted up can improve BP. Pharmacological therapy of supine hypertension can be considered in selected patient after individual risk-benefit consideration weighing potential benefits on cardiovascular risk against risk of fall and overall prognosis of the underlying disease.	II	C

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15. HYPERTENSION IN DIFFERENT DEMOGRAPHIC SITUATIONS

15.1 Blood pressure in children, adolescents and transition period

15.1.1 Blood pressure measurements in children and adolescents

There is a general consensus that starting from the age of 3 years (or earlier in children with risk factors for high BP), BP should be regularly measured [925–929]. Normality BP tables, derived from studies using manual auscultatory

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measurements, provide BP distributions according to sex, age and height percentile [925,930,931]. In children and adolescents, BP should be measured by manual auscultatory devices [925,931]. Automated devices are increasingly used, but they should be validated specifically in children (www.stridebp.org) [62], and the detection of a child's BP elevation by an electronic device, needs confirmation with auscultatory BP measurements [925,931]. A cuff with appropriate size for the individual child's arm circumference should be used. For manual auscultatory devices, the inflatable bladder length should cover 75–100% of the child's middle upper arm circumference and 37–50% of the upper arm width [62,925]. Use of automated electronic devices should follow the same rules as for standard BP measurements and physicians should follow the device's instructions.

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BP measurement in children and adolescents

Recommendations and statements	CoR	LoE
BP levels should be screened in children starting from the age of three years.	I	C
BP screening in children younger than three years is recommended in the presence of risk factors for high BP (e.g. congenital heart disease, CKD, solid organ transplantation, treatment with BP increasing drugs, history of preterm birth and others)	I	C
For BP measurement only devices validated for children should be used. www.stridebp.org	I	B
It is recommended to define hypertension as BP ≥95th percentile for individuals aged 0-15 years, or BP ≥140/90 mmHg in those aged ≥16 years.	I	B
Diagnosis of hypertension should be established on repeated measurements using a manual auscultatory device. Data from automated devices should be confirmed by using a manual auscultatory device.	I	B
ABPM can be a source of a variety of important information and its use is recommended whenever possible.	II	C
HBPM may be considered for the long-term follow-up of children treated for hypertension.	II	C

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15.1.2 Hypertension in children and adolescents

In children and adolescents, BP increases with age and body size, making it impossible to use a single BP cutoff value to define hypertension. Hypertension in the age range of 1–15 years is diagnosed when office BP values are found to be equal or above the 95th percentile of the normative BP distribution for age, sex and height percentile, persistently on at least three separate occasions [62,925,932]. Because of its superior reproducibility and association with HMOD compared to office BP [62,925,927,933,934], ABPM can be a valuable source of additional information, its elevation being also based on 24-h mean values ≥95% percentile [62,925]. ABPM is also indicated for the evaluation of BP control during treatment, the confirmation of resistant hypertension [62,925] and the identification of WCH and MH, which are also not uncommon in children [925,935]. Information on HBPM in children is limited [936], but it should be considered that in primary care, HBPM is more easily accessible and practical, particularly for monitoring children treated for hypertension [927,936]. Other diagnostic steps involve detection of secondary hypertension, which is more frequent than in adults, as well as of additional CV risk factors and HMOD. In the absence of outcome trials, the treatment goal is to reduce office BP below the 95th percentile, but lower BP targets (below the 90th percentile) are regarded as desirable in children with HMOD or secondary hypertension. Stricter BP targets, i.e. below the 75th percentile or below the 50th percentile for 24 h mean BP, are recommended for CKD either with or without proteinuria, respectively [925,937,938]. Treatment should start with lifestyle changes, within which loss of body weight has a primary importance because of the close association of hypertension and obesity in adolescents [925,939,940]. The decision to use antihypertensive drugs should be based on failure to reach BP control and also, concomitantly with lifestyle interventions, on the BP level (grade 2 or 3 hypertension), the presence of signs or symptoms related to the BP elevation and the evidence of HMOD. Drug treatment should be implemented according to a step care approach. The same five major drug classes validated in adult hypertensive patients are recommended [925,939,940].

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15.1.3 Transition period to adulthood

In hypertensive adolescents aged 16 years or older, the consensus is to shift to the diagnostic and treatment criteria largely similar to those used in adult hypertensive patients. That is, to (i) identify hypertension by office BP values ≥140 mmHg for SBP and/or ≥90 mmHg for DBP, (ii) pursue an office BP target of <130/80 mmHg aiming at <125/75 mmHg in the presence of HMOD or CKD [4] and (iii) lower BP by the same nonpharmacological and pharmacological treatment strategies used in adults. The transition of an adolescent with hypertension from pediatric to adult-like care is a well recognized difficult period for a variety of reasons. Full acceptance of new doctors by the patient may take time. Diagnostic steps and therapeutic adjustments may interfere with the educational challenges and intense social and community life of adolescents. The asymptomatic nature of the BP elevation and the remoteness of its possible adverse consequences may favor under-appreciation of the risks and poor adherence to the prescribed treatment. Adherence has been reported to be frequently low in the transition period [941]. During transition, close collaboration and sharing of clinical information between pediatricians and adulthood physicians is of crucial importance. The age and the duration of the transition period should be flexible, depending on the maturation of individual adolescents, family, socioeconomic characteristics and the disease severity and comorbidities. Parents' involvement plays an important role. After transition is completed, patients should be closely followed to detect the BP trajectories in the subsequent years, which include, in some cases, spontaneous BP normalization.

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BP measurement in children and adolescents

Recommendations and statements	CoR	LoE
BP levels should be screened in children starting from the age of three years.	I	C
BP screening in children younger than three years is recommended in the presence of risk factors for high BP (e.g. congenital heart disease, CKD, solid organ transplantation, treatment with BP increasing drugs, history of preterm birth and others)	I	C
For BP measurement, only devices validated for children should be used. www.stridebp.org	I	B
Hypertension is defined as BP ≥95th percentile for individuals aged 0-15 years, or BP ≥140/90 mmHg in those aged ≥16 years.	I	B
Diagnosis of hypertension should be established on repeated measurements using a manual auscultatory device. Data from automated devices should be confirmed by using a manual auscultatory device.	I	B
ABPM can be a source of a variety of important information, and its use is recommended whenever possible.	I	C
HBPM may be considered for the long-term follow-up of children treated for hypertension.	II	C

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15.2 Hypertension in young adults

Recent large-scale longitudinal studies have expanded knowledge on the relationship of high BP with nonfatal CV events and mortality [942,943] in young people. In a subgroup of young patients ($n = 5000$, age <40 years) from the CARDIA study followed for about 19 years [944], the risk of CV events increased progressively with a BP increase, and in hypertension, (SBP ≥140 mmHg) it was 8.4 times greater than in normotension [945]. This was the case also in another study, based on almost 25 million young Korean individuals (20–39 years old, median age 31 years) in whom an SBP between 130 and 139 mmHg and a DBP between 80 and 89 mmHg (grade 1 hypertension according to the ACC/AHA classification) were accompanied by a 25% increase in the risk of CV events [43]. The increase was seen in men and women, it was related to either SBP or DBP, and it was visible also in conditions of ISH and IDH [862], although in either case, it was less than when the elevation involved both SBP and DBP values. Finally, the association between BP and CV events has been documented also by a meta-analysis of 17 observational studies, including more than 4.5 million young adults (age18–45 years) followed for about 15 years [946].

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This leaves no doubt that the relationship between BP and adverse CV outcomes is similar in young as compared with middle-aged and older people, although predictably in studies on younger people, the absolute number of events was lower. On the other hand, whether and how much in young people (i) the hypertension-related risk can be reduced by BP-lowering treatment and (ii) some drugs, e.g. those which more effectively delay, prevent or regress subclinical HMOD, are more protective than others remains an unresolved problem. This is the case because, although in most outcome-based RCTs in hypertension recruitment criteria included patients aged 18 years or above, data on young people have invariably been extremely scarce. In a large individual-participant meta-analysis of RCTs on hypertension, the BP reduction was associated with reduction of CV outcome, regardless of the patient age, at least up to 85 years [479]. However, in the youngest group from which data were available(<55 years of age), the median age was around 50 years. Unfortunately, this evidence gap can hardly be reduced by a study on young people from Korea [43], in which the risk of CV outcomes was modestly and not significantly greater in the treated fraction of the population than in normotensive controls, because of the potential confounding of observational studies in which therapeutic interventions are addressed. While waiting for the urgently needed outcome-based RCTs in young hypertensive patients, the only option left is to extrapolate the results obtained in middle-aged and old people to hypertensive young patients and treat them according to the same recommendations. This finds support by the now clearly demonstrated relationship of BP to CV outcome at a young age. In this context, it is also urgent to develop specific risk charts for younger people, given that the SCORE2 system provides risk quantification only starting from 40 years of age [33].

15.3 Hypertension in older persons

Hypertension is extremely frequent in older individuals, where it is accompanied by an increase in the risk of CV and kidney outcomes almost throughout the entire old age range. In old people, SBP is prognostically much more important than DBP, and ISH is the predominant hypertension phenotype, particularly above 70 years of age. Some studies have shown that in old people, a pulse pressure >65 mmHg could be an independent risk factor for CV morbidity and mortality [947]. Although chronological age is not invariably the most important criterion for defining diagnostic and therapeutic strategies for hypertension, a number of considerations suggest that two age thresholds might be usefully considered. One age threshold is 65 years, i.e. the age at which an acceleration of arterial aging is observed, leading to a sharp increase in SBP and pulse pressure with a concomitant decrease in DBP [948]. Moreover, after this age, most people become inactive professionally, with a significant impact on somatic and psychological health. However, the majority of people aged 65–79 years have a good functional status and do not need help for most of their daily living activities. For individuals of this age group with significant alterations of functional status and autonomy, the strategies described for the group aged 80+ years (Section 15.3.2) should be applied. The second age threshold is 80+, an age range within which a large number of individuals present with several comorbidities, frailty and loss of functionality [949]. At the same time, a significant percentage of this population maintains well preserved somatic, cognitive and psychological health. The consequence is that the 80+ years are a most heterogeneous age group in terms of functionality while being at the same time the most markedly growing age group in the world, especially in Europe [950].

15.3.1 Patients 65–79 years old

15.3.1.1 Threshold and target for drug treatment

There is strong evidence from RCTs that in this age range, antihypertensive therapy significantly reduces CV morbidity as well as CV and all-cause mortality. In addition, antihypertensive treatment can generally be well tolerated [951,952]. The previous guidelines [953] supported BP thresholds for drug treatment similar to those of younger people, i.e. ≥140 mmHg SBP or ≥90 mmHg DBP. Target SBP values within the range of 130–139/80–89 mmHg aiming at a BP close to 130/80 mmHg, if well tolerated, was further recommended. However, more recent data suggest that lower BP targets might be considered. In hypertensive people aged 60–80 years, the STEP trial [492] has shown that treatment to an SBP target of 110–129 mmHg (mean 126.7 mmHg) resulted in a lower incidence of CV events compared to standard treatment, with a 130–149 mmHg SBP target. A reduced number of events has also been shown in older patients of the SPRINT [497] trial to reach an average on-treatment SBP of about 122 mmHg compared an on-treatment value between 130 and 139 mmHg. However, the SPRINT trial [947] has the limitations discussed above and in the previous guidelines [953]. This is the case also for the STEP trial, which made use of a reference group that included patients with uncontrolled BP (i.e. >140 mmHg), possibly amplifying the incidence of outcomes [954]. Furthermore, STEP used drug deprescription to randomize patients with initially lower BP values to the higher target BP group, again with possible outcome amplification. Nevertheless, in a meta-analysis of 32 RCTs in 96 549 patients largely confined to a 65–80 years of age group (i) antihypertensive treatment was associated with a reduction of CV outcomes when patients had a baseline SBP ≥140 mmHg; (ii) reducing SBP to <130 mmHg was associated with an incremental reduction of CV events and mortality compared to patients in whom the SBP reduction left on-treatment SBP values in the 139–130 mmHg range and (iii) this was also the case when DBP was reduced to <80 mmHg compared with remaining in the 80–89 mmHg range. Data in older patients were similar to what was seen in younger patients and indeed, the linear relationship between BP reductions and outcomes over a 40 mmHg SBP change was almost superimposable in the two age groups [143,144,488,955]. Thus, it seems appropriate for the present guidelines to somewhat modify the previously recommended BP targets in hypertensive patients aged 65–79 years. That is, (i) to emphasize the recommendation to have as the initial goal a reduction of SBP to between 140 and 130 mmHg, because this guarantees an appropriate trade-off between the degree of CV protection and the incidence of side effects (ii) to consider, if treatment is

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well tolerated and no overt signs of organ hypoperfusion emerge, a further SBP reduction to <130 mmHg (iii) to reduce DBP, which is of lesser importance in this age range, to <80 mmHg and (iv) to make no attempt to decrease SBP/DBP to <120/70 mmHg. It is important to mention that threshold and target BP values are not identical to those of patients with ISH aged 65–79 years. In trials documenting the benefit of antihypertensive treatment in ISH, initial SBP was ≥160 mmHg while on-treatment SBP was confined to the 149–140 mmHg range [143,144,497,498], which supports the recommendation to treat patients with grade 2 or 3 ISH and to reduce their SBP to <150 mmHg, a conservative target that might diminish the risk of an excessive DBP reduction. However, as addressed in Section 14.6, a considerable number of older patients with ISH or a prevalent SBP elevation was included in RCTs showing CV protection at lower SBP threshold and target values, i.e.140–159 and <140 mmHg SBP, respectively [499,501]. This provides a rationale for the additional recommendation that in ISH patients (i) can consider treatment also with a grade 1 SBP elevation and (ii) cautiously aim at on-treatment SBP values between 130 and 139 mmHg, if treatment is well tolerated and DBP does not show a reduction below the safety values.

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15.3.1.2 Antihypertensive treatment strategies

Treatment of older patients should make use of lifestyle interventions as in younger patients. However, in subjects 80 years or older the measures indicated for younger patients (Section 7) may have to be adapted. Although overweight and obesity remain deleterious for CV and metabolic health, weight loss programs may lead to muscle mass loss, sarcopenia and malnutrition. Therefore, except for the case of severe obesity or with robust old people, weight loss is not recommended. Also, salt restriction may contribute to loss of appetite with deleterious effects on nutritional status and therefore should not be adopted, except in cases of very high salt consumption (e.g. NaCl >10 g day). In these patients a particular effort should be devoted to the promotion of physical activity, adapted to the individual's capacity and cultural context. Collective physical activities (e.g. dance, tai-chi or walking) should be preferred to also promote social contacts and fight loneliness and social isolation in older people. Because older patients (even those in healthy conditions) experience more drug-related side effects compared with younger patients [956], medical efforts should aim at achieving the BP goal and at the same time avoid side effects, the risk of which increases with the number of prescribed drugs. Therefore, in old patients and particularly frail patients, initial monotherapy should be considered the first treatment step more frequently than in younger patients, especially with grade 1 hypertension. However, because controlling the SBP elevation of older patients is particularly difficult, even in grade 1 hypertension, physicians should consider an initial two-drug combination treatment or be prepared to uptitrate treatment with the addition of a second and, if needed, a third drug. Combination treatment is necessary in the vast majority of the patients with grade 2 or 3 hypertension, and in these patients, it can usually be considered as first step treatment because initial combination treatment favors better adherence to treatment and reduced treatment inertia [608], also in old patients. This is particularly important because due to their multimorbidity, more than half of older patients are exposed to polypharmacy, i.e. are treated with at least five agents [957,958]. As a general rule, and although delayed achievement of BP control should be avoided, it may be wise to start antihypertensive drugs with lower doses and uptitrate treatment somewhat more slowly in older than in younger patients.

15.3.1.3 Antihypertensive drugs

In the absence of specific indications, there is no evidence of more pronounced long-term benefits or harms of any specific drug class. Therefore, any of the five major drug classes can be used. However, older patients are more susceptible to side effects associated with BBs, most importantly fatigue, sleep-related disorders (unusual dreams or insomnia) and depression [959] that can negatively impact on the quality of life. Therefore, in older individuals, BBs should not be a general first choice for treatment in the absence of GDMT indications or other conditions where their use is recommended (Table 16). However, in clinical practice there are many cardiac, vascular and non-CV conditions, for which BBs are indicated, and their prevalence is high in old people as well [588]. Specific prescription rules for older patients are available and may be of major help for reducing drug-related adverse effects [960].

15.3.1.4 Monitoring the effects of treatment

The search for orthostatic hypotension should be systematic in people aged 65–79 years, even in the absence of symptoms. HBPM should be implemented and help to better define the usual BP values in the face of the higher SBP variability in this age group. These measurements can be proposed even in patients with mild-to-moderate dementia, including patients with Alzheimer disease and other neurocognitive disorders. ABPM can be useful, especially in patients with polypharmacy, to identify hypotensive episodes and obtain information on the presence and magnitude of the night-time BP reduction.

15.3.2 Patients 80 years old or beyond

There is only one outcome-based RCT in this age group, i.e. the HYVET trial [501], showing that in hypertensive patients aged 80 years or more (mean age 83 years), antihypertensive treatment was accompanied by a reduced risk of CV events and all-cause mortality [compared to placebo (relative risk – 21%), with a major benefit for HF (relative risk – 64%)]. Globally, the benefits of BP-lowering treatment in moderately frail octogenarians seems not to be different compared with those observed in fit older adults. For example, in a post hoc analysis of its database, the HYVET study showed that frailty did not modify the favorable impact of antihypertensive treatment [961]. Furthermore, the SPRINT study reported that in a subgroup of patients aged >75 years, the benefit of intensive BP control was observed independently of their frailty level [502]. In both studies, the therapeutic strategies and the threshold and target BP values were superimposable to those of the entire study

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populations. Finally, a recent analysis of a very large real-life population from northern Italy, old patients defined as frail by a large number of comorbidities and a high risk of mortality within few years, exhibited a reduced risk of death, if their adherence to antihypertensive drug prescription was high [510]. In very old hypertensive patients definable as fit for their age or only moderately frail, antihypertensive drug treatment should be implemented together with lifestyle modifications, including promotion of mild physical activity, preferentially in a collective group context. As mentioned in Section 15.3.1.2, social contacts should also be favored in order to avoid isolation and depression. Unless very old patients are robust or severely obese, weight loss programs should be considered with caution because of possible deleterious consequences such as loss of muscle mass and malnutrition. A well tolerated treatment regimen should not be downtitrated or stopped in very old people even if BP values are below those recommended by guidelines.

No RCTs are available in patients close to 90 years of age or beyond. Data on therapeutic strategies and BP targets are also missing in patients with documented severe loss of autonomy due to the fact that trials on antihypertensive therapy in older people target healthier individuals and exclude those with loss of autonomy and limited life expectancy [962,963]. Several observational studies have shown that the relationship between BP and mortality is influenced by the level of frailty [506,964] and that in the most frail old patients, the rates of morbidity and mortality are higher at low BP (mainly SBP <130 mmHg), especially when low BP levels are observed in the presence of antihypertensive treatment [957,965–968]. In these patients, the treatment strategy is frequently referred to as 'start low and go slow'. Overall, the evidence appear to favor the beneficial effects of BP-lowering interventions in old, moderately frail hypertensive individuals, albeit the opposite may happen in very frail individuals. In general, no information is available on whether and to what extent treatment BP thresholds, treatment BP targets and drugs should differ between, e.g. a robust 85-year-old patient person with high physical, social and cognitive capacities, and a very frail 85-year-old person with total loss of autonomy. The amount of loss of functionality and increased risk of death that should lead to changes in treatment strategies are also not established [38,957]. Despite these limitations, in patients aged >80 years, frailty and functionality should be part of the diagnostic work-up. How to assess frailty and functionality at clinical practice level is reported below together with some suggestions on how to adapt treatment strategies to the frailty level.

15.3.3 How to assess the level of frailty/functionality

Tools that can be used by physicians, nurses or other healthcare professionals in daily practice need clinical validation, standardization, limited requirement of time to be completed (less than 15 min), no need of complicated/expensive specific devices and no requirement of specialized skills (except for a short course for a minimal theoretical education and practical training). The clinical frailty scale [969] is a validated scale classifying the 80+ year-old people according to their frailty level, in an easy, rapid and standardized way (Table 21). This tool should be employed before the initiation of treatment and repeated annually in order to monitor the evolution of a patient's functionality/autonomy. For fit patients with an ADL (Activities of Daily Living) score of ≥5/6 [970], absence of clinically significant dementia and capacity of routine walking activities, treatment strategies and objectives should be similar to those of the 65–79 years group. For patients with intermediate functional status, i.e. patients with moderate functionality impairment and partial loss of autonomy, antihypertensive treatment strategies should be more conservative, i.e. treatment should start when SBP ≥160 mmHg, targeting an SBP range between 140 and 150 mmHg. Progressive reduction of antihypertensive drug treatment could be considered if SBP is <120 mmHg or in the presence of orthostatic hypotension [971], although little information is available on the consequences of 'deprescribing' from studies in old patients [972]. For Group 3, i.e. patients with severe loss of functionality/autonomy (ADL ≤2, with severe dementia, chronic bedridden or end of life), indication of treatment should be individually decided according to symptoms, comorbidities and polypharmacy. Progressive deprescription should be considered if SBP is <130 mmHg or in the presence of orthostatic hypotension. The results of ongoing RCTs in very frail individuals will provide more evidence on the benefits/risks of reduction of treatment in these patients.

TABLE 21. Adapting BP-lowering strategies in patients older than 80 years according to their functional/autonomy status

	Group 1	Group 2	Group 3
Characteristics	**Fit**	**Slowed but autonomous for most activities**	**Severely dependent**
Diagnosis	-ADL (Katz) ≥5/6 and -absence of clinically significant dementia (MMSE≤20/30) and -routine walking activities	-Profile between Groups 1 and 3	-ADL (Katz) ≤2/6 or -severe dementia or -(MMSE ≤10/30), chronic bedridden or -end of life
Therapeutic strategy	- As recommended below	-Individualize treatment	-Individualize treatment -Prioritize therapeutic strategies according to comorbidities and polypharmacy issues

Katz Index of Independence in Activities of Daily Living (ADL) is a scale rated from 0 (completely dependent) to 6 (completely autonomous). This scale comprises 6 ADL: Bathing, Dressing, Toileting, Transferring, Feeding and Continence. For each ADL, '0' means that the person is unable to do it without assistance, 0.5 need of some assistance, 1 no need of any assistance [970]. MMSE, Mini mental status evaluation.

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Recommendations and statements	CoR	LoE
Patients 65 to 79 years old		
The recommended office threshold for initiation of drug treatment is 140/90 mmHg.	I	A
The primary goal of treatment is to lower BP to <140/80mmHg	I	A
However, lowering BP to below 130/80mmHg can be considered if treatment is well tolerated.	I	B
Patients 65 to 79 years old with ISH		
The primary goal of treatment is to lower SBP in the 140 to 150 mmHg range.	I	A
However, a reduction of office SBP in the 130 to 139 mmHg range may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B
In dedicated RCTs in older patients with ISH, CCBs and Thiazide/Thiazide-like diuretics have been mainly used. However, all other major drug classes can be used, because of the frequent co-existence of compelling indications and the need of combination therapy to control SBP.	I	A
Initiation of treatment with a two-drug combination is also recommended in most older patients with ISH, who are not frail.	I	C
Patients ≥80 years old		
The recommended office SBP threshold for initiation of drug treatment is 160 mmHg.	I	A
However, a lower SBP threshold in the 140 to 160 mmHg range may be considered.	II	C
Office BP should be lowered to a SBP in the 140 to 150 mmHg range and to a DBP <80mmHg.	I	A
However, reduction of office SBP between 130 to 139 mmHg may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B
Additional recommendations		
In frail patients, initiation of drug treatment and the treatment	I	C
Do not aim to target office SBP below 120 mmHg or DBP below target for office SBP and DBP should be individualised. 70 mmHg during drug treatment.	III	C
However, in patients with low office DBP, i.e. below 70 mmHg, SBP should be still lowered, albeit cautiously, if on-treatment SBP is still well above target values	II	C
Reduction of treatment can be considered in patients age 80 years or older with a low SBP (<120mmHg or in the presence of severe orthostatic hypotension or a high frailty level	III	C
Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥ 80 years, is not recommended, if treatment is well tolerated.	III	B
In older patients, treatment should start with lower doses and uptitration should be slower.	I	C
The search for orthostatic hypotension in old patients should be systematic, even in the absence of symptoms. Back titration or discontinuation of BP lowering drugs should be considered in patients with orthostatic hypotension.	I	C
In old patients with hypertension there should always be an assessment of functional/autonomy status including cognitive function.	I	C
In patients with reduced functional/autonomy status and/or dementia treatment should be individualized.	I	C

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15.4 Sex and gender aspects in hypertension

15.4.1 Epidemiology and pathophysiology

In hypertension, as in many other diseases, there are sex (a biological characteristic) and gender (a social construct) differences that have an important impact on its pathophysiology, epidemiology and clinical management. In 2019, the worldwide age-standardized prevalence of hypertension, defined by SBP ≥140 mmHg and/or DBP ≥90 mmHg, or taking medication for hypertension, was 32% in women and 34% in men [37]. However, large disparities were observed within world regions. Thus, in Western Europe, the prevalence of hypertension in individuals aged 30–79 years ranged between 17.5 and 30% in women and 26 and 43% in men, whereas in Eastern Europe, it ranged between 34 and 46% in women and 43 and 56% in men [37] The main difference between men and women is the life trajectory of BP that is apparent already from age 12 [37,973]. Hypertension prevalence increases with age in both sexes [973], but it tends to be lower in premenopausal women than in men of the same age, with a marked rise in women after menopause [39]. After the age of 65, the prevalence of hypertension in female exceeds that of male individuals [37,39,973].

The differences exhibited by women in BP development over the life course and the age-related hypertension can be explained by differences of BP regulatory mechanisms in male and female individuals – most likely a combination of sex and gender-specific factors [37,973]. In premenopausal female individuals, estrogens contribute to lower BP in the context of their general vascular protective effect. Protection is mediated through different mechanisms including endothelial vasodilatation via upregulation of the nitric oxide pathway and inhibition of the activity of SNS and RAS. Moreover, estrogens decrease endothelin production, decrease oxidative stress and reduce inflammation [974]. After the menopause, the marked decrease in estrogen levels partially explains why BP and the risk of hypertension increase [37,974]. In postmenopausal women, androgens may contribute to increased BP and the age-associated CV risk as they do in men [975]. In this context, young women with estrogen/androgen imbalance and conditions such as premature ovarian insufficiency, polycystic ovarian disorders and infertility are at increased risk of developing hypertension [976]. Although estrogens have a protective role in premenopausal women, the administration of exogenous estrogens to menopaused women has no effect on BP and does not affect the risk of CV outcomes.

15.4.2 Blood pressure and cardiovascular risk

In the pooled data of the IDACO study, the absolute CV risk was lower in women than in men, while the increase in risk associated with 24-h and night-time BP was steeper in women than in men. The proportion of events potentially preventable by BP lowering may, therefore, be greater in women [977], making a wider implementation of ABPM in women desirable. In a meta-analysis of 27 542 individuals without baseline CVD (54% females), the increased risk for CV events, including myocardial infarction, HF and stroke, associated with SBP elevations was visible at lower SBP ranges in female than in male patients, suggesting that the definition of optimal SBP might differ between men and women [978]. One important issue is that several sex-specific events occurring in women, including hypertensive disorders of pregnancy or the polycystic ovary syndrome, are associated with a greater long-term risk of hypertension and CVD. Unfortunately, a large proportion of women are not aware of their increased CV risk due to insufficient screening, particularly among younger women, ethnic minorities and low socioeconomic groups [979].

15.4.3 Differences in clinical phenotypes

15.4.3.1 White-coat hypertension and masked hypertension

The IDACO study reported that WCH exponentially increased from individuals aged 18–30 years to individuals aged ≥70 years, with limited differences between men and women (8.0 versus 6.1%; $P = 0.0003$). However, data from national and international registries consistently report a higher prevalence of WCH in women [980]. A high prevalence of WCH was observed in older individuals and pregnant women [981]. In contrast, MH is generally more prevalent in men than in women as shown by the Spanish ABPM registry (43 versus 26%) [982] and the IDACO registry (21.1 versus 11.4%) [983].

15.4.3.2 Hypertension-mediated organ damage

Female and male patients develop HMOD, but differences in HMOD frequency, severity and reversibility occur according to sex [984]. LVH is more prevalent and less modifiable by antihypertensive treatment in women than in men [985,986]. In the Campania Salute Network project, new LVH was more frequently detected in women [987], and women with LVH had about the same CV risk as men. LA dilatation, an early sign of hypertensive heart disease, has been reported to be more common in women than in men with hypertension [988,989].

Regarding arterial stiffness, PWV decreases in women after puberty. Thereafter, both sexes experience an increase in arterial stiffness with age, with women showing a more rapid increase after menopause. Older women experience greater aortic stiffness and arterial pulsatility than their male counterparts, seemingly contributing to ISH, uncontrolled hypertension, HfpEF and aortic stenosis, all being more common in women [990]. A greater adverse prognostic significance in women of arterial stiffness has been observed in patients with CAD [991–994].

There is also evidence that the impact of hypertension on kidney function and disease progression may have a sex-dependent component [995]. The prevalence of albuminuria was lower in postmenopausal female individuals than in male individuals. In a cohort of 2379 Chinese individuals, the association between BP and eGFR differed in male and female

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individuals, suggesting that men were more sensitive to hypertension-induced changes in kidney function over time than women [996]. Moreover, in a meta-analysis of 68 studies of patients with various forms of CKD, a less rapid decline in renal function was observed in women [997].

15.4.4 Sex differences in hypertension outcomes

The development of CV outcomes in relation to hypertension is also influenced by gender. An important observation is that hypertension-related outcomes, e.g. myocardial infraction, HF, stroke and CV disease, may occur at lower SBP levels in women [978]. In the INTERHEART study, the increased risk of myocardial infarction associated with hypertension was greater in older female than in male patients [529]. In a similar age, Norwegian population-based study that enrolled 33 859 individuals (51% women), men were at greater risk of myocardial infarction as BP increased [995]. But both for SBP and DBP increases, the association with BP was closer for female patients. Similar conclusions were drawn from a large UK cohort study [996] as well as from studies in younger individuals [863,997]. In the Hordaland Health study, which had a 16.2 years follow-up, stage 1 hypertension in the fourth decade doubled the risk of myocardial infarction in midlife female individuals, while this relationship was not observed in male individuals [997]. Hypertension increases the risk of HF in both sexes [998], but the increase in risk is greater in female than in male individuals [999]. Clustering of female patients was observed among patients with HfpEF, where females represent 55–70% of patients. This is different for HfrEF, in which females have been reported to be 30–40% of the overall number of patients with HfrEF [202,1000–1002]. Although differences in the age distribution of the patients at risk (because of the longer life expectancy of female individuals) may have contributed, hypertensive female patients have been reported to develop more LVH, vascular and myocardial dysfunction compared with hypertensive male patients [974,988], with, thus, a possible sex-related contribution to the development of CAD and HF [987,1000]. A Norwegian study reported a stronger association of an elevated SBP with incident AF in female than in male patients [1003], but this finding has not been consistently confirmed by other studies [1004,1005]. Recent studies also suggest that, in line with previous evidence, stroke risk starts to increase at a lower BP in female patients [978,1006]. Hypertension also seems to be a stronger risk factor for dementia in female individuals for cognitive decline [1007,1008].

15.4.5 Benefits of antihypertensive treatment and target blood pressure

Do women receive the same CV outcome benefits from antihypertensive treatment than men? Because of the global under-representation of women in trials, answering this question is difficult. Moreover, the statistical analyses of interventional trials commonly used a binary approach that does not appropriately capture the clinical specificities of men and women. Only few clinical trials in hypertension report treatment results stratified by sex. The NORDIL study showed similar treatment effects in both sexes [1009]. The LIFE trial found similar treatment effects in both sexes, but female participants randomized to treatment with losartan had a greater reduction of the primary endpoint, all-cause mortality, and new-onset diabetes [1010]. Three other studies showed sex differences favoring treatment in women. In the HOT trial, the target DBP of <80 mmHg reduced myocardial infarction in women but not in men. On the other hand, low-dose acetylsalicylic acid reduced incident myocardial infarction only in men but not in women [1011]. In the ANBP-2 trial, the benefit of ACEi treatment was only demonstrated in male participants [1012] and in the VALUE trial, amlodipine lowered BP and reduced the primary endpoint (composite of cardiac mortality and morbidity) more effectively in female than in male individuals. A meta-analysis of RCTs (103 268 men and 87 349 women) found comparable reductions in BP and incidence of CV events in both sexes for treatments based on BBs, ACEis, ARBs, CCBs or diuretics [952]. Limited information from RCTs is available on whether BP targets should be different in women compared with men, in part because no trial was adequately powered to investigate outcomes at different on-treatment BP levels separately in the two sexes, a limitation that was particularly evident in women because of their lower number of CV outcomes [1013]. In a post hoc analysis of SPRINT, in which data were analyzed separately for men and women, the primary composite CV outcome was achieved in men but not in women [1014]. In another post hoc analysis of the same study in which a propensity score matching was used to equalize patients' baseline characteristics (in SPRINT, randomization was not stratified according to sex), women also did not exhibit as significant an outcome difference at standard versus intensified treatment. The low baseline CV risk in female patients may have accounted for this finding [1015]. Given the low number and the limitations of the available studies, there is insufficient evidence to recommend different BP targets in women compared to men.

15.4.6 Sex differences in hypertension management

Lifestyle modifications are important for nonpharmacological management of hypertension, and sex differences in their effects have been noted. In the DASH trial, dietary sodium restriction induced pronounced BP reductions only in female individuals. Regarding physical activity, a meta-analysis of 93 trials assessing the impact of a structured aerobic exercise therapy found that exercise induced a greater BP reduction in male than in female participants [358,1016]. Regarding drug therapy, it is important to mention that there are disparities in the prescription of antihypertensive drugs between male and female individuals, indicating that female patients are less likely to receive antihypertensive therapies than male patients for comparable BP values [1017]. In a recent real-world analysis conducted in Sweden, hypertensive women had a higher BP, less antihypertensive treatment and a worse BP control, with female sex being a significant predictor of less intensive antihypertensive therapy [1018]. Women may differ from men for drug absorption, metabolism and elimination [1019], but the clinical impact of these pharmacokinetic differences is unclear, and sex-specific dosing for BP-lowering drugs has not been established. This applies also to the unclear relevance of differences in body weight and body composition between

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men and women. Adverse effects from antihypertensive drugs are reported more often for women than for men, even when women are taking fewer drugs [1020], and women have a 50% greater risk of suffering from adverse reactions compared to men [1021]. A higher incidence of ACEi –induced cough and CB-induced ankle edema has been observed in women [1022]. Women were more likely to experience hypokalemia and hyponatremia with diuretics, although less likely to experience gout [1023]. There is no consistent data on sex differences in the efficacy of antihypertensive drugs. Therefore, drug selection and dosing should not be based on the sex, but treatment individualization should consider also sex-specific adverse drug reactions. Clearly, specific caution and contraindications must be considered for women planning pregnancy or who are pregnant (Section 16.1). Whether drug adherence is better or worse in female compared with male individuals remains controversial. No difference in adherence was found between sexes in a meta-analysis of 82 studies [1024]. In studies on resistant hypertension, where adherence was assessed using highly sensitive methods measuring drugs in urine, drug adherence was lower in women [674]. This may be explained, at least in part, by depression, a known risk factor for nonadherence, which has a greater prevalence in women.

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15.4.7 Infertility treatments and hypertension in women

Following any invasive assisted reproductive therapy, the risk ratios for gestational hypertension, preeclampsia and a combination of both, increase by 54% independently of the gestation order [1025]. Moreover, a recent meta-analysis has confirmed that pregnancies conceived by in-vitro fertilization, with or without intracytoplasmic sperm fertilization, are at higher risk of being complicated by HDP including preeclampsia, compared with spontaneously conceived pregnancies [1026].

15.4.8. Oral contraceptive pills and hypertension

Physicians counselling women with CV risk factors, including hypertension, should balance the potential risks of contraceptive methods against those of an unintended pregnancy. Older studies have demonstrated a relationship between the use of a combined estrogen–progestin oral contraceptive pill (mostly with a higher dose of estrogens), venous thromboembolism, and, to a lesser extent, myocardial infarction (especially with a concomitant smoking history) and stroke [1027,1028]. However, the dose or type of estrogen in the combined pill may change the strength of this association [1028–1030]. The evidence so far supports that progestin-only pills do not increase thrombotic events, while injectable forms of progestins require further evaluation [1031–1033]. In normotensive women, contemporary formulations of oral low-dose estrogen–progestin (i.e. 30 35 mg or less of estrogen) are associated with a 5 mmHg increase of either SBP or DBP [1034]. The development of hypertension is almost 2% over 4 years [1035]. Initiation of low-dose estrogen–progestin formulations can be advised for normotensive women without CV complications or additional risk factors after careful BP monitoring that should be regularly repeated (every 3–6 months) [1036]. In newly diagnosed women with grade 1 hypertension or treated hypertensive women with BP levels within the target range, a combined estrogen–progestin pill may be considered, if no other method is appropriate. Newly diagnosed women with (i) higher hypertension grades, (ii) on-treatment uncontrolled hypertension or (iii) a history or a high risk of CV disease, should not receive estrogen-based contraceptive pills [1037], and alternative forms of contraception should be advised. Discontinuation of combined estrogen–progestin oral contraceptives in women with hypertension may improve BP control because BP usually decreases promptly following pill withdrawal [1038]. Progestin-only pills have no significant effect on BP levels, and measurement of BP at initiation or during contraception is not required [1037,1039]. However, in women with more severe forms of hypertension, the initiation of progestin-only pills should be individualized within the context of additional risk factors. At the same time, it should be carefully considered in women with a history of CV disease irrespective of BP levels [1037]. Combined hormonal contraceptives are not recommended in smokers aged 35 years or older [1039]. In premenopausal women, estrogen use with an oral contraceptive pill increases BP. Although SNS and RAS activation may be underlying mechanisms, whether this is because of the effects of estrogen, progesterone or a complex interaction between the two is not well understood. Studies on the effects of progesterone are limited, with short-term follow-ups and mostly observational designs. Nevertheless, as of today, data do not suggest any increased risk of hypertension or short-term cardiometabolic outcomes with progesterone-only contraceptive pills.

15.4.9 Hormone-replacement therapy and hypertension

Cross-sectional studies have long established that menopause doubles the risk of developing hypertension, even after adjusting for factors such as age and BMI [1040]. Although hormone-replacement therapy contains estrogens, there is no convincing evidence that BP will increase significantly in menopausal women with or without hypertension [1041]. However, after the initiation of hormone-replacement therapy, it is reasonable to measure BP to confirm persisting normotensive BP values or regular BP control by treatment. In the case of uncontrolled BP, hormone-replacement therapy should be stopped. In summary, current evidence suggests that the use of hormone-replacement therapy is not associated with an increase in BP. If BP levels can be controlled with antihypertensive medications, women may receive hormone-replacement therapy.

15.4.10 Gender-affirming hormone therapy and hypertension

According to the Global Health 50/50 definition, gender refers to the socially constructed norms that impose and determine roles, relationships, and positional power for all people across their lifetime [1042]. Gender-affirming therapy (i.e. testosterone, estrogens, antiandrogens and gonadotropin-releasing hormone analogs) is used in transgender individuals

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to favorably modulate their secondary sex characteristics in line with gender identity. There is conflicting evidence from small studies of limited duration on the direction or extent of BP changes in transgender individuals receiving gender-affirming therapies [1043]. It is also undetermined whether transgender hormonal treatments are associated with increased CV risk. As for other individuals receiving sex hormone treatment for different purposes (e.g. hormone replacement therapy, oral contraceptive agents), it seems reasonable to recommend that transgender individuals should regularly measure their BP during gender-affirming treatments to ensure persistency of BP normality or, if hypertensive, BP control by treatment [1044].

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15.5 Hypertension and ethnicity

15.5.1 Nomenclature and relevance

Given the degree of African and Asian migration to Europe, attention to factors and differences in the management of hypertension related to ethnicity is mandatory. In the United States, the notion is consolidated that in African Americans, hypertension is more common, possibly more severe, more risky for CV and kidney events, and more difficult to control. A major research agenda to improve the hypertensive burden among African-Americans was proposed some years ago [1045]. The intensive search for genetic links to excess 'African' hypertension yielded less success than expected [1037,1046], but nevertheless several specific new pathophysiological, clinical and even genetic traits have emerged. With regard to European immigrants, early arterial stiffening (indicating premature vascular aging independent of BP), has been observed in African Americans but only inconsistently in African origin groups in Europe [1047–1051]. Varying degrees of hyperaldosteronism have been found to raise BP disproportionally in people of SSA, African Caribbean and African American origin, probably via underlying salt-sensitivity [1052,1053]. In a recent diagnostic trial for primary aldosteronism, MATCH, 40% of patients were of African origin compared with <20% in the local population [1054]. Somatic (not germ-line) adrenal mutations of the Ca++ channel were more frequent in African-origin patients, with K+ channel mutations more common in Europeans [1055]. Clearly, the present scarcity of European research needs to be amended and expanded beyond the present general knowledge that, as in USA, immigrants to Europe have more hypertension associated with greater CV risk than the European ancestry population. So far, some evidence has been obtained that differences may be related to in utero and postnatal development and growth, including overt malnutrition, malaria in pregnancy or epigenetic influences [1056–1059]. Persistent social disadvantages from individual and structural racism, including neighborhood segregation [1060–1062], ethnic disparities or inequalities in access to care are increasingly recognized as driving factors for resulting differences in hypertension and increased CV morbidity and mortality [1063,1064]. Disparities in hypertension control have also been attributed to patient-level rather than provider or system-level factors, both converging to promote therapeutic inertia [1065]. Other studies on extra-European origin migrant communities reflect the USA-derived knowledge that hypertension is more prevalent in European immigrants of heterogeneous African origin than in local populations [1066]. Ethnic and socioeconomic results from UK and Dutch cohorts [1063,1067] have found major risks of CV events (not only mainly stroke but also CAD) in Caribbeans and Asians minorities affected by hypertension.

15.5.2 Management

Lifestyle modifications are vital for reducing BP and risk across the life-span in all hypertensive patients. Differences in BP response to antihypertensive drugs by ancestry have been associated with BP levels rather than 'race' [465], and no consistent interethnic factors have been detected in antihypertensive drug pharmacokinetics. BP associations with CV risk have also been broadly consistent across ethnic groupings [1068]. Based on systematic reviews [1065,1069] in people of SSA ancestry, CCB and diuretic monotherapies appear to be more effective than BB and ACEi monotherapies, with combination therapy between major drug classes allowing a substantial group of patients (50–70%) to reach BP control [1065,1069]. This is similar to the results of the ALLHAT trial in the USA, which included 33% African Americans [563,1070] and found that BP control at 4 years was 63, 60 and 54% with chlorthalidone, amlodipine, and lisinopril-based therapy, respectively, However, 24, 28 and 41% of patients of the corresponding groups received ≥3 drugs, including the BB atenolol. A recent systematic review and meta-analysis [1065] indicated that, in hypertensive adults of African ancestry, BP reduction was similar across initially administered dual combination therapy containing an RAS inhibitor with a CCB, or a diuretic while with a BB in combination therapy, SBP showed a 3.8 mmHg higher SBP compared with other combinations [1065]. An RCT with African patients from seven SSA countries has also shown an effective BP reduction (ABPM) using a CCB in combination with either a Thiazide or an ACEi [648].

To date, only the ACCOMPLISH trial ($n = 11\,506$, mean age 68 years) has provided outcome data with initial combination therapy [627]. The trial was not powered for separate analysis of the African American subgroup (12%), However, the combined morbidity/mortality was 8.9% for Thiazide diuretic plus ACEi treatment and 6.6% for CCB plus ACEi treatment, with a significant 35% outcome benefit in African Americans ($N = 1414$) versus only a 23% benefit in the total study population ($N = 11\,506$).

The above limited evidence suggests that in hypertensive adults of African ancestry, antihypertensive treatment should be largely based on CCBs but also that CCB plus ACEi and CCB plus diuretic combinations can both effectively lower BP, with some suggestion of a greater CV protection by the former combination. A systemic review has shown no different response to antihypertensive drugs in south Asian patients with a relatively high CV risk [1065].

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16. HYPERTENSION IN SPECIFIC SETTINGS

16.1 Hypertension disorders in pregnancy

Hypertension disorders affect almost 10% of pregnancies worldwide and are the major cause of maternal, fetal or neonatal morbidity and mortality [1071]. Maternal risks include the following: placental abruption, stroke, pulmonary edema, thromboembolic events, multiple organ failure and disseminated intravascular coagulation. The fetus is at high risk of intrauterine growth retardation (25% of cases of preeclampsia), prematurity (27% of cases of preeclampsia) and intrauterine death (4% of cases of preeclampsia). Neonates are exposed to preterm birth with low birth weight, prolonged high-level neonatal care and postnatal death [1072]. The definition and classification of hypertension disorders in pregnancy are summarized in Table 22 and addressed in detail below.

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TABLE 22. Classification of hypertensive disorders in pregnancy

A. Preexisting (chronic) hypertension

Hypertension either preceding pregnancy or developing before 20 weeks gestation, usually persisting for more than 42 days postpartum, and may be associated with proteinuria.

1. Primary hypertension
2. Secondary hypertension
3. White-coat hypertension
4. Masked hypertension

B. Gestational hypertension

Hypertension develops after 20 weeks gestation and usually resolves within 42 days postpartum.

Transient gestational hypertension

– Usually detected in the clinic but then settles with repeated BP measurements taken over several hours, it is associated with a 40% risk of developing true gestational hypertension or preeclampsia in the remainder of the pregnancy, thus requiring careful follow-up.

Preeclampsia is gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks gestation:

– Proteinuria (urinary albumin excretion in a 24 h urine sample >0.3 g/day or UACR in a random spot urine sample >30 mg/mmol (0.3 mg/mg)
– Other maternal organ dysfunction
– Acute kidney injury (serum creatinine ≥90 μmol/l; 1 mg/dL)
– Liver involvement (elevated ALT or AST >40 IU/l; 0.67 >μkat/l with or without
– right upper quadrant or epigastric abdominal pain)
– Neurological complications (e.g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)
– Hematological complications (platelet count <150000/μl, DIC, hemolysis)
– Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth)

C. Preexisting hypertension + superimposed preeclampsia

Preexisting hypertension associated with any of the above maternal organ dysfunctions consistent with preeclampsia or a further increase in BP with new-onset proteinuria

D. Antenatally unclassifiable hypertension

When BP is first recorded after 20 weeks gestation, and hypertension is diagnosed, reassessment is necessary at or after 42 days postpartum. If hypertension resolves, it should be reclassified as gestational hypertension, whereas if hypertension persists, it should be reclassified as preexisting hypertension.

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16.1.1 Definition and classification of hypertension in pregnancy

The definition of hypertension in pregnancy is based on office BP values, i.e. SBP ≥140 mmHg and/or DBP ≥90 mmHg [1072,1073] and is classified as mild (140–159/90–109 mmHg) or severe (≥160/110 mmHg), at variance from the general hypertension grading (Table 1). HDPs are further classified according to the onset of hypertension in pregnancy. Hypertension known before pregnancy or present in the first 20 weeks can be distinguished as preexisting (chronic) hypertension (essential or secondary), WCH (elevated office and normal out-of-office BP), and MH (normal office and elevated out-of-office BP). Hypertension that develops *de novo* at or after 20 weeks of pregnancy is classified as gestational hypertension, transient gestational hypertension, or preeclampsia *de novo* or superimposed on preexisting hypertension. Prepregnancy or early first-trimester BP measurements should be available to avoid misclassification of hypertensive disorders in pregnancy. Early second-trimester BP measurements in women without previous BP measurements should be interpreted with caution because of the physiological second-trimester BP fall. However, women with hypertensive BP levels after 20 weeks and unknown BP levels before 20 weeks should be managed as those with gestational hypertension. In these women with prepartum pregnancy unclassifiable hypertension, BP reassessment 6 weeks postpartum will help to distinguish preexisting hypertension from gestational hypertension. Transient gestational hypertension (diagnosed at the clinic after 20 weeks) is characterized by BP normalization after consecutive BP measurements over several hours. However, almost 40% of women with transient gestational hypertension develop sustained gestational hypertension [1074]. The preexisting form of hypertension termed MH should not be routinely searched for unless there is evidence of early pregnancy or prepregnancy HMOD [1073].

The present guidelines adopt the broader definition of preeclampsia previously endorsed by the International Society for the Study of Hypertension in Pregnancy [1073]. Accordingly, preeclampsia is a gestational hypertension in the presence of one or more of the following new-onset conditions at or after 20 weeks of gestation: (i) significant proteinuria (ACR ≥ 30 mg/g or albuminuria ≥300 mg/24 hour), (ii) maternal organ dysfunction [i.e. acute kidney injury (serum creatinine ≥1 mg/dl; 90 μ/l); liver injury (elevated transaminases >40 UI/l; 67 μkat/l) with or without right upper quadrant or epigastric

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pain; neurological manifestations (convulsions, altered mental status, blindness, scotoma or headache); hematological manifestations (platelet count <150 000/μl, disseminated intravascular coagulation, hemolysis)] and (iii) uteroplacental dysfunction (i.e. fetal growth restriction, abnormal umbilical artery Doppler waves or stillbirth). The combination of hemolysis, thrombocytopenia and elevated transaminases defines the HELLP syndrome and, therefore, additional features of preeclampsia should be evaluated. Clinicians should always consider preeclampsia a serious disease with rather unpredictable consequences. In clinical practice, it is not recommended anymore to use the previous classification of preeclampsia based on clinical features such as mild or severe.

Among women with preexisting hypertension, almost 25% will develop superimposed preeclampsia [1075]. In these women, the diagnosis is made when a de novo development of proteinuria is detected, or other maternal organ dysfunctions develop after 20 weeks. This is usually associated with an abrupt or progressive BP elevation.

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16.1.2 Blood pressure measurement in pregnancy

During pregnancy, BP should be measured in the sitting position (or in the left lateral recumbent position during labor) with an appropriately sized arm cuff at heart level using the manual auscultatory method and Korotkoff phase V for DBP [1076]. Manual auscultation remains the gold standard for BP measurement in pregnancy, because automated devices tend to under-record the BP and are unreliable in severe preeclampsia. Only devices validated specifically for pregnancy should be used [1076]. ABPM is superior to office BP measurement for predicting pregnancy outcomes [1077], and ABPM devices recommended for use in pregnancy are more accurate than those used for office measurement or HBPM. ABPM helps to avoid unnecessary treatment in WCH and is useful in the management of high-risk pregnant women with hypertension and those with diabetic or hypertensive nephropathy. According to the BUMP-1 trial [1078], among pregnant individuals at higher risk of preeclampsia, HBPM did not lead to earlier clinic-based detection of hypertension. However, the BUMP-1 trial also suggests that HBPM and office BP measurements may be used alternatively or in complement to diagnose hypertensive disorders during pregnancy in women at risk of preeclampsia. In the BUMP-2 trial [1079], HBPM was not associated with better BP control among pregnant individuals with preexisting or gestational hypertension compared with scheduled office BP measurements. Again, the BUMP-2 trial suggests that BP control according to HBPM can be used alternatively or complementarily to office BP measurements because both methods achieved similar rates of BP control.

16.1.3 Laboratory examinations in pregnancy

Basic laboratory investigations are recommended for monitoring pregnant hypertensive women, including urine analysis, blood count, hematocrit, liver enzymes, serum creatinine and serum uric acid (increased in clinically evident preeclampsia). Hyperuricemia in hypertensive pregnancies identifies women at increased risk of adverse maternal and fetal outcomes [1080]. All pregnant women should be assessed for proteinuria in early pregnancy to detect preexisting renal disease and, in the second half of pregnancy, to screen for preeclampsia. However, the presence of proteinuria is no longer a '*sine qua non*' criterion for the diagnosis of preeclampsia. Occasionally, proteinuria may anticipate a subsequent rise of BP in the natural course of preeclampsia. A dipstick test of at least 1+ should prompt evaluation of ACR in a single spot urine sample, and a value of less than 30 mg/mmol can reliably rule out proteinuria [1081,1082]. Other investigations to be considered are: (i) renal ultrasound if serum creatinine or any of the urine testing is abnormal and (ii) Doppler ultrasound of uterine and umbilical arteries (performed after 20 weeks of gestation) to detect those at a higher risk of gestational hypertension, preeclampsia and intrauterine growth retardation.

16.1.4 Prediction and prevention of preeclampsia

Women at high or moderate risk of preeclampsia should be advised to take 100–150 mg of aspirin daily (at bedtime), preferably before 16 weeks and ideally from weeks 11 to 14 until 36 weeks of gestation [1083–1086].

High risk of preeclampsia includes any of the following:

1. Hypertensive disorders during a previous pregnancy
2. Chronic hypertension
3. Chronic kidney disease
4. Type 1 or type 2 diabetes mellitus
5. Autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome
6. Assisted reproductive therapy in the current pregnancy

Moderate risk of preeclampsia includes two or more of the following risk factors:

1. Nulliparity
2. Age 40 years or older
3. Pregnancy interval of more than 10 years
4. BMI of 35 kg/m^2 or more at the first visit
5. Family history of preeclampsia
6. Multifetal pregnancy

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Beyond clinical and ultrasonographic parameters, several laboratory markers have been tested during early pregnancy for the prediction of preeclampsia:

1. Angiogenic factors [endoglin, PIGF, soluble fms-like tyrosine kinase-1 (sFlt-1) and sFlt-1/PIGF ratio]
2. Pregnancy-associated plasma protein A (PAPP-A) in association with clinical (e.g. blood pressure, maternal risk factors) and ultrasonographic characteristics (e.g. uterine artery Doppler) [1087].

However, more studies are desirable to refine the role of the above markers separately or in combination with clinical characteristics for predicting preeclampsia. Although prospective evidence is limited [1088,1089], a sFlt-1/PIGF ratio of at least 38 may be considered to exclude the development of preeclampsia when clinically suspected [1089].

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16.1.5 Lifestyle interventions

Unless contraindicated [1039], aerobic exercise (three to four times per week for 30–60 min sessions until delivery) should be recommended in pregnant women to maintain ideal body weight and reduce adverse pregnancy outcomes, including hypertensive disorders [1090–1092]. In addition, calcium supplementation at a dose of at least 1 g/day may be considered to reduce preeclampsia risk in women with low calcium intake (i.e. <600 mg/day) [1093]. Finally, although salt restriction is not advised to reduce hypertensive disorders during pregnancy, it is reasonable that women with preexisting hypertension should continue pursuing a limited salt intake diet [1085].

16.1.6 Clinical management of hypertension in pregnancy

16.1.6.1 Mild preexisting essential hypertension

During the first trimester, all RAS blockers, i.e. ACEis, ARBs or direct renin inhibitors should be stopped. Clinicians should decide on an individual basis whether drug treatment during fetal organogenesis (until week 16) overcomes the risk of fetal drug effects because any drug may be potentially hazardous during the first trimester, including alpha-methyldopa [1094]. The decision to use or discontinue antihypertensive treatment during the first and early second trimester may be individualized based on (i) the prepregnancy untreated BP levels, (ii) the early on-treatment first trimester BP values, (iii) the presence of HMOD and (iv) the BP values after a potential short-term trial of antihypertensive treatment withdrawal in selected cases. In the early first trimester, for a woman with office BP levels of <130/80 mmHg, BP-lowering treatment may be discontinued or de-escalated under a careful follow-up of BP levels until week 16. Antihypertensive treatment should restart in case of BP >140/90 mmHg at any gestational age. In preexisting hypertension, the absence of mild antihypertensive treatment during the early second trimester may prevent a profuse BP drop, potentially accompanied by miscarriage because of the physiological BP reduction during this pregnancy period.

In the large CHIPS [1095] and CHAP [1096] trials, tight versus less tight DBP control or drug treatment versus placebo in women with preexisting hypertension was more beneficial and carried no harm. Furthermore, in a posthoc analysis of the CHIPS trial [1095], the BP-lowering effect was beneficial for the primary outcome of the CHAP study, i.e. severe features, medically indicated preterm birth at less than 35 weeks gestation, placental abruption or fetal/neonatal death. The pregnancy-related composite outcome was reduced by 35% in the CHIPS and by 18%, in the CHAP trial; both studies indicating a reduction of severe preeclampsia. However, the CHIP trial observed a small-for-gestational age newborn outcome increase, albeit this was not found in the CHAP trial. This maintains alive the problem of the safety margin guaranteed by lower BP values. In light of the on-treatment BP values observed in CHIPS and CHAP trials (133/85 and 129/79 mmHg, respectively), we suggest that the threshold for BP-lowering treatment initiation or potentiation may be ≥140/90 mmHg and that in general, intensified BP-lowering should not be pursued because of the risk of fetal hypoperfusion. Labetalol and alpha-methyldopa are the first-choice drugs for BP control in women with preexisting hypertension [1086,1095,1096]. An alternative agent to use is extended-release nifedipine[1086]. However, the use of labetolol is controversial and not a choice in several countries in which it was removed from market 30 years ago, because of hepatotoxicity, which may also occur when used in pregnancy [1097].

16.1.6.2 Mild gestational hypertension

Although the CHIPS trial [1095] included a limited number of women with gestational hypertension, secondary analyses did not indicate a differential outcome effect between women with gestational and preexisting hypertension, both for primary and secondary outcomes. A treatment initiation at values ≥140/90 mmHg appears to be reasonable, while a DBP reduction to <80 mmHg is not recommended. The same drugs recommended for preexisting hypertension (see above) can be used in women with gestational hypertension.

16.1.6.3 Preeclampsia

All women with preeclampsia should be hospitalized and carefully monitored at first diagnosis. A diagnosis of preeclampsia at or after 37 weeks of gestation underscores the need for hypertension control and prompt delivery. Clinically stable women with preeclampsia before 37 weeks of gestation can be managed on an outpatient basis. However, despite optimal antihypertensive treatment, delivery is indicated even before 37 weeks, whenever hypertension remains severe. Delivery induction before 37 weeks is also recommended with (i) emerging maternal (neurological, hematological or cardiovascular) manifestations or (ii) a nonreassuring fetal status [1073].

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The management of hypertension in preeclamptic women with mild or severe hypertension does not differ from women without preeclampsia (see above sections), although evidence is limited. Preeclampsia with severe features (severe hypertension with or without proteinuria, any hypertension grade with neurological, hematological, or cardiovascular complications, liver dysfunction or renal dysfunction) should be managed with $MgSO_4$ infusion (and delivery) to prevent eclampsia. Infusion of $MgSO_4$ for the 24 h postpartum seems reasonable for prevention purposes [28], and $MgSO_4$ remains the treatment of choice for eclamptic seizures. Hypertension control can be achieved by labetalol (unless contraindicated) alone or with the combination of labetalol, nifedipine extended-release and/or alpha-methyldopa.

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16.1.6.4 Severe hypertension

In severe hypertension, hospitalization is mandatory to allow gradual BP reduction to <160/105 mmHg and exclude preeclampsia. Continuous cardiotocographic monitoring is also mandatory [1073]. The selection of antihypertensive drugs and the route of administration depends on (i) the initial diagnosis, (ii) the expected delivery time and (iii) the presence or absence of preeclampsia and also preferences and experience of attending physicians. A recent comprehensive network meta-analysis indicated that nifedipine could be recommended as a strategy for BP management in pregnant women with severe hypertension and that labetalol and hydralazine showed in fact limited efficacy [1098]. However, in cases of preeclampsia with severe features, persistent severe hypertension or recurrent severe hypertension despite orally administered agents, i.v. application of labetalol or urapidil should be used before, during and frequently after delivery. In case of preeclampsia without severe features or severe hypertension without preeclampsia, an effective and gradually escalated antihypertensive multiple drug regimen should be used to lower BP to target [1095], while before delivery, hydralazine should be avoided because of its association with more adverse perinatal effects than other drugs. Hydralazine should be reserved to cases of unavailability of labetalol or urapidil, failure to reduce BP, II or III degree AV block, severe HF, asthma, bradycardia or severe postpartum hypertension. Sodium nitroprusside should be used as the last resource because of an increased risk of fetal cyanide poisoning with prolonged administration. When preeclampsia is associated with pulmonary edema, the drug of choice is nitroglycerin, given as an i.v. infusion of 5 mg/min and a gradual increase every 3–5 min to a maximum dose of 100 mg/min [1099]. In a pregnant woman with severe hypertension living in a rural area away from a maternity hospital, 10 mg short-acting nifedipine may be administered orally and a second dose should be given after 1 h if severe hypertension persists. Sublingual short-acting nifedipine is contraindicated.

16.1.6.5 Preexisting secondary hypertension

Women with known preexisting hypertension should receive preconception counseling, including ruling out secondary hypertension causes. Renal Doppler ultrasounds should be performed in all women with hypertension planning a pregnancy. In women diagnosed with fibromuscular dysplasia (FMD) before pregnancy, further evaluation of other vascular beds should be performed to exclude any additional arterial damage [341]. Achievement of optimal BP control and, if indicated, renal artery revascularization are recommended before conception, because undiagnosed and untreated FMD can increase the risk of pregnancy-related complications [1100].

Women with primary aldosteronism should be discouraged from pregnancy because of the competitive antagonism of progesterone and aldosterone in excess at the level of the id mineralocorticoid receptors [1101]. However, close laboratory work-up should be performed in women with known preconception hyperaldosteronism or clinical suspicion of the disease in early pregnancy. After the second trimester, eplerenone on top of the usual BP-lowering treatment may be considered for uncontrolled hypertension with or without hypokalemia [1102]. The drop in progesterone levels postpartum may increase BP and aggravate hypokalemia [1101,1102].

Pheochromocytoma in pregnancy is one of the most life-threatening conditions for the mother and fetus. Although extraordinarily rare, with a frequency of 0.002% of all pregnancies, this disease is notorious for its devastating consequences [1103]. As in nonpregnant patients, the signs and symptoms are quite variable and poorly specific, with hypertension being one of the most dominant signs. If undiagnosed, maternal and fetal mortality is around 50%. Early detection and proper treatment during pregnancy decrease maternal and fetal mortality to <5 and <15%, respectively. For the biochemical diagnosis, plasma or urinary metanephrines are the tests of choice, as they have the highest sensitivity and lowest falsely negative diagnostic value. For reliable localization, MRI is the most suitable technique with a sensitivity over 90%. When a pheochromocytoma is diagnosed during pregnancy, laparoscopic adrenalectomy should be performed after 10–14 days of drug pretreatment as in nonpregnant patients (alpha-adrenoreceptor blockade combined with beta-adrenergic blockade some days later). If the pheochromocytoma is diagnosed in the third trimester, the patient should be managed until the fetus is viable, using the same drug regimen as for the surgical preparation. Caesarian section with tumor removal in the same session or at a later stage is preferred as vaginal delivery may be associated with higher mortality.

HDP are observed in almost half of pregnant women with CKD. Therefore, it is important to know the degree of CKD, level of eGFR or degree of proteinuria, before pregnancy rather than the underlying cause [1104]. Women without significant proteinuria, normal BP levels at early pregnancy and mild renal impairment usually experience an uneventful pregnancy course. By contrast, women with moderate or more advanced CKD are at increased risk of fetal complications as well as maternal complications and deterioration of the already impaired kidney function [1105]. A woman with a GFR of less than 40 ml/min per 1.73 m^2 and proteinuria of more than 1 g/day should be considered at very high risk for pregnancy and kidney outcomes, including kidney replacement therapy.

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16.1.7 Blood pressure during puerperium

Postpartum hypertension is common during the first week. Also, in women with a normotensive pregnancy, a BP elevation during the first-day postpartum is usually associated with (i) the use of vasoactive drugs to favor uterine contraction (oxytocin, methergine), (ii) blood transfusions, (iii) the physiological uterine 'auto-transfusion phenomenon' or (iv) an excessive fluid intake. In women with preeclampsia, a reduced diuresis during 12–36 h postpartum is observed because of a delayed fluid redistribution associated with a greater colloid osmotic pressure drop compared to a normal pregnancy [1106]. In a small randomized placebo-controlled trial on women with hypertension in pregnancy, administration of furosemide 20 mg daily during the first 5 days postpartum prevented 1 woman out of 13 from developing postpartum hypertension [1107]. However, a wide use of furosemide postpartum needs confirmation from larger studies.

During puerperium, BP levels usually normalize within the first 6 weeks in women with gestational hypertension or preeclampsia. By contrast, women with preexisting hypertension or superimposed preeclampsia perpetuate elevated BP values beyond the 6 weeks of puerperium. A further unusual postpartum hypertension phenotype is the so-called 'late postpartum hypertension' phenotype, which appears 6 months after delivery and resolves several months later [1108]. The pathogenesis of this condition is unknown, but one possibility is that the return of postpartum menses increases BP through a spillover of the excess of progesterone and an activation of mineralocorticoid receptors. This is similar to the Geller syndrome, which exhibits an exacerbated hypertension in the third trimester of pregnancy [1108,1109].

All antihypertensive agents used during pregnancy may be used during puerperium to achieve BP control. However, the use of ACEis in the postpartum period should be reserved for women with cardiorenal comorbidities and is, thus, not recommended in healthy women with hypertensive disorders during puerperium. Methyldopa should be used with caution because of the risk of postpartum depression.

16.1.8 Postpartum hypertension and breastfeeding

Antihypertensive drugs taken by the nursing mother are excreted into breast milk, mostly in very low concentrations. Proper information on prescribable drugs in breastfeeding women is important [1072,1110]. Nifedipine and verapamil are considered compatible with breastfeeding. Although diuretics are not contraindicated, they may be associated with reduced milk production. Similarly, alpha-methyldopa is compatible with breastfeeding, although it is not a drug of first choice during puerperium because it increases the risk of postpartum depression. ACEis are compatible with breastfeeding and can be used in women with HDP and underlying CVD or CKD. ARBs are not currently recommended in lactating women because of a limited safety evidence [1110].

16.1.9 Risk of recurrence of hypertensive disorders in a subsequent pregnancy

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

16.1.10 Long-term cardiovascular consequences of hypertensive disorders in pregnancy

Several registries [1111,1112] have demonstrated that pregnant women with hypertension and hypertensive disorders are at an increased risk for future CV events [1111,1112]. Compared to women with normotensive pregnancies, the risk shows a multifold increase in pregnant hypertensive women [33,1113], and the increase also involves the risk of developing future sustained hypertension [48,1114]. A meta-analysis of cohort studies showed that preeclampsia with more severe features was associated with a greater extent of future disease compared with preeclampsia with less severe features [49]. A genome-wide genetic association study using Mendelian randomization provided genetic evidence supporting an association between HDP and higher risk of CAD and stroke, which is only partially mediated by cardiometabolic factors. This study supports classification of HDPs as risk factors for CVD [1115]. In women who experienced HDP, lifestyle modifications are indicated to reduce the risk of complications in subsequent pregnancies as well as to reduce CV risk in general [33,1113]. Annual visits by the primary care physician, frequent BP measurements and CV risk assessment are recommended.

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Hypertension management in pregnancy

Recommendations and statements	CoR	LoE
In women with hypertensive disorders in pregnancy, initiation or intensification of drug treatment is recommended when SBP is ≥ 140 mmHg and/or DBP ≥ 90 mmHg.	I	C
In women with pre-existing hypertension (with or without superimposed pre-eclampsia), BP should be lowered to a target below 140/90 mmHg.	I	A
In women with gestational hypertension (with or without pre-eclampsia), BP should be lowered to a target below 140/90 mmHg.	I	C
In women with hypertensive disorders in pregnancy, too marked BP-lowering should be avoided. On-treatment DBP <80 mmHg is not recommended.	III	C
Labetalol[a] and α-methyl-DOPA are the first choice BP-lowering agents for hypertensive disorders in pregnancy unless contraindicated.	I	B
Extended-release nifedipine is recommended as an alternative BP-lowering agent during pregnancy.	I	B
Up-titration of monotherapy should precede any combination drug treatment.	II	C
Combination drug treatment between labetalol, extended-release nifedipine, or α-methyldopa may be reasonable to achieve the desirable BP target after the failure of up-titrated monotherapy.	II	C
ACE inhibitors, ARBs, or direct renin inhibitors are not recommended during pregnancy.	III	C
Aspirin (100-150 mg, at bedtime, weeks 11-35) should be administered in pregnant women at high or moderate risk of pre-eclampsia.	I	A
Severe hypertension (≥160/110 mmHg) in a pregnant woman requires prompt hospital admission.	I	C
In pre-eclampsia with severe features, magnesium sulfate should be administered without delay.	I	C
HBPM can be a reasonable alternative to conventional office BP measurement to detect new-onset hypertension in women at risk for pre-eclampsia without pre-existing hypertension.	II	B
HBPM can be a reasonable alternative to conventional office BP measurement to achieve BP control in women with gestational or pre-existing hypertension.	II	B

[a]Not available in several countries

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16.2 Hypertensive urgencies and emergencies

The proper management of patients who come to the Emergency Department for BP elevation faces a number of difficulties. A major challenge for the physician is to identify and discriminate the patients at immediate risk of CV or kidney complications from those in whom the BP elevation does not carry any immediate risk for health. While the former patients require immediate attention and treatment, the latter are in no need of hospitalization or even treatment. FU and treatment of patients after discharge from the Emergency Department is still poorly defined and often inadequate [1116,1117].

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16.2.1 Definitions of hypertensive urgencies and emergencies

Hypertension emergencies are conditions in which severe hypertension (grade 3) is associated with acute symptomatic HMOD. Hypertension emergencies, can be life-threatening and require immediate intervention to lower BP, usually with intravenous (i.v.) therapy [1117]. The rate of the increase in BP may be at least as important as the absolute BP level in determining the clinical severity of the situation and the magnitude of organ injury [1117,1118]. Typical clinical presentations of a hypertension emergency are:

1. Severe hypertension associated with conditions that need intensified BP management: acute stroke (hemorrhagic or ischemic/thromboembolic), aortic aneurysm or dissection, acute HF, acute coronary syndrome and kidney failure. These emergency conditions are compatible also with a relatively modest BP increase, which is sufficient to precipitate organ failure.
2. Hypertension caused by phaeochromocytoma or exogenous sympathomimetics substances (e.g. substance abuse). Ingestion of sympathomimetic drugs such as meta-amphetamine or cocaine may precipitate acute and severe BP increases that may result in hypertension emergencies when there is evidence of acute HMOD.
3. Severe forms of HDP, including preeclampsia/eclampsia with a HELLP syndrome (Section16.1 [1117]).

Malignant hypertension with or without thrombotic microangiopathy or acute kidney failure is a hypertensive emergency characterized by small artery fibrinoid necrosis in the kidney, retina and brain. There might be also funduscopic changes (flame hemorrhages and papilloedema), microangiopathy, disseminated intravascular coagulation, encephalopathy (15% of cases) or acute HF [1119]. Whether this traditional definition fully corresponds to the extent of the microvascular damage is still a matter of debate [1120]. The term 'malignant' reflects the very poor prognosis of this condition if untreated [1119,1121–1123]. The Birmingham, Bordeaux and Amsterdam malignant hypertension registries have shown that malignant hypertension is rising in Europe [1117,1119,1124]. The emergency symptoms depend on the organs affected and may include headache, visual disturbances, dizziness and other neurological deficits as well as chest pain and dyspnea. In patients with hypertensive encephalopathy, the presence of somnolence, lethargy, tonic clonic seizures and cortical blindness may precede loss of consciousness. Focal neurological lesions are rare and should raise the suspicion of acute stroke [4,1117,1118,1125,1126]. An acute stroke, especially intracerebral hemorrhage, is associated with severe hypertension and has often been included among the hypertensive emergencies. However, it is an emergency that requires specific strategies to govern the BP reduction, because of the complex effects that its magnitude, speed and relationship with the existing BP level can have on the ischemic brain area surrounding the core brain lesion (Section 17.5). This condition should be handled by specialized (stroke) units.

The term 'hypertension urgency' has been used to describe severe hypertension in patients in whom there is no evidence of acute HMOD [1117,1121–1124]. The burden of hypertensive urgencies is not well defined mainly because of the different criteria used for the definition of this condition. Furthermore, the ambiguity of the term 'hypertension urgency' versus the so called 'hypertensive crisis' has influenced epidemiological data [1116,1122–1124].

For patients with a suspected hypertension emergency, the diagnostic work-up is shown in Table 23.

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TABLE 23. Diagnostic work-up of hypertension emergencies and urgencies

Common tests
Fundoscopy
ECG 12 leads
Hemoglobin, platelet count, fibrinogen, peripheral smear
Creatinine, eGFR, electrolytes, LDH, haptoglobin
UACR, urine microscopy for red blood cells, leucocytes and/or casts
Pregnancy test in women of child-bearing age
Specific tests
Troponin, (suspected HF and/or acute coronary syndrome) NT-proBNP
Chest X-ray or ultrasound (pulmonary congestion and fluid overload)
Echocardiography (heart failure, acute ischemia, aortic dissection)
CT angiography of thorax and/or abdomen in suspected aortic disease (aortic dissection)
CT or MRI brain (nervous system involvement)
Kidney ultrasound (renal impairment or suspected renal artery stenosis)
Urine drug collection (cocaine or methamphetamine use)

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16.2.2 Hospital work-up, treatments and follow-up

Hypertensive emergencies, including BP ≥170/110 mmHg in a pregnant woman, should be hospitalized. Except for acute BP lowering in stroke, there are no RCTs on the management of these conditions. It should first be established, which organs are affected to determine whether (i) they require any specific intervention other than BP lowering and (ii) there is a precipitating cause for the acute rise in BP that might affect the treatment plan (e.g. pregnancy). Then a decision should be made on the timescale and magnitude of the BP lowering as well as on the type of drug treatment that might be appropriate. Intravenous treatment with a drug that has a short half-life is ideal to allow careful titration of the BP response, keeping the patient in a close clinical area under continuous hemodynamic monitoring (Table 24). Rapid uncontrolled BP lowering is not recommended [4] and, thus, low initial doses with cautious dose uptitration should be used. Oral therapy with ACEis, ARBs or BBs (at low initial doses and cautious upward titration) is sometimes effective in malignant hypertension because the RAS may be activated by the associated kidney ischemia [1119]. Recommended drugs are shown in Table 25, and further details can be found in dedicated publications [4,1117,1127].

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TABLE 24. Hypertensive emergencies requiring immediate BP-lowering with i.v. drug therapy

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

[a]Not available in several countries.

TABLE 25. Drug types, dose and characteristics for treatment of hypertension emergencies

Drug	Onset of action	Duration of action	Dose	Contraindications	Adverse effects
Esmolol	1 min	10–30 min	0.5–1 mg/kg i.v. bolus; 50–300 μg/kg/min i.v. infusion	Second-degree or third-degree AV block, systolic heart failure, asthma, bradycardia	Bradycardia
Metoprolol	1–2 min	5–8 h	2.5–5 mg i.v. bolus over 2 min; may repeat every 5 min to a maximum dose of 15 mg	Second-degree or third-degree AV block, systolic heart failure, asthma, bradycardia	Bradycardia
Labetalol[a]	5–10 min	3–6 h	10–20 mg i.v. bolus in 1 min; incremental doses ≥20 mg may be administered i.v. at 10 min intervals (max 80 mg) or 1–3 mg/min i.v. infusion until goal BP is reached	Second-degree or third-degree degree AV block; systolic heart failure, asthma, bradycardia	Bronchocostriction, fetal bradycardia
Fenoldopam	5–15 min	30–60 min	0.1–0.3 μg/kg/min i.v. infusion, increase every 15 min with 0.1 μg/kg/min increments until goal BP is reached	Caution in glaucoma	
Clevidipine	2 min	10 min	1–2 mg/h i.v. infusion, increase every 2 min with 2 mg/h until goal BP, then titrate by smaller increments every 5–10 min		Headache, reflex tachycardia
Nicardipine	5–15 min	4–6 h	5–15 mg/h i.v. infusion, starting dose 5 mg/h, increase every 15–30 min with 2.5 mg until goal BP, maximum 15 mg/h	Liver failure	Headache, reflex tachycardia
Nitrogly-cerine	1–5 min	5–10 min	5–200 μg/min i.v. infusion, 5 μg/min increase every 5 min		Headache, reflex tachycardia
Nitro-prusside	Immediate	1–3 min	0.3–0.5 μg/kg/min i.v. infusion, increase by 0.5 μg/kg/min every 5 min until goal BP (maximum dose 10 μg/kg/min)	Liver/kidney failure (relative)	Cyanide intoxication
Enalaprilat	5–15 min	4–6 h	0.62–1.25 mg i.v. bolus given over 5 min every 6 h	History of angioedema	
Urapidil	3–5 min	4–6 h	12.5–25 mg i.v. bolus; 5–40 mg/h as continuous infusion		
Clonidine	30 min	4–6 h	0.2–0.5 μg/kg/min i.v.		Sedation, rebound hypertension
Phentol-amine	1–2 min	10–30 min	1–5 mg i.v. bolus or continuous i.v. infusion at a rate of 0.5–20 μg/kg/min		Tachyarrhythmia, chest pain

[a]Not available in serveral countries.

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Patients with hypertensive urgencies do not usually require hospitalization. However, they require BP reduction, which can be obtained by oral administration of antihypertensive drugs, aimed at lowering BP gradually over 24–48 h. Oral treatment may include reinstitution or intensification of previous treatment or starting new treatment. DHP-CCBs are suggested as first choice in an untreated patient as they have few or no contraindications and do not interfere with the diagnostic work-up for secondary hypertension. Sublingual, rapidly acting, administration of nifedipine should be avoided because the degree of BP decrease cannot be anticipated and may often be too fast and larger than desirable [4,1117]. Clinical surveillance in a short-stay observation unit is usually appropriate before discharge [1128]. As BP may remain elevated after Emergency Department discharge [1129], these patients need subsequent office and out-of-office BP measurements.

The survival of patients with hypertension emergencies has improved strikingly over past decades [1119], but these patients remain at high risk [4,1119,1122–1126,1130]. After discharge from hospital, when BP has reached a safe and stable level on oral therapy, an early FU and then frequent (at least monthly) medical visits and supervision by a hypertension specialist or a specialized hypertension center are recommended [4,1131,1132].

16.2.3 Blood pressure in the emergency department

BP measurements in the emergency department usually do not follow guidelines and may, thus, be inaccurate [4]. BP elevation is common, and hypertensive BP values in 48% of all patients referred to the Emergency Department during a 1-year period have been reported [1133]. However, the clinical significance of a BP elevation in the Emergency Department is not entirely clear, and available evidence is not univocal. In many patients, even a marked BP elevation is restored to normal when pain, distress and anxiety are relieved, thus originating from an alerting reaction [1134,1135]. However, some studies have not shown a close relationship of BP with pain, stress or anxiety in the Emergency Department [1090]. In addition, although in general BP values in the Emergency Department are not recommended for stratification of CV risk, an association of Emergency Department-measured BP and CV outcomes has been reported [1131]. In all patients, previous intake of some medications (e.g. NSAIDs) or other substances that may cause a BP elevation or oppose the BP reduction by treatment should be searched for. If BP is not severely elevated and the clinical picture does not suggest a hypertensive emergency, unattended BP measurements should be performed with the patient alone in a separate quiet room because unattended BP measurements are usually not accompanied by an alerting reaction [95]. BP measurements should be repeated at intervals for at least an hour. Evidence is available that in 30% of the patients, BP decreases to grade 2 or lower values in 30 min [1128].

16.3 Perioperative hypertension and its management

Because of its high prevalence and association with age, hypertension is an extremely common condition in patients undergoing surgery, in several cases with no awareness of the high BP status by the patient. A BP elevation at the time of a surgical intervention is not an innocent association because severe hypertension has been found to be accompanied by an increased incidence of surgery-related complications, including bleeding [1136]. Thus, at the presurgery visits, accurate office BP measurements and implementation of the other steps required to clinically characterize hypertension are mandatory. Although no study has defined the BP threshold on which to base the decision, it seems appropriate to suggest not to avoid or postpone surgery in untreated patients with grade 1 hypertension or in those in whom treatment has achieved controlled or almost controlled BP values. In untreated patients with grade 2 or 3 hypertension or in badly uncontrolled treated patients, surgery should be deferred until BP control is reached. Except for emergency surgical interventions, this should be the rule when SBP is $\geq$180 mmHg or DBP $\geq$110 mmHg [160,1137]. Decision about deferral may find help from out-of-office BP measurements (ABPM or HBPM) because a white-coat effect may be frequent in patients with scheduled surgery [1138]. Data are not entirely univocal, but it seems appropriate not to discontinue antihypertensive drugs during the days before surgery, although discontinuation has been advocated for fear of arrhythmias, volume depletion, electrolyte alterations, bradycardia and intra-operative and postoperative hypotension. Discontinuation should also be avoided in the case of BB treatment preceding noncardiac or cardiac surgery, as preexisting BB treatment has been reported to have a protective effect [1139], while abrupt discontinuation may lead to rebound heart rate and perhaps BP elevations [1140,1141]. If for any reason BBs are discontinued, transdermal clonidine may attenuate the rebound phenomenon. Continuation of antihypertensive treatment during the perioperative period may also minimize BP fluctuations, which in a RCT that enrolled patients undergoing abdominal surgery was found to be associated with surgery-related complications [1142].

Hypertension may occur during induction of anesthesia, the intubation maneuvers, the operation or in the early postanesthesia period. Induction of anesthesia generates pain and stress, and intubation evokes reflexes that may lead to cardiac and vascular sympathetic activation, increasing the odds of a rise in BP and heart rate as well as of excessive BP fluctuations and arrhythmias [1136]. BP increases may also be favored by i.v. application of vasopressor drugs during surgery. On the other hand, induction and maintenance of anesthesia may also cause vasodilatation, volume depletion and BP reduction, having blood loss as an adjunctive factor. Both intraoperative hypotension and hypertension may have an unfavorable effect on perioperative complications, also because of impairment of blood flow autoregulation, especially in old patients [1143]. No consensus is available on thresholds and targets to guide intraoperative BP management. As mentioned above, throughout the perioperative period, the BP management should focus on keeping BP within a safety

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range, avoiding large BP fluctuations and in general pursuing hemodynamic stability. During the postoperative period, hypertension may be present during the first 2 h and can usually disappear in a few hours after resumption of antihypertensive treatment. Oral BBs may be restarted immediately. Oral diuretics and RAS blockers can be restarted within 48 h after surgery, after assessing the BP level and fluid status, and according to the type of surgical intervention (cardiac versus noncardiac).

Perioperative hypertension and its management

Recommendations	CoR	LoR
It is recommended that newly diagnosed hypertensive patients who are scheduled for elective surgery should be preoperatively screened for HMOD (ECG, kidney function parameters, and evidence of heart failure) and CV risk.	I	B
Preexisting antihypertensive treatment should be continued in most patients. This helps to avoid large BP fluctuations in the perioperative period.	I	C
In selected patients, transient preoperative discontinuation of RAS-blockers or diuretics might be considered in patients with hypertension undergoing non-cardiac surgery.	II	C
Abrupt discontinuation of pre-existing therapy with beta-blockers or centrally acting agents (e.g. clonidine) is potentially harmful and is not recommended.	III	B
Non cardiac surgery should not routinely be deferred in patients with grade 1 or 2 hypertension (SBP < 180 mmHg and DBP < 110 mmHg).	III	C

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17. HYPERTENSION IN ESTABLISHED CARDIOVASCULAR DISORDERS

17.1 Coronary artery disease

Hypertension is one of the major risk factors for CAD in its various clinical aspects (myocardial infarction, angina pectoris, acute coronary syndrome and chronic coronary syndromes), together with other risk factors including smoking, dyslipidemia and type-2 diabetes [529,1144]. There is a linear correlation between BP levels and the risk of CAD within a wide range of BP values, starting from 110 to 115 mmHg SBP and 70 to 75 mmHg DBP [35,1145]. Hypertension explains approximately 25% of the risk of myocardial infarction at a population level. The presence of CAD classifies a patient at a very high CV risk, even if SBP is below 140 mmHg or DBP below 90 mmHg. A large number of outcome-based RCTs and their meta-analyses have shown not only that BP-lowering treatment significantly reduces the risk of CAD (although the relative size of the reduction is less than that of stroke and HF [1146]) but also that the benefit extends to overall CV outcomes [1147]. In several outcome-based RCTs on antihypertensive treatment, CAD patients were a large fraction of the recruited patients and had an initial office SBP $\geq$140 mmHg or DBP $\geq$90 mmHg. Thus, antihypertensive treatment should be initiated at these BP levels [1148]. Whether lower BP thresholds for treatment should be considered has been a matter of debate for years because studies showing CV protection by BP reductions from baseline BP values <140/90 mmHg (usually in the high-normal BP range) have been mostly obtained in studies in which patients were already on background antihypertensive treatment [556]. However, there is evidence from a meta-analysis of RCTs that BP-lowering treatment in largely untreated patients with high-normal BP did not lower the risk of events if their CV risk was below the very high risk category but it reduced the incidence of stroke (and stroke plus CAD) if the risk was very high due to a history of CV events. The previous

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event was mainly a myocardial infarction [1149], which makes CAD patients candidates for antihypertensive drug treatment when BP values are in the high-normal range. In this meta-analysis, the benefit was obtained with an SBP reduction of a few mmHg, which means that it was established at an average SBP target close to or less than 130 mmHg. This finds confirmation in a number of, although not in all, dedicated trials in CAD or in trials including CAD patients, which have shown that in these patients, outcomes further decrease if target BP values within the range between 120 and 129 mmHg or 70 and 79 mmHg are achieved [610]. Thus, the present guidelines recommend these values as the target to pursue in CAD patients, based on RCTs performed in patients in whom a history of CAD was largely predominant [522,1149]. As already mentioned (Sections 9 and 10), it should not be forgotten that CAD patients are almost invariably under treatment with BP-lowering drugs such as RAS blockers, BBs or CCBs, which are part of the CAD treatment strategy, independently from their BP values and for benefits regarded as unrelated to BP reductions [556,1149]. Thus, at a practical level, the question is not whether to give BP-lowering drugs to CAD patients with a high-normal BP, but to modulate their number and doses to reduce BP to the recommended target. Posthoc analyses of trials or prospective registries exclusively or largely based on CAD patients have not infrequently reported a J-shaped or U-shaped outcome incidence at achieved BP values <120/70 mmHg or even <130/80 mmHg [535,1147,1150–1153]. It has also been reported that, within the above SBP values, a J-curve can be observed for myocardial infarction but not for cerebrovascular events [1152], suggesting an impaired ability to maintain myocardial perfusion at reduced BP values in coronary disease [1154,1155]. In a post hoc analysis of the INVEST trial, the J-curve for myocardial infarction was more evident in patients without than in those with coronary revascularization [1135]. Given the limitations of the post hoc and in general the observational approach to treatment effects, this should not discourage clinicians from pursuing the recommended BP target. However, attention to symptoms and signs of possible coronary underperfusion can be appropriate because at lower BP targets, there may be a small safety margin for adequate coronary perfusion, and more so if, as in CAD, coronary vessels are anatomically abnormal. Furthermore, LVH is common in CAD patients, and the increased cardiac oxygen needs and impaired microcirculation associated with this condition may favor ischemia at perfusion pressures that are too low [532,534] (Section 10.5).

Prevention of coronary artery disease (CAD) in hypertension

Recommendations and statements	CoR	LoE
Antihypertensive treatment of hypertension is recommended to effectively prevent CAD	I	A
Antihypertensive treatment with all major antihypertensive drug classes including ACEis, ARBs, BBs, CCBs and Thiazide/Thiazide-like diuretics can be used for the prevention of CAD.	I	A

17.1.2 Treatment of hypertensive patients with coronary artery disease

BBs, DHP-CCBs and nondihydropyridine CCBs are the preferred drugs for the treatment of hypertension in symptomatic CAD patients with angina, with a DHP-CCB and a BB in combination if needed. In patients with a recent myocardial infarction, BBs also improve prognosis [1156–1159] and should be prescribed unless contraindicated. The duration of the BB-related benefits is uncertain. However, in the absence of specific inconveniences, there is no reason to stop BB therapy [1158,1160,1161]. In this context, it is important to mention that increased heart rate correlates linearly with CV events, and the benefit of heart-rate reduction as a treatment goal in CAD patients has been demonstrated by several drugs including BBs [595,1162]. Thus, targeting a lower heart rate to a value below 80 bpm and close to 70 bpm, seems a wise additional treatment goal in hypertensive patients with CAD. BBs or non-DHP-CCBs can be used for this purpose. ACEis have been shown to reduce CV outcomes in high CV risk patients including patients with CAD in RCTs [1163,1164], which supports their use in CAD as part of the antihypertensive combination therapy, while ARBs can substitute ACEis in patients with hypertension and CAD who are intolerant to ACEis (Fig. 15).

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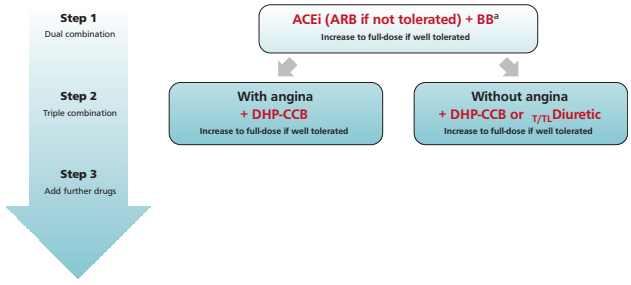


FIGURE 15 BP lowering therapy in patients with Hypertension and Coronary Artery Disease.
[a]Target heart rate below 80 beats per minute, if BBs are contraindicated or not tolerated consider use of non-DHP CCB at any step instead of DHP-CCB.

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Treatment of hypertension in coronary artery disease (CAD)

Recommendations and statements	CoR	LoE
In adult patients with CAD, drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg).	I	A
The same treatment targets as in the general hypertensive population apply also to patients with CAD.	I	A
In patients with hypertension and CAD it is recommended to use drugs with documented favorable effects in CAD such as ACEis (ARBs if not tolerated) or BBs.	I	A
In patients with hypertension and CAD with angina pectoris, BBs and both DHP and non-DHP CCBs are particularly useful.	I	A
To lower heart rate to a range between 60 to 80 beats per minute is an additional treatment goal in hypertensive patients with CAD for which BB or non-DHP CCBs can be used.	I	B
BBs should usually not be combined with non-DHP CCBs (e.g. diltiazem or verapamil).	III	C
In patients with very low heart rate (< 50 beats per min) BB or non-DHP should be not initiated.	III	C
Hypertension and LVH is frequently associated with myocardial ischaemia and no obstructive coronary artery disease (INOCA) including patients with myocardial infarction with no obstructive coronary artery disease (MINOCA). Treatment with RAS-inhibitors, BBs, and CCBs can be used in this condidtion.	II	B

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17.2 Heart failure

17.2.1 Prevention of heart failure in hypertension

Prevention of HF received less attention than prevention of stroke and myocardial infarction until a review of the placebo-controlled RCTs in hypertension [1165] showed a HF reduction of 50% or more by antihypertensive treatment. Considering that RCTs were analyzed as 'intention to treat' and not 'per treatment' protocol, this indicated that the true prevention of HF was probably greater because large fractions of patients in the RCTs stopped taking the drugs they were randomized to, or changed from placebo to active treatment [1165]. The mechanisms for prevention of HF were explained by prevention of CAD (in particular, myocardial infarction), prevention of LVH, regression of LVH during antihypertensive treatment [227,228] or prevention of arrhythmias, mostly AF with rapid ventricular frequency on top of CAD or LVH. Prevention of LVH development and its regression are important goals for antihypertensive treatment and have a profound impact on prevention of HF [192]. Treatment with all major antihypertensive drugs reduces LVH, although BBs and diuretics may be relatively less effective [192]. Several analyses from the LIFE study have shown that in patients with hypertension, LVH regression induced by antihypertensive treatment was accompanied by improvements in indices of both diastolic function and systolic performance [230]. Additionally, reduction in LVH was associated with lower rates of clinical endpoints including new-onset HF independently of BP reduction [227]. Although similar evidence regarding LVH regression in patients with HFpEF has not yet been collected, available data in hypertensive patients with LVH support also pursuing LV mass reduction in patients with HFpEF, using strategies that lower cardiac afterload, such as reduction of peripheral vascular resistance and central BP [192]. However, it has also been reported that even after effective LVH regression, CV risk remains higher than for control individuals [1166], emphasizing the importance of relying on LVH prevention rather than treatment.

A few RCTs have received special attention because of the HF findings. Their results, as well as those of large meta-analyses of RCTs [80,579], can be summarized as follows. One, the protective effect of BP-lowering treatment on HF extends to the very old population in which the size of the protection appears to be particularly marked. HF is markedly reduced by lowering SBP to <140 mmHg, but single RCTs and large meta-analyses have shown that, compared with a target SBP within the 130–139 mmHg range, an SBP reduction within the 129–120 mmHg range is accompanied by a significant and sizeable incremental benefit for HF. Unfortunately, this is accompanied by a noticeable increase of side effects (especially an increase of adverse kidney effects) leading to treatment discontinuation. Three, in hypertensive patients, diuretics, BBs, ACEis, ARBs and CCBs all have all been shown to reduce HF compared with a control group, with the protection exerted by diuretics extending to Thiazides, chlortalidone and indapamide. This strongly suggests the major protective factor to be BP lowering 'per se'. Four, meta-analyses of RCTs have reported that for a similar BP reduction, diuretics have a greater and CCBs a lower protective effect compared to the remaining drugs. However, these findings should be interpreted with caution, because the greater protective effect of diuretics might have derived from the previously discussed results of the large ALLHAT trial [563,1167] as well as by a possible masking effect of diuretics on HF symptoms and signs, at least in the early and milder HF phase. Ankle edema (especially if associated with obesity or shortness of breath) may have also favored a spurious diagnosis of HF with CCBs. The overall conclusion is that all major antihypertensive drug classes importantly prevent incident HF in patients with hypertension and that thus all can be used for this purpose. The BP threshold and target for treatment do not differ from those recommended for general CV prevention by antihypertensive treatment. Alpha-1 blockers (doxazosin and others) can be added to the major drug classes, especially in combination with a Thiazide/Thiazide-like diuretic and a BB to minimize fluid retention and reflex tachycardia, i.e. symptoms resembling or explained by HF. The adverse effect of doxazosin on incident HF reported by ALLHAT [563,1167] has not been confirmed by its use in patients with difficult BP control in the ASCOT trial [597].

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Prevention of heart failure in hypertension

Recommendations and statements	CoR	LoE
Treatment of hypertension is recommended to effectively prevent heart failure.	I	A
Hypertension treatment with all major antihypertensive drug classes, including ACEis, ARBs, BBs, CCBs and Thiazide/Thiazide-like diuretics, can be used for the prevention of heart failure.	I	A
Alpha-1 blockers (e.g. doxazosin) can be used for the prevention of heart failure in hypertension, preferably in combination with Thiazide/Thiazide-like diuretics and BBs to avoid fluid retension and tachycardia.	I	B
SGLT2is should be used for the prevention of heart failure in patients with type-2 diabetes.	I	A

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17.2.2 Heart failure with reduced ejection fraction (HFrEF)

Hypertension is a major risk factor for HFrEF, against which antihypertensive treatment has a major protective effect. However, in patients with clinically manifest HFrEF, an elevated BP is an uncommon problem because the reduced cardiac output counterbalances or overrides the increase in systemic vascular resistance typical of hypertension, usually leading to a normal or reduced BP. According to outcome-based RCTs, four drug classes in combination therapy are recommended for treatment of HFrEF in current HF guidelines [1168,1169]: RAS-blockers (ACEis or ARNI), BBs, steroidal MRAs and SGLT2is (Fig. 16). With the exception of SGLT2is, all these drugs are also recommended for the treatment of hypertension (Fig. 14). ACEis and BBs are part of the basic antihypertensive treatment strategy, while MRAs are recommended in patients with resistant hypertension (Section 12). Additionally, diuretics are recommended to manage fluid balance and reduce

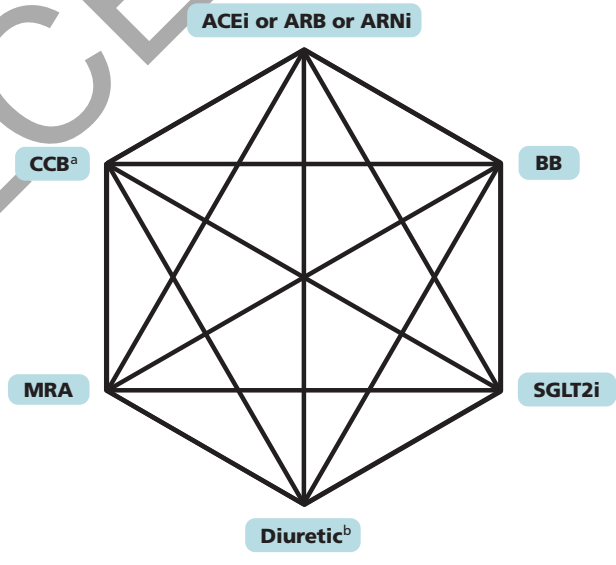


FIGURE 16 BP-lowering drugs in hypertension and heart failure. (a) Non-DHP CCB are not recommended in HFrEF and should not be combined with BB. (b) Use of Diuretics: Use $_{T/TL}$Diuretic if eGFR >45 ml/min/1.73 m^2. Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2. Use loop Diuretic if eGFR <30 ml/min/1.73 m2 or in patients with fluid retention/oedema.

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congestion, and are another antihypertensive treatment cornerstone. Thiazide/Thiazide-like diuretics are preferable if fluid retention is not a major problem or there is sufficient kidney function. Treatment with a loop-diuretic (furosemide, torsemide) is given to patients with severe fluid retention, in particular if they have suffered from pulmonary edema or have advanced CKD (eGFR <30 ml/min/1.73 m^2). In the rare cases in which the above drugs in combination therapy at maximum tolerated doses are not sufficient to lower an elevated BP to control values (<130/80 mmHg, if tolerated), DHP-CCBs may offer an additional option because they have been shown to be safe when added to existing treatments in HFrEF and are indicated when HFrEF is associated with CAD and angina (Section 17.1). However, in the last few years, use of ARNI (a compound that combines an ARB with the endopeptidase neprylisin inhibitor sacubitril) has made an uncontrolled BP in HFrEF even more unlikely, because this drug has a BP-lowering effect as shown in hypertensive patients [605]. Moreover, in HFrEF, a further BP-lowering effect can also be provided by use of SGLT2is (Section 18). The multiple options that are available for the treatment of hypertension in HFrEF should be modulated according to its coexistence with CAD, myocardial infarction, LVH, AF, diabetes, COPD or other conditions.

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Treatment of hypertension in heart failure with reduced ejection fraction (HFrEF)

Recommendations and statements	CoR	LoE
In patients with hypertension and heart failure with reduced ejection fraction (HFrEF) it is recommended to combine drugs with documented outcome benefits including ACEis (ARBs if not tolerated),which could be substituted by ARNI (sacubitril/valsartan), BBs, MRAs, and SGLT2is, if not contraindicated and well tolerated.	I	A
If patients remain with uncontrolled hypertension despite up-titration of drugs from the four major drug classes (RAS-inhibitors, BBs, MRAs, and SGLT2is) and use of additional treatment with a diuretic to manage fluid balance, a DHP-CCB can be added for BP control.	I	B
Use of non-DHP-CCB is not recommended in HFrEF due to their pronounced negative-inotropic effect	III	C

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17.2.3 Heart failure with preserved ejection fraction (HFpEF)

HFpEF accounts for about half of all HF patients, and hypertension is by far the most frequent precursor of and comorbidity for this condition [192,1170]. This accounts, at least in part, for the high prevalence of LVH in HFpEF as well as for the appearance and progression of diastolic dysfunction, which is the hallmark of HFpEF [192,1170]. Outcome-based RCT evidence is limited for HFpEF, and no trial with major antihypertensive agents has clearly documented that any specific antihypertensive drug class is associated with a reduction in mortality and hospitalization [192,1170]. However, (i) the close pathophysiological association of HFpEF with hypertension and cardiac HMOD and (ii) the marked reduction in the risk of any HF type with drug-based control of BP elevations [465] have led to the agreement that reduction of an elevated BP per se can be an appropriate therapeutic intervention in HFpEF. However, the SGLT2i class of drugs has recently SGLT2is have been shown to importantly improve the primary outcomes in dedicated RCTs on HFpEF [771,1171,1172] in both diabetic and nondiabetic patients, and can, therefore, be used to treat this condition [1168]. Treatment with ARNI [770] or MRA (spironolactone preferred) [1172] can be also considered [192,1168]. Based on available evidence, we recommend to lower SBP to 130 mmHg in HFpEF patients. Replacement of RAS blockers by ARNI or addition of SGLT2is can be considered, the latter independently of the presence of diabetes (Fig. 17).

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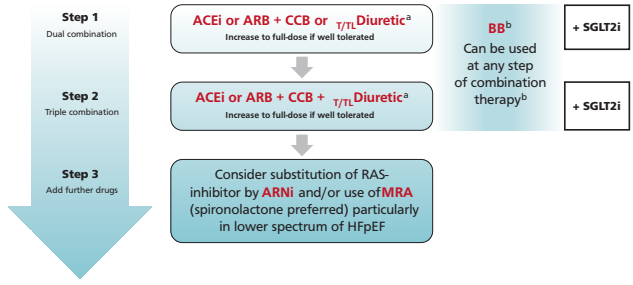


FIGURE 17 BP-lowering therapy in hypertension and HFpEF. (a) Use of Diuretics: Use $_{T/TL}$Diuretic if eGFR >45 ml/min/1.73 m^2. Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2. Use loop Diuretic if eGFR <30 ml/min/1.73 m^2 or in patients with fluid retention/oedema. (b) BB should be used as guideline directed medical therapy in respective indications or considered in several other conditions (Table 16).

Treatment of hypertension in heart failure with preserved ejection fraction (HFpEF)

Recommendations and statements	CoR	LoE
Treatment of hypertension with all major antihypertensive drug classes (ACEis or ARBs, BBs, CCBs, and Thiazide/Thiazide-like diuretics) is recommended in patients with HFpEF.	I	A
SGLT2is are recommended independently from the presence of type 2 diabetes.	I	A
Substitution of a RAS-inhibitor by an ARNI (sacubitril/valsartan) can be considered, particularly in the lower HFpEF spectrum.	II	B
Treatment with a MRA (spironolactone) regardless of diagnosed resistant hypertension can be considered, particularly in the lower HFpEF spectrum.	II	B

17.2.4 Overall management of heart failure and classification

Optimal management of HF patients includes special care programs for both hospitalized patients and outpatients who can be managed in HF clinics, in which the problem of long-term drug adherence is also addressed [1173]. Patients with very low EF (<20%) may need to be stabilized in hospital as they frequently present with tachycardia as a compensatory mechanism to maintain cardiac output. Treatment can make use of BBs, which should be titrated carefully from initial small doses. Hospitalization is also indicated in patients known to be hypertensive who show a low BP in a severe decompensated HF condition. Under these circumstances, the hemodynamic hallmark is a very high systemic vascular resistance, and it may take several days or even up to 2 weeks to re-establish acceptable BP values. Finally, it should be mentioned that after decades of an HF classification based on reduced, intermediate or preserved ejection fraction, this practice is gradually declining because of the evidence that HFrEF and HFpEF are not characterized by selective systolic and diastolic dysfunction, respectively, but by the coexistence of the two abnormalities in either condition. This is especially evident in HFpEF, in which patients also have extensive systolic dysfunction [228] seen as a lack of longitudinal axis shortening in systole, poor mid-wall contractility or low stroke volume at echocardiography. Furthermore, the effects of virtually all drugs in HF are independent on the ejection fraction value [192,1170]. In this regard, the field seems to be moving towards a unified pathophysiologically based classification of HF, which might lead to a therapeutic unification as well.

17.3 Hypertension and atrial fibrillation

AF is by far the most common arrhythmia in adults, and both its persistent and paroxysmal (more or less frequent AF episodes of variable duration) phenotypes are associated not only with increased risk of stroke but also with an increase of overall CV morbidity and mortality, including the risk of developing HF [1174,1175]. It is estimated that worldwide approximately 2–4% of adults suffer from AF, with a progressive increase with age and a prevalence up to 10% in older

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people and 20% in octogenarians [1174–1176]. The prevalence of AF will probably increase over the next decades because of the aging population [1177] as well as the expected increase in the prevalence of the risk factors for this condition [1174–1176]. Hypertension is the most common risk factor for the onset of AF because of (i) its large prevalence in the population and (ii) its role in the determination of cardiac alterations that favor AF such as LVH, LA enlargement and structural LA wall changes [1178]. Even a high-normal BP in apparently healthy people predicts AF [1179,1180]. Hypertension and AF are the two most important risk factors for ischemic thromboembolic and hemorrhagic stroke [4,1174–1176]. An elevated BP increases the risk of ischemic stroke, intracranial hemorrhage, major CV events and all-cause death in both oral anticoagulant-naive [1181] and oral anticoagulant-treated patients with AF [1182]. In patients eligible for anticoagulation treatment (because of increased stroke risk) a meta-analysis of RCTs (71 683 patients) indicated that hypertension was clearly the most prevalent comorbidity (88% of the patients) in the older population (mean age 71.5 years) [1183].

17.3.1 Blood pressure measurement in atrial fibrillation

Accurate measurement of BP matters in patients with AF who are usually older and more frequently hypertensive than people without AF [1184]. However, BP measurement in the presence of AF (and to a lesser degree of other major arrhythmias) can be problematic because of marked variations in ventricular filling time, ventricular contractility and stroke volume, all of which contribute to a marked increase of beat-to-beat BP variability [1184]. The previous 2018 ESC/ESH guidelines [4] recommended multiple BP measurements by auscultation in AF patients to account for the varying BP values. No less than three readings should be used to define the office BP representative of a given visit or circumstance. However, use of automated oscillatory methods should not be excluded because a recent meta-analysis of validation studies that have made use of different methodologies has shown that in AF patients, oscillatory methods satisfactorily measure SBP and only modestly overestimated (2.1 mmHg) DBP [1184]. This is clinically relevant because AF patients are usually older (i.e. when SBP is prognostically more important than DBP) and more frequently affected by ISH. In addition, despite the methodological limitations, both auscultation and automated oscillatory BP measurements have prognostic value in AF patients and can thus be used for office measurements, while only the automated oscillatory method can be used for home and ambulatory BP assessment [127,1185]. Recently, specific algorithms for accurately detecting AF during BP measurements [105,1185–1189] have been included in automated oscillatory BP monitors. This may increase the potential for an extended AF detection because a large fraction of AF episodes is asymptomatic [1174,1175].

17.3.2 Detection of atrial fibrillation

Because the lifetime risk for development of AF in adults is high (one of three Europeans >50 years of age) [1176], detection of AF is of fundamental importance. Detection of AF is based on pulse palpation, ECG and 24 h Holter monitoring. Holter monitoring can be prolonged to 48 h or longer to increase the chance of detecting asymptomatic or misinterpreted episodes. When assessing ambulatory BP, use of automated BP devices with an algorithm that detects arrhythmias may be considered [1187]. In a meta-analysis that included six clinical trials (2332 patients), the diagnostic accuracy of AF detection with automated BP measurement [1187] showed a sensitivity of 0.98 and a specificity of 0.92. Wearable and cuff-less devices allowing the detection of AF are evolving, and their use may allow more extensive and earlier detection of AF in the future [1190].

17.3.3 Prevention and treatment of atrial fibrillation in hypertension

Prevention and treatment strategies for AF do not substantially differ in patients with and without hypertension. BBs combine their BP-lowering effect with heart rate reduction in patients with hypertension and rapid AF, thereby helping to achieve heart rate control, which is central in AF management [1191]. Digoxin may be added to a BB but often has a limited effect. Heart rate control can also be achieved with a non-DHP-CCB (diltiazem or verapamil), which should generally not be used in combination with BBs [1191]. An exception are hypertensive patients with severe palpitations and rapid AF, who may be candidates for cautious use of a BB in combination with a non-DHP-CCB. With this approach, the addition of amiodarone with its potentially serious adverse effects during long-term treatment can be avoided. Control of heart rate below 110 bpm is advisable for all AF patients targeting a resting heart rate below 80 bpm based on ECG analysis, while the optimal heart rate target remains to be documented [1191].

Although several small studies suggest a moderate decrease of AF recurrence rate by BBs, the effect of these drugs on clinically relevant outcomes (stroke, systemic embolism or HF) remains to be established [1192]. Nevertheless, in the absence of contraindications or side effects, BBs may have been preferentially used in hypertensive patients with AF. All major antihypertensive drug classes favor LVH regression (via reduction of the afterload), which is therapeutically appropriate in AF, because LVH predisposes to development and relapse of AF. ACEis, ARBs and CCBs are more effective on LVH regression than BBs and diuretics, with encouraging results for ACEis and ARBs in preventing AF in patients with LV dysfunction, LVH or alterations of the anatomical structure of the LA [1193–1196]. ARBs are also more effective than CCBs in preventing AF in patients with high-risk hypertension [1197], but no reduction of the AF burden with the use of ARBs in patients without structural heart disease has been reported [1198]. Furthermore, ARBs did not avoid relapse of AF after electroconversion in patients mostly without hypertension [1199]. Use of MRAs may decrease new-onset AF in patients with HF and preserved [1197] or reduced ejection fraction [1200]. Recent data have shown that the use of SGLT2is is associated with a significant decrease in the risk of incident AF in patients with or without diabetes [1201,1202]. However, there is not yet evidence that SGLT2is prevent stroke in these patients. When compared with DPP-4 inhibitors or GLP-1 RA, the risk of incident AF was significantly lower with SGLT2is [1203].

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Prevention of atrial fibrillation in hypertension

Recommendations and statements	CoR	LoE
Work-up for hypertension is recommended in patients at risk for AF, such as those with high normal BP, LVH and left atrial dilatation. The detection of AF can be facilitated by using BP monitoring devices that are validated for this purpose.	I	C
Antihypertensive treatment is recommended to reduce the risk of incident and recurrent AF. The thresholds and targets for BP lowering treatment are the same as for the general hypertensive population.	I	A
All major antihypertensive drug classes can be used to prevent incident or recurrent AF.	I	A
RAS-blockers and BBs may be considered in patients with AF to prevent recurrent AF.	II	B

Treatment of hypertension in atrial fibrillation

Recommendations and statements	CoR	LoE
Treatment of hypertension reduces the risk of stroke and other CV outcomes in patients with AF. The BP threshold and targets as well as the drug treatment strategies should be the same as for the general hypertensive population.	I	A
At least three office BP measurements by auscultation are recommended in patients with AF to account for the varying BP values.	I	B
Automated oscillatory methods can be used for BP measurement in patients having AF, because they satisfactorily measure SBP and only modestly overestimate DBP.	II	B
BBs are the preferred drug class for heart rate control in patients having AF. Resting heart rate should be lowered below 110 beats per minute, targeting a heart rate < 80 beats per min based on ECG analysis, particularly in symptomatic patients.	I	B
Digoxin may be added to BBs to improve HR control in AF.	II	B
BBs should usually not be combined with Non-DHP CCBs.	III	C

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17.3.4 Oral anticoagulation and BP control

In AF, the administration of anticoagulants has become mandatory if the risk of stroke is high and greater than the risk of major bleeding associated with these drugs [1174,1175]. This can be assessed by scores that weight and balance the respective favoring factors [1174,1175]. However, treatment of hypertension and achievement of BP control has not lost its importance [1204] for two main reasons. The first reason is that multiple studies and meta-analyses have shown that in patients with AF, an elevated office BP or a diagnosis of hypertension is accompanied by a marked increase in the risk of stroke, systemic embolism, intracranial hemorrhage and CV morbidity and mortality. The risk includes different ethnicities and extends to very old people [1205,1206]. The outcome incidence increased significantly also in patients with a home SBP ≥145 mmHg compared with a home SBP <125 mmHg (approximately equivalent to <130 mmHg office SBP), incidentally supporting the usefulness of HBPM in this clinical circumstance [127]. The second reason is that the BP level is a most important factor favoring major bleeding, including intracranial hemorrhage [1207]. This was documented early by a posthoc analysis of the PROGRESS study on patients with a history of cerebrovascular events and warfarin treatment, who showed a progressively lower incidence of intracranial hemorrhage, as BP was reduced by antihypertensive treatment to an SBP value of <130 mmHg [1206]. In addition, data from RCTs comparing warfarin with direct oral anticoagulants in AF showed a significant increase in the risk of ischemic or hemorrhagic stroke if SBP values were >140 mmHg [1208,1209]. This evidence has confirmed the inclusion of hypertension, as defined by an SBP >160 mmHg, as an important modifiable risk factor for bleeding in the HAS-BLED score [1181], although based on the available evidence mentioned above a rapid reduction of SBP values to <140 mmHg before initiation of anticoagulant treatment appears to be a more adequate safety measure. According to the present guidelines, BP needs close monitoring in patients with AF who are under anticoagulant treatment, and uncontrolled hypertension should be avoided by appropriate BP-lowering therapy. The SBP target should be <140 mmHg but values <130 mmHg should be cautiously pursued, if treatment is well tolerated, because many patients with AF have LVH, which may require cardiac perfusion pressures higher than in patients without LVH (Section 10.5). There should be no attempt to lower SBP below <120 mmHg because the cautionary reasons mentioned in Section 10 apply also to patients with AF, in whom there is some evidence that BP levels and outcomes may be linked by a 'J-shaped' curve [593,1181,1210]. HBPM may help evaluation of antihypertensive treatment effectiveness over time. Oral anticoagulants in patients with an elevation of SBP >160 mmHg, may be halted until BP control is improved or achieved. Most first-line BP-lowering drugs are safe in patients undergoing oral anticoagulation without a significant risk of clinically relevant drug interactions. Non-DHP-CCBs (verapamil and diltiazem) are an exception [1211], because they are moderate inhibitors of the cytochrome P 450 isoenzyme 3A4 and P-glycoprotein and may, therefore, increase the plasma concentration of oral anticoagulants and thus the bleeding risk (Fig. 18) [1212,1213].

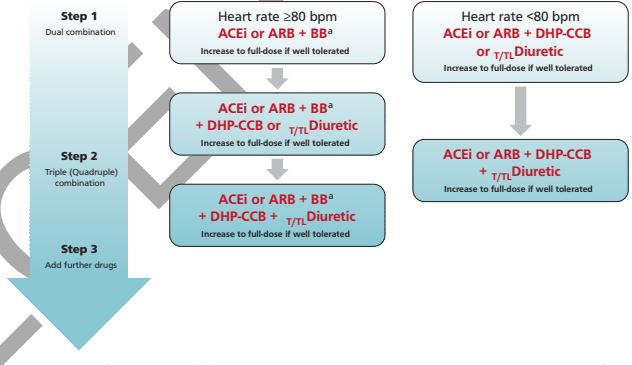


FIGURE 18 BP-lowering therapy in hypertension and atrial fibrillation. (a) Target heart rate below 80 beats per minute, if BBs are contraindicated or not tolerated consider use of non-DHP CCB at any step instead of DHP-CCB.

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Management of patients with hypertension and AF during oral anticoagulation

Recommendations and statements	CoR	LoE
Stroke prevention with oral anticoagulants should be considered in AF patients with hypertension, even when hypertension is the single additional risk factor (CHA_2DS_2-VASc score of 1 in men and 2 in women).	II	B
Initiation of oral anticoagulation should ideally start if SBP is below 160 mmHg. If SBP is ≥160 mmHg, it is recommended in priority to reduce BP to reduce the risk of major bleeding including intracranial haemorrhage.	I	B
In hypertensive patients with AF receiving oral anticoagulation, the same treatment targets and choice of agents are recommended as for the general population.	I	B
Non-DHP CCBs (Diltiazem and verapamil) for rate control should be used with caution because they may interfere with oral anticoagulants and increase bleeding risk.	III	B

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17.4 Valvular heart disease

The most common valve disorders of the heart are aortic stenosis (AS), aortic regurgitation (aortic insufficiency) and mitral regurgitation (mitral insufficiency). Detection is usually obtained by auscultation of murmur and subsequent echocardiography. In patients with progressive AS severity, ultimate treatment is open valve surgery or catheter-based valve replacement or repair. At a later stage, cardiac valve disease may be a component of the HF syndrome, and patients should receive HF treatment. Hypertension is common in patients with valvular heart diseases and particularly in patients with AS.

17.4.1 Aortic stenosis

AS is a degeneration of the aortic valve with fibrotic tissue and calcification. A bicuspid valve predisposes to this development. The pathophysiological mechanism is different from atherosclerosis with plaque formation in the intima of large arteries because intensive lipid-lowering treatment does not prevent worsening of aortic stenosis [1214]. At least two-thirds of patients with AS have hypertension, which plays a pathophysiological role. There is no major RCT on the role of antihypertensive medication to prevent worsening from moderate-to-severe AS. Thus, treatment of hypertension in patients with AS depends on learning from small mechanistic studies, clinical experience and data from observational studies [1215–1217]. Severe AS is associated with syncope, arrhythmias, chest pain because of myocardial ischemia (related to LVH or CAD) or HF. Most clinicians are somewhat cautious with antihypertensive treatment in patients with severe AS, who have suffered a syncope in order to avoid a sudden BP fall and recurrent syncope. An interesting, albeit still unresolved, question is whether LVH develops because of longstanding hypertension or in response to the aortic valve disease itself. At any rate, before and after surgery or catheter-based intervention, antihypertensive treatment in patients with AS should follow the general treatment algorithm, including target BP values, the choice of drugs and the specific indications for CAD, HF or arrhythmias [1215–1217]. Postoperative echocardiographic follow-up should be implemented until normalization of the cardiac geometry.

17.4.2. Aortic regurgitation

Hypertension with aortic regurgitation (insufficiency) should be treated according to the general treatment guidelines until the valve disease needs surgery or catheter-based treatment, which usually takes place when a dilated left ventricle is detected by echocardiography. An RCT performed three decades ago showed that treatment with nifedipine could delay the time point for surgery [1218], and thus treatment with CCBs is common in aortic regurgitation with the purpose of reducing the afterload by systemic vasodilatation. However, other vasodilators (e.g. RAS blockers) can serve the same purpose. In people with aortic regurgitation, the heart itself generates a high SBP because of a higher stroke volume.

17.4.3 Mitral regurgitation

Numerous cardiac diseases may be associated with damage of the mitral valve and mitral regurgitation (insufficiency). Longstanding or severe hypertension may cause mild or even moderate-to-severe mitral regurgitation through dilatation of the left ventricle and thus stretching of the chorda tendineae, separation of the two mitral leaflets in systole and leakage of blood into the left atrium. This appears to be a sequence of events that is not rare, because in a British population study [1219], each 20 mmHg increment of SBP was associated with a 26% higher risk of mitral regurgitation. Antihypertensive treatment and BP control can be cardioprotective when mitral regurgitation is diagnosed according to the general

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recommendations for the treatment of hypertension. Patients should be followed by echocardiography for the regression of the LV dilatation and reversal of mitral regurgitation. The mitral valve is usually intact, and valve repair is not indicated if antihypertensive or HF medications reverse the regurgitation. Valve repair is indicated if rupture of the chordae contributes to a severe mitral valve leakage or the chordae are damaged and the leaflets do not clog up the leakage.

Hypertension and cardiac valve disorders

Recommendations and statements	CoR	LoE
In patients with AS, the BP thresholds and targets as well as the drug treatment strategies should be the same as for the general hypertensive population.	I	C
In patients with high-grade AS, particularly with history of syncope, BP lowering should be implemented more cautiously to avoid an excessive fall in BP and recurrent syncope.	I	C
In patients with AI, the BP thresholds and targets should be the same as for the general hypertensive population.	I	C
Treatment with drugs reducing afterload, including RAS-blockers and CCBs, is recommended in patients with AI.	II	B
Antihypertensive treatment is recommended to prevent MI, and to reduce symptoms of MI, through reduced afterload of the left ventricle.	II	C

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17.5 Cerebrovascular disease and cognition

17.5.1 Management of elevated BP in acute stroke

17.5.1.1 Acute hemorrhagic stroke

In acute intracerebral hemorrhage, an increase of BP is common and associated with a greater risk of hematoma expansion, death and reduced chance of neurological recovery [1220,1221]. Management of the BP increase is different according to whether the BP-lowering intervention starts <6 or >6 h after onset of symptoms. Two earlier RCTs suggested that in patients treated <6 h after onset of symptoms lowering SBP to >140 mmHg from much higher initial values reduced disability and death whereas SBP reductions to <140 mmHg led to no benefit, and in one of the two RCTs, increased adverse kidney events [1222,1223]. However, a continuous association between the degree of the first 24 h BP reduction and the improvement of functional neurological status has been unveiled by an analysis of 3809 patients in whom treatment started on average 3.6 h after the onset of symptoms [1224]. Furthermore, in a meta-analysis of five RCTs, patients with small-to-moderate hematoma volumes at admission showed an improvement of the functional neurological status with a BP reduction to <140/90 mmHg [1225]. Thus, more rigorous BP targets may now be recommended for early BP-lowering treatment in patients with acute intracranial hemorrhage. Nevertheless, a caveat against excessive BP-lowering effects remains because a pooled analysis of the patients enrolled in the INTERACT2 and the ATTACH-II trials showed that patients with an SBP decrease greater than 60 mmHg had a worse prognosis compared with those with lesser SBP reduction [1226].

In patients with acute intracranial hemorrhage and an SBP <220 mmHg, current evidence for initiation of BP-lowering treatment >6 h after onset of symptoms, current evidence is not entirely univocal. Recently, an individual patient data meta-analysis of 16 studies (6221 participants) has shown that a moderate SBP reduction (12.1 mmHg achieved over several hours) reduced the hematoma expansion, although with no clear effect on the chance of clinical recovery. Therefore, slow and moderate BP reductions are preferable over intensive BP targets [1225,1227]. Fewer data are available in patients with acute intracerebral hemorrhage and an SBP ≥220 mmHg. A meta-analysis [1228] and secondary outcome data from one RCT [1222] suggest an improvement of functional recovery with an SBP reduction to <180 mmHg. However, in the ATTACH-II trial, patients with SBP ≥220 mmHg showed a higher rate of clinical deterioration by an SBP reduction to <140/90 mmHg [1229]. Thus, in patients with acute intracerebral hemorrhage and an SBP ≥220 mmHg, a cautious BP reduction to SBP <180 mmHg, possibly via i.v. drug therapy, seems the wisest therapeutic option (Fig. 19).

17.5.1.2 Acute ischemic stroke

The beneficial effects of BP reduction are even less clear in acute ischemic stroke. In most patients, initial BP values are high or very high and show a spontaneous progressive reduction during the first 48–72 h after stroke [1230]. Elevated BP levels during this time frame are associated with a worse clinical and/or neurological outcome but this association cannot translate

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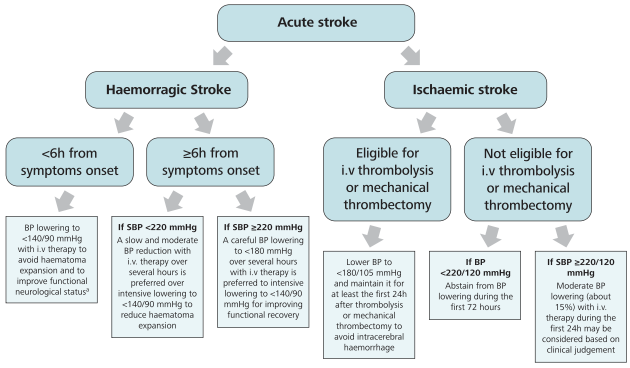


FIGURE 19 BP management in acute stroke. (a) Avoid absolute reductions of SBP >60 mmHg from initial SBP.

into the decision to pharmacologically reduce BP because most RCTs and meta-analyses have not reported reduction of death or dependency by early BP reduction after acute ischemic stroke [1225,1231–1237]. A further difficulty is that RCT evidence has been obtained with different measures of the benefit in patients differing for the type of stroke (lacunar, large vessel occlusion, cardio-embolic), the age and clinical features (e.g. a history of previous hypertension or HF), the magnitude of spontaneous BP changes during the first few hours after stroke, the infarct size and intracranial pressure, which may have concealed benefit or harm of BP-lowering interventions in some patient categories [1238]. A pragmatic recommendation can be to consider a cautious and slow BP reduction (15% over the 24 h after stroke) in patients with markedly elevated SBP or DBP values (i.e. ≥220/120 mmHg) [1234,1235,1239], and to abstain from BP-lowering treatments when BP is <220/120 mmHg during the 72 h after stroke, because under these circumstances, no benefit of a BP reduction has been consistently reported [1236,1240].

Patients with an acute ischemic stroke who have or will receive reperfusion interventions such as intravenous thrombolysis or mechanical thrombectomy are a special category, because observational studies have reported that these interventions increase the risk of intracerebral hemorrhage if BP is markedly elevated [1241,1242]. In these patients, BP should be lowered to <180/105 mmHg for at least the first 24 h after thrombolysis or thrombectomy [1243]. BP should be maintained stable at the lower BP values because a meta-analysis of seven studies (5874 patients) has reported a 20% increase of intracranial hemorrhage (and 12% increase of worse neurological outcome) for any 10 mmHg BP increase [1244]. On the other hand, no benefit has been found in these patients with an SBP reduction to <130 mmHg [1245,1246] (Fig. 19). For stable patients, who remain hypertensive (≥140/90 mmHg) more than 3 days after an acute ischemic stroke, initiation or reintroduction of BP-lowering medications should be considered [1247].

Management of blood pressure in acute stroke

Recommendations and statements	CoR	LoE
In patients with haemorraghic stroke and < 6h after symptom onset, a BP <140/90 mmHg is recommended to avoid haematoma expansion.	II	B
In patients with haemorraghic stroke >6h after symptom onset, an SBP ≥220 mmHg may be carefully lowered with i.v. therapy to <180 mmHg. If SBP < 220 mmHg, slow and moderate BP reductions are preferable over intensive BP to <140/90 mmHg.	II	B
In patients with acute ischemic stroke eligible for i.v. thrombolysis (IVT) or mechanical thrombectomy (MT), BP should be carefully lowered and maintained at <180/105 mmHg for at least the first 24 after intervention.	II	B
In patients not eligible for IVT or MT with BP ≥220/120 mmHg, drug therapy may be considered based on clinical judgement, to reduce BP by 15% during the first 24 h after the stroke onset.	II	B
In patients with acute ischemic stroke Routine BP lowering with antihypertensive therapy is not recommended.	III	A

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17.5.2 Management of elevated BP in patients with previous stroke or transient ischemic attack

Placebo-controlled RCTs of antihypertensive treatment in clinically stable hypertensive patients (BP ≥140/90 mmHg) with a previous stroke or TIA [1248,1249] have shown that BP lowering reduces the risk of recurrent stroke as well as CV events. Thus, initiation or resumption of BP-lowering therapy several days after stroke, when the clinical conditions are stabilized, or immediately after TIA, is recommended for untreated or previously treated patients with hypertension [1250]. No placebo-controlled trial has explored whether in patients with a previous stroke, antihypertensive treatment reduces stroke recurrency and CV events also when BP is in the high-normal range [1251] or lower. The optimal BP targets to prevent recurrent stroke are also uncertain, but a consistent finding of several trials and meta-analyses has been that within the 120–140 mmHg SBP range, the lower the achieved SBP, the lesser the risk of stroke recurrence [465,1251–1258]. It must be emphasized that these results are mainly applicable to individuals with an average age below 70 years, and that, when dealing with the secondary prevention of stroke, the target BP to aim at should be decided based on the functional status, frailty, cognition and associated conditions of the patient. The first and main goal should be to reduce BP to <140/80 mmHg, and then, whenever possible and under clinical control, achieve BP below 130/80 mmHg, if tolerated [1259]. SBP values <120 mmHg should be avoided.

Prevention of stroke has been observed in large RCTs using different drug regimens. However, RCTs comparing different treatment regimens [626,1260] and meta-analyses [465,579,580,1261] suggest that BBs are less effective for stroke prevention than the other major classes of antihypertensive agents, although also showing a sizeable protection against stroke in BP-lowering placebo-controlled trials [580,626,1260]. The factors involved in the lower cerebrovascular protection of BBs are not clear because there is no evidence that BBs exert a damaging effect on the brain or impair cerebral blood flow autoregulation. In a large meta-analysis of RCTs, the risk of stroke did not differ significantly between BBs and RAS blockers or diuretics, but it was greater when compared with CCBs [626,1260], raising the possibility of an origin from a slightly greater BP-lowering effect of CCBs to which stroke incidence might be especially sensitive [626,1260,1262,1263]. At any rate, mindful of the fact that the most common recurrent event after stroke is a further stroke rather than myocardial infarction [1264–1266], antihypertensive treatment for secondary stroke prevention should not consider BBs as the preferred drugs. Under these circumstances, BBs can be used in combination treatment, considering their specific indications and comorbidities (Table 16).

17.5.3 Management of patients with cognitive dysfunction and dementia

In the last 25 years, the incidence of dementia has sizably increased, mainly because of the increase in population aging. Dementia is more frequent in women than in men and is the fifth most common cause of death in the world [1267]. Several epidemiological and clinical studies have shown that hypertension in midlife predicts cognitive decline and both Alzheimer's disease and vascular dementia in older patients [1267,1268]. Furthermore, long-term cumulative BP is independently associated with subsequent cognitive decline and incident dementia among cognitively healthy adults [313,1269]. The pathophysiology of cognitive function in hypertension is related to remodeling of cerebral small vessels, leading to subclinical cerebral white matter lesions, microbleeds and lacunar infarcts [1270]. Arterial stiffness of large arteries and flow pulsatility contribute to cerebral small vessel disease, which results into blood flow reduction in specific brain regions related to cognition such as the basal ganglia and hippocampus [309,1271–1273]. Therefore, in hypertensive patients, routine clinical assessment should include attention to possible cognitive impairment, at least in those aged 65 years and older [301]. Evidence on the beneficial effects of BP lowering on cognitive decline has been conflicting for years. However, a recent meta-analysis [1274] of five RCTs (28 008 patients) used multilevel logistic regression of pooled individual participant data to evaluate the treatment effect on incident dementia. During a median follow-up of 4.3 years, antihypertensive treatment reduced the risk of incident dementia by 13% with a mean SBP/DBP lowering of 10/4 mmHg. In addition, several studies have shown that strict BP control, i.e. SBP <130 mmHg, reduces the progression of cerebral white matter lesions and the decrease in global cognitive performance [470,1275,1276].

The question if some antihypertensive drugs or strategies are better than others in preventing cognitive decline and dementia is still under debate. Several observational studies and data from international registries suggested that ARBs, DHP-CCBs and Thiazide/Thiazide-like diuretics may be better than ACEis, non-DHP-CCBs and BBs in reducing the progression of cognitive decline and the incidence of dementia [1277,1278]. This suggestion seems to be supported by a very recent post hoc analysis of two RCTs, the PreDIVA trial [1279] and the SPRINT-MIND trial [1280]. Both trials have shown that treatment with ARBs, DHP-CCBs and Thiazide/Thiazide-like diuretics had lower rates of incident cognitive impairment (−24%) compared to ACEis, non-DHP and BBs. Further prospective controlled trials designed to confirm this observations are warranted. Current evidence supports the recommendation to implement antihypertensive treatment and pursue strict BP control in late-mid and later life to lower the risk of cognitive decline and dementia.

17.6 Vascular disease

17.6.1 Lower extremity arterial disease

LEAD is often a manifestation of more widespread atherosclerosis and especially of atherosclerotic renal artery disease. Indeed, an association has been found between LEAD and an increased risk for multiple adverse outcomes including CAD, HF, aortic aneurysm and CKD [1281], which means that patients with LEAD are at high or very high CV risk [1282]. LEAD is associated with BP levels and, in a large primary care registry from the UK, patients with a 20 mmHg higher than usual SBP exhibited a 63% greater risk of LEAD [1281]. The strength of the association declines with increasing age [1283]. So far, no RCT of different BP targets has been designed to specifically examine the effect of BP-lowering treatment on LEAD-related

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events as well as the BP targets to aim at and the antihypertensive drugs to use. Nevertheless, BP control by antihypertensive treatment can be recommended as an important part of the CV risk reduction strategy in LEAD patients with hypertension [483,484] to increase the current low rate of BP control that characterizes LEAD in clinical routine [1284]. Available evidence and extrapolation from the ALLHAT study suggests that major BP-lowering drug classes including diuretics, CCBs and RAS blockers prevent LEAD events with equal efficacy [1285,1286]. Therapeutic use also includes BBs (not primarily tested in ALLHAT) because these drugs have not been shown to worsen the symptoms of intermittent claudication in two meta-analyses [1287,1288]. In an RCT with the vasodilating beta-1-selective blocker nebivolol and the nonvasodilating β1-selective blocker metoprolol in patients with stable claudication [1289], both treatments were well tolerated, and there were no differences in quality of life, ABI and claudication distance. Thus, BBs remain one of the treatment options in hypertensive patients with LEAD, also considering the frequent association of this disease with CAD. When critical limb ischemia is present, BP reduction should be instituted slowly to reduce the risk of worsening ischemia. In the ALLHAT study, an on-treatment SBP <120 mmHg (and >160 mmHg) was associated with a higher hazard of a LEAD events (LEAD-related hospitalization, procedures, medical treatment or death), in comparison with an SBP between 120 and 129 mmHg. This was the case also for a low DBP (<60 mmHg) [1285]. Furthermore, in a large trial (EUCLID) [1290], an SBP >125 mmHg was associated with an increase in major CV and LEAD events, whereas SBP to ≤125 mmHg was associated with an increase of major CV, but not of LEAD events, and DBP was not associated with LEAD events at all. In patients with LEAD, antihypertensive treatment should include lifestyle changes, and especially smoking cessation. Lipid-lowering drugs and antiplatelet therapy [1291], are also frequently needed [1282].

17.6.2 Aortic dilatation, aneurysm and dissection

Hypertension can be associated with modest aortic root dilatation [1292]. When more extensive aortic root dilatation is present or the dilatation extends beyond the aortic root, an additional cause for aortopathy should be sought. All hypertensive patients with aortic dilatation, whether associated with Marfan syndrome, bicuspid aortic valve disease or not, should have their BP controlled [1293]. In patients with Marfan syndrome, prophylactic use of ARBs [1292] or BBs [1294] was associated with a reduction of either the progression of the aortic dilatation or the occurrence of complications as compared with no treatment. Both drugs were similarly effective [1295], at variance from a neutral effect of a losartan-based treatment in another study [1296]. In a recent individual patient data meta-analysis [1297], ARBs reduced the rate of increase of the aortic root diameter by about one-half, and the effect was similar with BBs. The authors suggested that combination therapy with both ARBs and BBs from the time of diagnosis would provide even greater reductions in the rate of aortic enlargement than either treatment alone, which, if maintained over a number of years, would be expected to lead to a delay in the need for aortic surgery. Antihypertensive drug treatment aimed at a 24-h SBP <130 mmHg has been recommended in the past and still seems a reasonable treatment goal [1298], although not firmly established by RCTs. There is no evidence on the efficacy of antihypertensive treatment in aortic disease of other etiologies.

Hypertension is an important risk factor for aortic dissection [1299], and under these circumstances, BP-lowering drug treatment must be implemented immediately. BP should be reduced at least to <130/80 mmHg [1292], but lower values, e.g. around 110 mmHg SBP [1298], should be pursued in the acute setting and possibly also, if tolerated, on a chronic basis. In a large retrospective cohort study from Taiwan [1300], including almost 7000 patients with aortic dissection, use of BBs, ACEis or ARBs after hospital discharge was associated with long-term mortality reduction.

Hypertension is also a risk factor for abdominal aortic aneurysm, and some studies suggest that special attention should be attributed to the DBP elevation [1283]. A meta-analysis including more than 15 000 patients under surveillance for abdominal aortic aneurysm [1301] has reported that BP values had no effect on aneurysm growth rate, but higher mean BP or pulse pressure were associated with greater aneurysm rupture rate. Data on the effect of antihypertensive treatment are not univocal. Antihypertensive drugs including ACEis, ARBs, CCBs and BBs in addition to statins and antiplatelet drugs have been associated with a lower 5-year all-cause mortality in patients with abdominal aortic aneurysm [1302]. A meta-analysis that included 10 RCTs (2045 patients) with asymptomatic abdominal aortic aneurysm has recently shown that BP-lowering medications did not reduce the aneurysm growth rate or related clinical events [1303]. Due to limitations in sample size and event rates, a small protective effect could not be ruled out. Although five cohort studies have raised the possibility of a benefit of BBs on abdominal aortic aneurysm growth rate, this has not been confirmed by three RCTs using BBs [1304]. Similarly, although a case–control study suggested a beneficial effect of ACEis in reducing the risk of abdominal aortic rupture [1305], these drugs were found to have only a borderline effect in another observational study [1306]. Nevertheless, it seems wise to reduce a chronically elevated BP in people with abdominal aortic aneurysm, with no drug preference, and complying with the general recommended target BP values for antihypertensive treatment.

18. HYPERTENSION AND DIABETES MELLITUS

18.1. Epidemiology and risk classification

Hypertension is common in type 1 and much more in type 2 diabetes. Type 1 diabetes develops mostly in children, adolescents and individuals usually below 30 years of age who show a prevalence of hypertension greater than that of nondiabetic individuals or the age-matched general population. Prevalence of hypertension varies in different studies, and in an old large Danish population study has been reported to be about 15% of type 1 diabetic patients [1307,1308]. Similar rates have been found in a study on more than 3000 patients from 16 European countries [1309]. The cause of hypertension is

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regarded as being diabetic nephropathy (usually documentable by increased urinary protein excretion), although some patients (frequently with a strong family history of hypertension) may develop a BP elevation in absence of manifest renal disease [1308]. Hypertension is associated with its typical HMOD and outcome complications and antihypertensive treatment is needed. Treatment should be implemented according to the large body of evidence mainly collected for type 2 diabetic patients, on BP threshold for treatment (≥140/90 mmHg), BP target (<130/80 mmHg) and drug treatment strategies, i.e. use of drug combinations of the five major drug classes, including a RAS blocker [1310]. Hypertension is common in type 2 diabetes, with a prevalence that, after a few years' duration of the disease, involves the majority of the diabetic population. It is estimated that this association will grow in the future due to the progressive aging of the world population and the unfavorable influence of modern lifestyle. The prevalence of type 2 diabetes is steeply increasing in high-income countries, and the increase is even more pronounced in low-income countries [37]. However, the association between type 2 diabetes and hypertension is also because of common causal links and bidirectional interactive influences, such as the stimulating effect of insulin on the SNS and the increase of insulin resistance and serum insulin levels by sympathetic activation [1311,1312]. This can explain why a quantitative relationship has been reported between the prevalence of type 2 diabetes and BP values in the population [956]. It has also been recognized that, in diabetes, hypertension usually exhibits characteristics that differ from those of nondiabetic hypertensive patients. The most frequent characteristics are a greater SBP elevation, a wider pulse pressure, a higher BP variability, a nondipping pattern, salt-sensitivity, a trend to hyperkalemia and orthostatic hypotension, particularly as the duration of the diabetes increases [1313]. Furthermore, in patients with type 2 diabetes, the prevalence of MH is much higher than in the general population [1314]. Finally, type 2 diabetes is associated with a higher rate of resistant hypertension and is recognized to be one of the most important factors that can make achievement of BP control difficult [535]. The presence of diabetes mellitus in patients with hypertension has an important influence on CV risk per se, regardless of the concomitance of HMOD, CVD or CKD. Only diabetic patients with well controlled, short-standing duration of the disease (less than 10 years) with no evidence of HMOD and no additional CV risk factors are categorized as being at moderate risk [33]. Otherwise patients with diabetes are considered to be at high CV risk or even at very-high risk in the presence of established CVD or advanced CKD. Consequently, hypertensive patients with diabetes are candidates for immediate initiation of antihypertensive drug treatment together with lifestyle interventions.

18.2 Benefits of BP lowering

Overwhelming evidence supports the benefits of BP reduction in people with hypertension and type 2 diabetes to reduce macrovascular events and mortality, as well as to prevent microvascular complications, such as nephropathy and retinopathy [471,488,1315]. However, the protective effect of BP-lowering treatment is not clear for all diabetes-related microvascular complications, such as the potential protective effects of BP reduction on diabetic-related dysautonomia The recommended lifestyle interventions (Section 7) that lower BP are very important in type 2 diabetic patients, with particular emphasis on interventions targeting overweight and obesity that improve the blood glucose and the dysmetabolic profile. Pharmacological treatment should be started when SBP is ≥140 mmHg or DBP is ≥90 mmHg, to achieve, if well tolerated, a goal of <130/80 mmHg, which has been found to offer incremental protection compared to higher BP values, particularly against stroke in meta-analyses of RCTs [488,1315]. Support for an SBP target <130 mmHg is provided also by the ACCORD trial, which found that in type 2 diabetic patients, on-treatment SBP values of about 122 mmHg were associated with a clear reduction in the risk of stroke compared to on-treatment SBP values between 130 and 139 mmHg [1316]. In ACCORD, the intense SBP reduction was not accompanied by a reduction of combined CV events and all-cause mortality, but it was later recognized that this finding was probably due to the confounding effect of the factorial design of the trial [1316]. When the detrimental effect of the concomitant intense blood glucose reduction was accounted for, the benefit of intense BP reduction extended to the composite CV outcomes [1155]. Although recent studies advocate a SBP goal <120 mmHg [1316–1318], other observations do not support these lowest BP targets [465,471,556,1319–1321]. The present guidelines recommend antihypertensive treatment of type 2 diabetic patients to reach an SBP <130 mmHg but not <120 mmHg. This recommendation extends to a DBP <80 mmHg but not below 70 mmHg [1317]. Interestingly, in the ONTARGET trial, an increased risk of events was observed at DBP values slightly <70 mmHg [535], but in another study, the impact of intensive BP lowering was found to be independent of the baseline DBP value, suggesting that low baseline DBP should not be an impediment to pursuing optimal SBP targets [1322]. If a target <130/80 mmHg cannot be obtained or is not tolerated, maintaining BP within the 130–139/80–89 mmHg range guarantees a sizeable degree of protection compared to BP values ≥140/90 mmHg [182,1323].

18.3 Antihypertensive drug treatment

The generally recommended strategy for antihypertensive drug treatment (Section 11), i.e. starting with dual combination therapy and using drug combinations in the majority of the patients, is even more necessary for diabetic patients, considering the difficulties of BP control in diabetes and the importance to achieve BP targets in patients with high CV risk [183]. However, treatment intensity should be implemented considering potential suppress minimize inconveniences such as orthostatic hypotension, particularly in old patients and long-lasting diabetes, and possibly dysautonomia. All major antihypertensive drug classes have been shown to reduce CV outcomes in type 2 diabetes [1324]. Treatment should include a RAS blocker, because outcome-based RCTs indicate that RAS blockers prevent appearance and progression of kidney complications of diabetes more effectively than other major antihypertensive drugs, as measured by the reduced incidence of new-onset microalbuminuria, the reduction of protein excretion in proteinuric patients, the attenuated decline of GFR in diabetic and nondiabetic nephropathy and the prevention of ESKD [1325].

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Newer antidiabetic agents, i.e. SGLT2is and the glucagon-like peptide 1 receptor agonists (GLP-1 RA) have been shown to reduce macrovascular and microvascular complications in type 2 diabetes [1326]. In addition to glucose control, SGLT2is have demonstrated a marked protective effect against HF (Section 17.2) and kidney outcomes (Section 19) [1327], while GLP-1 RA have demonstrated a reduction of CV events and a sizeable weight loss [1328–1330]. Use of these drugs has been recommended by the ESC/EASD guidelines as first step treatment in diabetic patients with a previous CV event, HMOD or multiple risk factors [1331]. An important additional aspect of the action of these drugs is that they can reduce office BP and ABPM by several mmHg [1328,1332,1333] even when diabetic patients are under multiple treatment with antihypertensive drugs, such as RAS blockers and diuretics [182]. Both classes of drugs may thus help to improve BP control, which is especially difficult in diabetes [183]. Although protective effects of SGLT2is against HF and kidney outcomes have been clearly documented, a less consolidated degree of cardiorenal protection has been reported for GLP-1 RA in diabetes [762]. The new non-steroidal MRA finerenone has also been shown to provide cardiac and renal protection in patients with diabetic nephropathy (see section 19.1.4). In this context, finerenone induced small but significant reductions in BP [578].

Treatment strategies in diabetes

Recommendations and statements	CoR	LoE
BP should be monitored to detect hypertension in all patients with diabetes, because it is a frequent comorbidity associated with an increase CV risk and risk for kidney events.	I	A
Non-dipping or elevated night-time BP are frequent in type 2 diabetes and should be monitored by ABPM or HBPM.	I	B
Antihypertensive treatment in type 2 diabetes is recommended to protect against macrovascular and microvascular complications.	I	A
Immediate lifestyle interventions and antihypertensive drug treatment are recommended for people with type 2 diabetes when office SBP is ≥ 140 mmHg and DBP is ≥ 90 mmHg.	I	A
Drug treatment strategies in patients with type 2 diabetes should be the same as for patients without diabetes but the primary aim is to lower BP below <130/80 mmHg	I	A
BP control is difficult in diabetes and combination treatment is almost always necessary.	I	B
SGLT2is are recommended to reduce cardiac and kidney events in type 2 diabetes. These agents have a BP lowering effect.	I	A
The non-steroidal MRA finerenone can be used, because of its nephroprotective and cardioprotective properties in patients with diabetic CKD and moderate to severe albuminuria. Finerenone has a BP lowering effect.	I	A
There are only limited data on the potential benefits of combining SGLT2is and finerenone.	II	C

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19. HYPERTENSION AND THE KIDNEY

Hypertension is a strong independent risk factor for development of CKD and progression of CKD to ESKD [1334,1335]. Hypertensive kidney disease per se is the second most common known cause of ESKD, after diabetic kidney disease [1336,1337]. The diagnosis of hypertension-induced kidney dysfunction is based on two pillars: (i) evaluation of the level of kidney function through estimation of glomerular filtration rate (eGFR), calculated by the 2009 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula [291] and (ii) detection of kidney damage by use of the urinary albumin: creatinine ratio (UACR), measured from a spot urine sample (preferably morning urine). eGFR and UACR are both independent and additive predictors of increased risk of CKD progression and increased CV risk [1337–1340]. To highlight its associated risk, albuminuria is currently divided into: (a) normal/mildly increased, UACR <30 mg/g (formerly termed normoalbuminuria); (b) moderately increased, UACR 30–300 mg/g (formerly termed microalbuminuria); and (c) severely increased, UACR >300 mg/g, (formerly termed macroalbuminuria). CKD is diagnosed in any individual with an eGFR <60 ml/min/1.73 m^2 at any level of albuminuria or a UACR >30 mg/g at any level of eGFR persisting for more than 3 months. Serum creatinine, eGFR and UACR should be documented in all patients at the initial evaluation for hypertension if CKD is diagnosed, and repeated at least annually thereafter. A negative urinary dipstick test does not rule out albuminuria, because it cannot detect UACR levels in the lower range [297]. However, urinary dipstick can offer information on other signs of kidney injury (i.e. microscopic hematuria, active urine sediment) and should be performed at least at the initial evaluation. The value of kidney imaging, including kidney ultrasound with Doppler measurements, is discussed in Section 5.5.3.

19.1 Treatment of hypertension in CKD

High BP is by far the most common modifiable factor for CKD progression [1341]. Treatment-resistant hypertension, elevated night-time BP and MH are common in patients with CKD, and associate with a lower eGFR, higher levels of albuminuria, and HMOD [1334,1342–1345]. In patients with CKD, several of the mechanisms that originate from the kidney and promote hypertension are exaggerated. These include increased sodium sensitivity, sodium/water retention, activation of the RAS and SNS, impaired endothelium-mediated vasodilatation and others [1335,1346]. Complications unique to CKD, such as secondary hyperparathyroidism and increased calcium-phosphate products leading to arterial stiffness, increased prevalence of OSA, and use of specific drugs such erythropoietin, glucocorticoids or calcineurin inhibitors may also be involved in the BP elevation in later CKD stages [1347,1348].

19.1.1 Treatment BP targets

Available evidence suggests that BP reduction with any type of the major antihypertensive drug classes can offer similar protection against major CV events (stroke, myocardial infarction or CV death) and all-cause death in individuals with CKD [1349]. However, for more than a decade, there has been considerable debate on the best (most protective) BP targets in patients with CKD, including CKD with comorbid diabetes [1350,1351]. Old observational data suggested an association between BP and the risk for ESKD, starting from an SBP level of >120 mmHg [1334]. More recent data from China obtained in untreated CKD patients without antihypertensive therapy followed prospectively for 5 years indicated that a BP >130/90 mmHg was associated with a significantly increased risk of CV and kidney outcomes [1352]. However, trial evidence on the most protective target BP in response to treatment of CKD, was missing. Current evidence originates mainly from two trials in nondiabetic CKD that randomized patients to different levels or ranges of mean BP and examined kidney outcomes. In the MDRD study, the projected eGFR decline within 3 years, and the risk of ESKD and death were not significantly different between groups of low and usual BP target [1353]. However, analyses by baseline proteinuria showed that, among patients with proteinuria >1 g/day, those in the low BP target group had a decrease in protein excretion and a slower GFR decline over time compared to patients in the usual BP target group [1354]. Similarly, in the AASK study, no difference in outcomes between different BP target groups was observed in the overall population [1355]; however, lower BP was associated with better kidney outcomes in the small subset of patients with proteinuria >1 g/day [1356]. Further analyses of MDRD and AASK combined the randomized trial periods with subsequent observational follow-up phases. In the MDRD long-term analysis, the lower BP target group was associated with reduced risk for ESKD or the composite of ESKD and death, again mainly driven by a beneficial effect in patients with baseline proteinuria >1 g/day [1357]. In the AASK long-term follow-up analysis, no difference in the risk of doubling of serum creatinine, ESKD or death was noted between the treatment groups. However, for patients with a UPCR >0.22 g/g (which roughly equals to a proteinuria of 0.25–0.3 g/day), the lower BP target carried a beneficial effect [1358]. A recent analysis combining these trials (1907 patients and a median follow-up of 14.9 years), showed that the lower target BP was associated with significant reductions in the risks of ESKD and mortality in the total population, and this effect was mainly driven by patients with UPCR >0.44 g/g [1357]. Thus, sustainability of BP reduction and extent of proteinuria are major determinants of nephroprotection in patients with nondiabetic CKD.

The results of the SPRINT study have little relevance to the question discussed above. SPRINT randomized 9361 hypertensive patients at increased CV risk to intensive (SBP <120 mmHg) or standard treatment (SBP <140 mmHg) [97]. About 28% had CKD with eGFR 20–60 ml/min/1.73 m^2, but very few patients had proteinuria because individuals with proteinuria >1 g/day or >1 g/g were excluded. Diabetes mellitus, i.e. the most common cause of ESKD, or prior stroke were also exclusion criteria. In the overall trial, the primary composite outcome (CV events as well as CV and total mortality) was

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significantly lower in the intensive-treatment group, but kidney outcomes did not differ between the two target groups. A sub-analysis of the SPRINT CKD subpopulation [1359] showed no difference between groups for the primary outcome or the prespecified kidney outcome but a lower total mortality rate in the intensive BP arm patients. All the above results must be interpreted with caution, as the SPRINT trial was not designed or powered to study kidney outcomes, which were very few (15 versus 16 in the two groups) in the trial. As a result, a recommendation to target SBP to <120 mmHg in patients with CKD cannot be made.

No direct evidence is available to answer the question of the optimal target BP in patients with CKD and type 2 diabetes mellitus. Older studies, including UKPDS38 [1360] and the sub-analysis of participants with diabetes in the HOT trial [708], offered insight on the DBP target, as they randomized patients to different on-treatment DBP levels. The ACCORD-BP trial randomized high-risk patients with type 2 diabetes to a target SBP <120 or <140 mmHg [1361]. Apart from showing no difference in the primary outcome (possibly because of interactions with other arms of the factorial design) (see Section 18.2) [1350], ACCORD-BP excluded individuals with serum creatinine >1.5 mg/dl, thus offering very little insight on the optimal BP target in patients with CKD and diabetes. A post hoc analysis of the RENAAL study showed that a baseline SBP of 140–159 mmHg increased the risk of ESKD or death by 38% compared to SBP <130 mmHg [1362]. A posthoc analysis from the IDNT showed that SBP >149 mmHg was associated with a 2.2-fold increase in the risk of doubling SCr or ESKD compared with SBP <134 mmHg. Moreover, progressive lowering of SBP down to 120 mmHg improved kidney and patient survival, while below 120 mmHg, all-cause mortality increased [1363]. Finally, although limited by the heterogeneity of the included studies [1350], a recent meta-analysis of studies in patients with CKD stage 3–5 has reported a mortality benefit by a SBP reduction of 16 mmHg and an absolute SBP of 132 mmHg with a nonsignificant benefit at achieved SBP values of <125 mmHg [1364]. In a more recent pooled analysis of four RCTs (AASK, ACCORD, MDRD and SPRINT), all-cause mortality showed a tendency to a reduction with intensive treatments (BP <130 mmHg), but this finding was not statistically significant (hazard ratio 0.87, 95% CI 0.69–1.08, $P = 0.21$). However, after excluding patients with higher GFR and those undergoing intensive glycemic control, lowering BP to <130 mmHg decreased all-cause mortality (hazard ratio 0.79, 95% CI 0.63–1.00, $P = 0.048$) when compared with a standard target of <140 mm Hg [1365].

Taking these largely indirect findings together and considering that, at least after development of proteinuria, progression of kidney injury tends to follow the same course in different situations, it may be suggested that (i) the BP target for proteinuric nondiabetic CKD applies to patients with proteinuric diabetic kidney disease as well and (ii) for both patient categories, a target SBP of <130 mmHg and DBP <80 mmHg, if well tolerated, can be associated with protection against CKD progression in individuals with an albuminuria >30 mg/g. A similar target may be associated with a reduction in mortality in most patients with CKD. Particularly in patients with advanced CKD in stage 4 and 5, careful monitoring of eGFR is recommended as a further functional, but reversible, decline of GFR may occur on a lower BP.

An office SBP of <120 mmHg and DBP <70 mmHg cannot be recommended because of the absence of relevant evidence. However, these guidelines acknowledge that these recommendations have a number of limitations: (i) none of the trials comparing different BP targets included patients with diabetes and CKD, thus current evidence cannot be readily extrapolated to this subpopulation; (ii) MDRD and AASK trials randomized participants to different mean BP levels, which cannot be readily extrapolated to SBP and DBP values; (iii) MDRD and AASK trials recruited patient populations of a relatively young age (mean age 51.7 and 54.6 years, respectively), and thus, their findings cannot be readily extrapolated to older patients with CKD and (iv) even for the long-term observational analyses, the benefits associated with lower BP targets were mainly apparent in individuals with proteinuria.

19.1.2 Antihypertensive drug treatment

People with CKD should receive lifestyle interventions, as reported in Section 7, with special attention to sodium restriction, as low-sodium diet reduces protein excretion in proteinuric CKD [1366]. Achieving the recommended BP targets in CKD usually requires combination therapy, which should consist of a RAS blocker with a CCB or a Thiazide/Thiazide-like diuretic, if eGFR levels are ≥45 ml/min/1.73 m^2 (CKD stages ≥3a). While in patients with an eGFR below 30 ml/min/1.73m^2, Thiazide/Thiazide-like diuretics should be generally replaced by loop diuretics, the transition from treatment with a Thiazide/Thiazide-like to a loop diuretic should be individualized in patients with eGFR values between 30 and 45 ml/min/1.73m^2. Clinical trials in people with diabetic [37–40] and nondiabetic CKD [1355,1367,1368] have established an ACEi or an ARB as the first treatment choice in hypertensive CKD patients, especially in those with moderate or severe albuminuria, where these agents were found to reduce proteinuria, the rate of GFR decline, and the risk of doubling of serum creatinine or progressing to ESKD. ACEis or ARBs should be given at the maximum tolerated doses to achieve optimal nephroprotection while dual combination of RAS blockers should be avoided because two outcome trials were prematurely terminated as a consequence of the increased risk of adverse events with the ACEi/ARB combination therapy [558,1369]. In normoalbuminuric individuals with hypertension, ACEis or ARBs are able to delay the progression to severely increased albuminuria compared with placebo [1370], but no evidence exists on whether these drugs lead to better preservation of kidney function compared with other major antihypertensive drug classes in the normoalbuminuric population [1371] (Fig. 20). Indeed, in a recent open-label trial in which patients with an eGFR were randomly assigned to either discontinuation or continuation of therapy with RAS inhibitors, discontinuation was not associated with a significant between-group difference in the long-term eGFR decline [1379].

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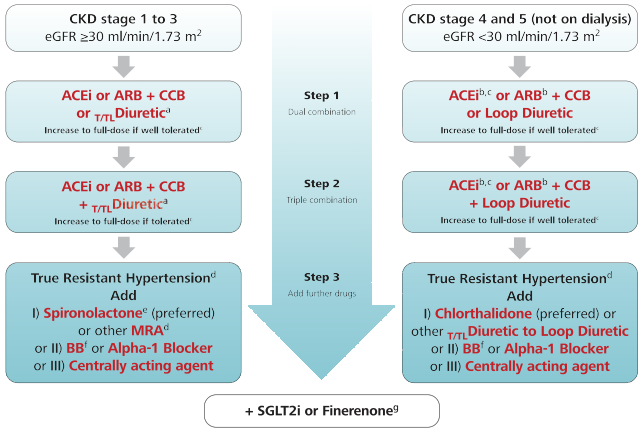


FIGURE 20 BP-lowering in patients with hypertension and chronic kidney disease. (a) Transition from T/TL Diuretic to Loop Diuretic should be individualized, in patients with eGFR < 45 ml/min/1.73 m^2. (b) Cautious start with low-dose. (c) Check for dose adjustment according to renal impairment for drugs with relevant renal excretion rate. (d) When SBP is ≥140mmHg or DBP is ≥90 mmHg provided that: maximum recommended and tolerated doses of a three-drug combination comprising a RAS blocker (either an ACEi or an ARB), a CCB and a T/TL Diuretic were used. adequate BP control has been confirmed by ABPM or by HBPM if ABPM is not feasible, various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension have been excluded (Section 12). (e) Caution if eGFR <45 ml/min/1.73 m^2 or serum potassium >4.5 mmol/l. (f) Should be used at any step as guideline directed medical therapy in respective indications or considered in several other conditions (Table 16). (g) SGLT2is and Finerenone should be used according to their approval for CKD treatment.

19.1.3 Special therapeutic challenges

CKD poses several additional difficult treatment problems. Firstly, the vasodilating effect of ACEis or ARBs on the efferent arteriole reduces intraglomerular pressure. This is frequently followed by eGFR reductions, on average 10–15% in the first weeks of treatment. A similar effect can be seen with large BP reductions by any antihypertensive agent. Thus, repeated monitoring of eGFR (as well as serum electrolytes, see the following) within the first 4–8 weeks of treatment (depending on baseline kidney function) is important when treatment is initiated. Clinicians should not be alarmed by this early GFR reduction, but if the decline in GFR continues or becomes more severe (>30%), the RAS blocker should be stopped, and the patient should be investigated for the presence of renovascular disease. Secondly, use of RAS blockers in CKD patients further increases the risk of hyperkalemia [1372]. Incident hyperkalemia is associated with increased mortality [1373] and is the most frequent reason for dose reduction or discontinuation of ACEi or ARB administration in CKD patients [1374,1375]. However, reducing the dose or discontinuing RAS blockers has been associated with increased risk of CV events in large surveys [1376–1378] and should be avoided.

Novel potassium binders (patiromer and sodium zirconium cyclosilicate) were shown to normalize elevated serum potassium and chronically maintain normal serum potassium levels in CKD patients treated with ACEis, ARBs or spironolactone, with a good tolerability [1380,1381]. These agents can be used to maintain serum potassium <5.5 mmol/l in patients with CKD [1382,1383]. Most patients with CKD will not achieve target BP control with ACEi or ARB monotherapy, and a DHP-CCB or a diuretic should almost always be included in the treatment regimen, most often both drugs [1384,1385]. DHP-CCBs may increase proteinuria when used in the absence of a RAS blocker in patients with proteinuric CKD [1386,1387]. Nevertheless, in the general hypertensive population, where the majority of patients has no or a mild albuminuria, DHB-CCBs have similar effects on kidney outcomes as RAS blockers or diuretics [1371]. In addition, in a study of hypertensive patients in whom 19% had moderate and only 5% severe albuminuria at baseline, a combination of a RAS blocker with a DHP-CCB was superior in reducing kidney outcomes compared with an RAS blocker in combination with a Thiazide [327]. Diuretics are particularly useful in CKD patients, because these patients are most often sodium-sensitive (especially if older, diabetic or obese) and have a high prevalence of treatment-resistant hypertension. Furthermore, diuretics can effectively reduce proteinuria when added to RAS blockers in proteinuric CKD [1366]. When GFR falls below 45 ml/min/1.73 m^2, Thiazide diuretics become less effective, because they cannot reach their tubular site of action because of competition for tubular secretion with other substances that accumulate in CKD [1388]. This is the case also for Thiazide-like diuretics, although a recent RCT that included 160 patients with CKD stage 4 reported a 10.5 mmHg 24 h SBP reduction in patients randomized to chlortalidone (mean dose 23 mg daily) [570]. In general, in patients with CKD stage 3b, eGFR 30–44 ml/min/1.73 m^2, diuretic therapy should be modified and the dosing individualized, while in patients with CKD stage 4, eGFR <30 ml/min/1.73 m^2, Thiazide should be substituted with a loop diuretic. Within this class, torasemide might be preferred to furosemide because of its longer half-life, which allows a less frequent dosing scheme and a better adherence to treatment [1336]. Finally, triple antihypertensive drug therapy may not control BP in a number of CKD patients. In these cases, BBs and alpha-1 blockers can offer important help, as sympathetic activity is increased in CKD [1389,1390]. However, their effects in CKD have not been tested in outcome kidney trials. Non-DHP-CCBs (if used with RAS blockers) were associated with reductions in proteinuria and decline of kidney function in proteinuric CKD [1391,1392], but when added to an RAS blocker in normoalbuminuric hypertensive patients, they did not seem to offer additional nephroprotection [1393]. In the PATHWAY-2, spironolactone was shown to be particularly

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effective for BP lowering when added to the standard triple-drug therapy, but patients with eGFR <45 ml/min/1.73 m^2 or potassium above 4.5 mmol/l were excluded in this trial [598] Section 12.4. In the AMBER trial that used spironolactone with addition of placebo or patiromer in patients with treatment-resistant hypertension and eGFR values between 25 and 45 ml/min/1.73 m^2, BP was effectively reduced in both groups, but the rates of hyperkalemia (potassium ≥5.5 mmol/l) were at about 60 and 35%, respectively, at 12 weeks [744]. Thus, use of spironolactone as a fourth antihypertensive agent in patients with CKD Stage 3b or higher is generally not advisable, unless in special circumstances, such as at low potassium levels, or when BP control is not achieved with addition of other agents. Use of novel potassium binders is advisable to maintain serum potassium below 5.5 mmol/l (Fig. 20).

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19.1.4 Use of additional drugs for cardiovascular- and nephroprotection in CKD

In addition to achieving BP control with the agents described above, progression of CKD and risk of CV events and mortality can be reduced in CKD patients by two novel drug classes that also have some BP-lowering effects, although they are not approved as antihypertensive agents. SGLT2is were first introduced as oral hypoglycemic agents that reduce plasma glucose levels by inhibiting renal glucose reabsorption through the SGLT-2 transporters, located in the proximal convoluted tubule. Early clinical studies in patients with type 2 diabetes suggested that these agents can reduce office SBP/DBP by 3–5/1–2 mmHg in hypertensive patients [1394]. This has been observed also for ABPM values [1395], and larger reductions have been described in patients with CKD Stage 4 (about 7 mmHg SBP) [1396]. The main antihypertensive mechanism is likely to be a mild natriuretic/diuretic effect (from inhibition of proximal sodium reabsorption) and osmotic diuresis [1396], although BP reductions have also been reported in patients under diuretic treatment [492]. These agents were also shown to reduce urine albumin excretion by 25–40%, depending on the baseline albuminuric levels [1397] and can reduce plasma uric acid, which is also important in CKD patients [1327].

CV outcome trials with SGLT2i in patients with type 2 diabetes have included large proportions of patients with CKD, showing impressive and homogeneous reductions (around 40%) of composite kidney endpoints [541,1328,1398]. The protective renal effects have been shown in three large trials on diabetic and nondiabetic CKD, in which SGLT2 inhibitors were used on top of standard therapy, including an ACEi or ARB at maximum tolerated doses [1399]. The CREDENCE trial (4401 patients with type 2 diabetes and CKD with severely increased albuminuria [1329]); the DAPA-CKD study (4304 patients with either diabetic or nondiabetic CKD and an UACR ≥200 mg/g) [1399]); and the EMPA-KIDNEY trial (6609 patients with either diabetic or nondiabetic CKD, an eGFR between 20 and <45 ml/min/1.73 m^2 and any level of albuminuria or 45 to <90 ml/min/1.73 m^2 with a UACR of ≥200 mg/g [1400]). All three trials were prematurely terminated due to significant reductions of the composite and individual kidney outcomes (doubling of SCr and ESKD) compared with placebo. In EMPA-KIDNEY, the reduction was evident across the whole range of eGFR and most striking in patients with severely increased albuminuria. The rate of eGFR loss was lower with empagliflozin in all UACR subgroups [1400]. At least in patients with diabetes, these benefits have been ascribed to direct kidney effects including a reduction in intraglomerular pressure and antifibrotic effects that are independent from glucose lowering [1401,1402]. A mild eGFR drop was present during the first weeks of treatment, and it was managed as in the case of RAS blockers. In CREDENCE and DAPA-CKD, SGLT2i were also able to reduce the risk of some CV events, and in DAPA-CKD, the risk of mortality was reduced [1403], a benefit that was not previously evident with RAS blockade or any other drug treatment in the CKD population [1403–1406]. Several previous studies have evaluated the addition of a steroidal MRA (spironolactone or eplerenone) on top of an ACEi or an ARB in patients with proteinuric diabetic CKD and showed significant reductions in urine albumin or protein excretion [1407–1409], independently of the BP-lowering effect. This antiprotenuric effect is ascribed to the inhibition of several deleterious genomic and nongenomic effects of aldosterone breakthrough, including kidney tissue inflammation and fibrosis mediated through mineralocorticoid receptor axis overactivation [1410]. However, in clinical practice, use of steroidal MRA in CKD is restricted by absence of evidence from outcome kidney trials and the increased risk of hyperkalemia [1411]. Finerenone is a novel, nonsteroidal MRA with a different duration of action and tissue distribution than steroidal MRAs, that inhibits binding of different coregulatory molecules to mineralocorticoid receptors. This allows reduction of inflammatory and fibrotic processes, with less interference with the mineralocorticoid-mediated actions in the distal tubule, e.g. with less BP reduction and less potassium increase than with steroidal MRAs [746,1410]. The BP reduction associated with finerenone appears to be less than that associated with spironolactone, and does not seem to substantially contribute to the organ-protective effects of the drug [578]. Recently, evidence of the dose-dependent reductions of albuminuria by finerenone [1412] has been shown in two outcome-based RCTs. In the FIDELIO-DKD trial (5734 participants with type-2 diabetes, CKD and moderate or severe albuminuria), finerenone on top of ACEi or ARB treatment was associated with significant reductions in the risk of kidney failure, eGFR decline (>40%), renal death and CV outcomes [542,543]. The SBP/DBP difference was 2.7/1.0 mmHg in favor of finerenone, consistently across all different baseline BP groups [578]. Hyperkalemia leading to discontinuation of the trial regimen was 2.3% with finerenone and 0.9% with placebo, and no fatal hyperkalemia related adverse events were reported [543]. However, this incidence comes from an RCT, and whether similar figures will be obtained in a real-world setting remains to be demonstrated. In the FIGARO-DKD trial (including 7437 participants) with characteristics similar to the FIDELIO-DKD trial, finerenone was associated with a 13% significant reduction in the risk of CV death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for HF (the primary outcome), with consistent beneficial effects on kidney outcomes and similar tolerability profile [1413]. In an on-treatment analysis combining the patient population of both trials, finerenone reduced mortality by 18% compared with placebo [1414]. Other nonsteroidal MRAs (esaxerenone and apararenone) have also

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shown to significantly reduce albuminuria in CKD patients in phase 2 clinical trials [1415], but they have not yet been tested in pivotal kidney outcome studies. In view of the above evidence, it is recommended to use SGLTis or finerenone in patients with CKD in addition to lifestyle interventions and antihypertensive drug therapy. Use of an SGLTis should be considered either in patients with diabetic and in patients with nondiabetic CKD with a moderate or severe increase of albuminuria, while use of finerenone is recommended in some patients with diabetic nephropathy and moderate or severe albuminuria. The order of addition of an SGLTis or finerenone has not been tested in clinical trials and can be based on the individual patient characteristics, including the need for improvement of glycemic control, potassium levels or persistent albuminuria (Fig. 20).

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19.2 Renovascular disease

Renovascular hypertension represents one of the most common forms of secondary hypertension, with a reported prevalence of around 2–5% of all hypertensive individuals and up to 30% of patients with secondary hypertension [1416,1417]. Traditionally, atherosclerotic renal vascular disease and FMD are regarded to account for 90 and 10% of these cases, respectively [1418,1419]. However, the actual prevalence of renovascular hypertension may be considerably higher in selected cohorts of patients, such as those with resistant hypertension [1420]. Atherosclerotic renal vascular disease has been reported in 6.8% of individuals over 65 years of age, 10–12% of patients with ESKD [1421], 15–30% of patients with CAD and up to 50% of patients with HF [1422,1423]. Renal FMD varies between <1 and 6% of individuals in observational studies [1424]. The overall prognosis of atherosclerotic renal vascular disease is unfavorable because the CV event rate after atherosclerotic renal vascular disease diagnosis can exceed that of the general population by a factor of 3–6 [1425]. In addition, CKD patients with atherosclerotic renal vascular disease not receiving dialysis have a mortality rate 1.5 times higher than patients with other causes of CKD, the mortality of those on dialysis being three times higher [1426]. Within patients with atherosclerotic renal vascular disease, prognosis varies considerably depending on the underlying clinical status and comorbid conditions. Patients presenting with flash pulmonary edema have a two-to-three-fold higher risk of CV events and death, compared with patients with low-risk phenotypes (those without flash pulmonary edema, refractory hypertension, or rapid loss of kidney function) [1427].

While revascularization with balloon angioplasty without stenting is the treatment of choice for patients with FMD and hemodynamically significant renal artery stenosis [341], the optimal treatment of atherosclerotic renal vascular disease has been matter of considerable debate for several years [1428,1429]. After some early years of little evidence-based support of revascularization, a few large RCTs attempted to test the effects of standard medical therapy plus percutaneous transluminal renal angioplasty compared with medical therapy alone in patients with atherosclerotic renal vascular disease, and showed no significant differences in BP levels, adverse CV or kidney outcomes between the two groups [1430–1432]. However, these trials met with severe criticisms because of methodological limitations, such as nonstandardized inclusion criteria, poor assessment of the stenosis severity, enrolment delays, protocol revisions during the trial, high crossover rates and low event rates. Most importantly, these trials included mainly patients with mild/asymptomatic atherosclerotic renal vascular disease, mild hypertension or advanced CKD and excluded patients in whom the clinical presentation was highly suggestive of critical renal artery stenosis, i.e. those with flash pulmonary edema, refractory hypertension, or rapidly declining kidney function [1419]. Several observational studies in patients with well documented severe atherosclerotic renal vascular disease (≥70% stenosis) and high-risk clinical profiles document significant benefits of revascularization in terms of BP control, preservation of kidney function and reductions in the risk of CV events and death [1427,1433]. Thus, the current consensus is to offer revascularization on top of medical therapy in patients with documented secondary hypertension because of atherosclerotic renal vascular disease or high-risk clinical profiles and documented high-grade stenosis (≥70%) [1423,1428,1429]. Medical therapy alone could be used for individuals with asymptomatic atherosclerotic renal vascular disease with <70% stenosis, patients with mild or moderate hypertension that is easily controlled with antihypertensive drugs and low-grade stenosis, or patients with nonviable kidney parenchyma, where revascularization has little to offer. In the medically treated patients, if treatment initiation with an ACEi or an ARB results in eGFR reduction of ≥30%, careful re-evaluation of the patient is warranted.

19.3 Hypertension in patients with kidney transplantation

Kidney transplantation is considered the optimal choice for kidney replacement therapy in patients with ESKD because of improved survival and quality of life compared with dialysis. This survival benefit has been attributed to kidney function improvement and delayed progression of CV disease [1434]. However, the residual CV risk remains significantly higher in kidney transplant recipients than in the general population, and CVD remains the leading cause of death in these patients during the 10 years post transplant [1435]. Kidney transplantation 'per se' is associated with significant BP reductions (24 h BP −8/−5 mmHg) in the short-term and mid-term posttransplant periods as well as with reduction in the use of antihypertensive agents [1436,1437]. ABPM values in transplanted patients are significantly lower than those of matched hemodialysis patients and similar to patients with CKD and matched kidney function [1438]. Despite these improvements, hypertension represents the most prevalent post-transplantation comorbidity, with ABPM studies estimating the presence of hypertension in >95% of the patients [1439]. Elevated BP is associated with kidney function decline, organ damage, CV events and reduced graft and patient survival [1410,1440,1441]. Several studies showed that misclassification of hypertension status by office BP is commonly encountered in these patients [1442], mostly because of a particularly high proportion of MH (20–40%)

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associated with a frequently impaired dipping status (around 50%) [1443] and high rates of nocturnal hypertension (up to 70–80%) [1444,1445]. Ambulatory BP is a much stronger predictor of kidney function decline and organ damage than office BP in kidney transplanted patients [1441], and thus use of ABPM is recommended for the management of hypertension in this condition.

The pathogenesis of hypertension in kidney transplanted patients is multifactorial, involving traditional risk factors, factors related to CKD (most commonly impaired sodium handling and activation of RAS and SNS) and factors related to transplantation and its treatment [1446]. Among major immunosuppressive classes, purine pathway inhibitors (mycophenolate mofetil or azathioprine), and mammalian target of rapamycin (mTOR) inhibitors (everolimus or sirolimus) do not affect BP control [1446,1447]. Glucocorticoid treatment is known to increase BP, and avoidance or withdrawal protocols in kidney transplanted patients are associated with a better BP profile [1448,1449]. Calcineurin inhibitors (cyclosporine or tacrolimus) are also associated with BP elevations, through increased sodium reabsorption via the Thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule, the increase of vasoconstrictive substances leading to increase of total peripheral resistance and vasoconstriction of afferent arteriole at the preglomerular site [1446,1447], and, for cyclosporine, a marked activation of sympathetic nerve firing [1450]. The effects of tacrolimus on BP appears less pronounced compared to cyclosporine.

BP targets for hypertension management in kidney transplanted patients are extrapolated from data in CKD populations as there are no specific RCTs that have tested different BP targets on major clinical endpoints. Yet, a target SBP of <130 mmHg is considered as a reasonable target for kidney transplant patients. Lifestyle modifications should be adopted on the basis of general recommendations for CKD, and drug combinations between major antihypertensive agents should be employed in most patients. Special benefits by ACEis/ARBs are not clearly established, because available studies provide conflicting results [1410,1447], although, in a recent meta-analysis, the risk of graft loss was reduced by 38% with ACEis/ARBs (9 studies, 1246 participants) without, however, any significant effect on nonfatal CV outcomes or death, and with an increased incidence of hyperkalemia [1451]. In kidney transplanted patients, DHP-CCBs have been consistently associated with benefits such as improved graft survival and minimization of the vasoconstrictive effects of calcineurin inhibitors at the preglomerular site. In the aforementioned meta-analysis, CCBs reduced the risk for graft loss by 42% (16 studies, 1327 participants), while in head-to-head comparisons with ACEis/ARBs, CCBs significantly increased GFR by 11.11 ml/min [1451]. Thus, CCBs can be preferentially used in the early posttransplantation period. Thiazide/Thiazide-like diuretics are also effective and useful in patients with kidney transplantation, because they block the cyclosporine-mediated sodium retention. At present, no data are available on the effect of antihypertensive drugs on long-term graft loss. Transplant renal artery stenosis is not uncommon in patients with kidney transplantation, and it should be effectively sought for in cases of uncontrolled or abrupt onset hypertension [1446]; PTRA has high success rates in these patients [1452].

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Treatment strategies in patients with kidney disease

Recommendations and statements	CoR	LoE
BP should be monitored at all stages of CKD, because hypertension is the second most important risk factor for end-stage kidney disease (ESKD).	I	A
Non-dipping or elevated night-time BP are frequent in CKD patients and should be monitored by ABPM or HBPM.	I	B
In both diabetic and non-diabetic CKD with hypertension, BP-lowering treatment slows the decline of kidney function and reduces the risk of ESKD and CV outcomes.	I	A
Immediate lifestyle interventions and antihypertensive drug treatment are recommended in most patients with CKD independently of the CKD stage if SBP≥ 140mmHg or DBP ≥90mmHg.	I	C
In all patients with CKD the primary goal is to lower office BP to <140 mmHg systolic and <90 mmHg diastolic.	I	A
In most CKD patients (young patients, patients with an albumin/creatinine ratio ≥ 300 mg/g, high CV risk patients) office BP should be lowered to <130/80 mmHg if tolerated.	II	B
In kidney transplant patients with hypertension, office BP should be lowered to <130 mmHg systolic and <80 mmHg diastolic.	II	B
In patients with CKD regardless of the presence of albuminuria, BP should not be lowered below 120/70 mmHg.	III	C
An ACEi or an ARB, titrated to the maximum tolerated doses is recommended for patients with CKD and moderate (UACR 30 to 300 mg/g) or severe (UACR > 300 mg/g) albuminuria.	I	A

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Dual combination of an ACEi with an ARB is not recommended.	III	A
BP control is difficult in CKD and resistant hypertension is very frequent. Therefore combination treatment is almost always recommended.	I	B
SGLT-2 inhibitors are recommended for patients with diabetic and non-diabetic nephropathies CKD if eGFR is at least 20 or 25 ml/min/1.73². [a]	I	A
The non-steroidal MRA finerenone is recomended in patients with CKD and albuminuria associated with type 2 diabetes mellitus if eGFR is at least 25 ml/min/1.73² and serrum potassium <5.0 mmo/L.	I	A
In CKD patients with hyperkalemia a potassium binder can be used to maintain normal or near normal serum potassium levels (<5.5 mmol/L) in order to allow optimal treatment with a RAS-blocker or a MRA to continue.	II	B

Additional eGFR and albuminuria criteria apply for initiation of treatment with different SGLT2is according to their respective approval.

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20. HYPERTENSION AND OTHER SELECTED COMORBIDITIES

20.1 Obesity

Obesity and arterial hypertension commonly occur in the same patients and often have type 2 diabetes has a third associated condition. Hypertensive obese patients may require more antihypertensive medications to have their BP controlled than nonobese individuals and are more likely to exhibit treatment-resistant hypertension [1453–1455], and metabolic side effects of antihypertensive medications may be particularly relevant in this population. There is a paucity of hypertension trials specifically dedicated to hypertensive, obese patients and data on combination of antihypertensive treatments and body weight management are also scarce. Nevertheless, based on available trials, observational studies and trial subgroup analyses, the following considerations and recommendations can be made.

20.1.1 Antihypertensive pharmacotherapy in obesity

When treating patients with obesity and hypertension, a sensible goal is to attain BP reduction without worsening obesity and associated metabolic risks. Although there is no evidence that BP targets differ between patients with and without obesity, achieving the target BP value is more difficult in the presence of obesity. For example, a retrospective analysis of the ALLHAT trial stratified patients according to BMI in normal weight (BMI <25 kg/m^2), overweight (BMI 25–29.9 kg/m^2) and obese (BMI >30 kg/m^2) groups [1456]. After 5 years of treatment, two-thirds of the patients achieved BP control, regardless of BMI, but patients with obesity required a larger number of medications [1456]. In patients with obesity and hypertension, it may be prudent to initiate antihypertensive therapy with ACEis, ARBs or CCBs, because none of these drug classes worsens insulin sensitivity or adiposity. RAS inhibitors may ameliorate glucose metabolism, although they do not necessarily prevent the greater risk of obese patients to develop type 2 diabetes mellitus [603,1457], because of the close and common association of obesity with insulin resistance, a precursor of type 2 diabetes [1458]. Thiazide/Thiazide-like diuretics, particularly at higher doses, may worsen glucose and lipid metabolism and increase the risk of type 2 diabetes, while BBs promote weight gain, have dyslipidemic effects, and may also increase the risk of type 2 diabetes, the diabetogenic influence being greater for the BB plus diuretic combination. These disadvantages are attenuated or absent with vasodilating BBs [1459–1461]. Potential metabolic side effects of these drugs in hypertensive dyslipidemic patients have to be weighed against their efficacy in lowering BP, because in many obese patients, adequate BP control can only be obtained by combination therapy, and diuretics are especially effective BP-lowering agents [1456], possibly because obesity is associated with abnormal salt handling and volume expansion [1462,1463]. The latter may be explained in part by reduced natriuretic

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peptide actions in obesity [21]. Furthermore, in patients with obesity, hypertension may be associated with comorbidities such as postmyocardial infarction or HFrEF, for which BBs are a compelling indication. A potential advantage of BBs is that they may attenuate the CV influence of the SNS, which is activated in patients with obesity, and more so in patients with obesity and hypertension [1464,1465]. In this context, a subgroup analysis of the ACCOMPLISH trial has shown that the risk of CV outcomes did not differ between obese patients treated with an ACEi either combined with a CCB or a diuretic [1466] supporting the use of diuretic-based combinations in this clinical condition, in which the efficacy of BP lowering may outbalance the potential metabolic disadvantages of this drug class. Other drug classes with antihypertensive effects have been tested in smaller trials in patients with obesity, including renin inhibitors and valsartan/sacubitril [1467,1468].

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20.1.2 Role of nonpharmacological weight loss intervention

Strong evidence is available that in addition to improving metabolic risk factors, weight loss can have a beneficial effect on BP control [1469]. In individuals with high-normal BP randomized to a nutritional intervention, 2.7 kg body weight loss was associated with an incidence of hypertension of 8.8% compared with 19.2% in the control group [1470]. In the TOHP Phase I study [1471], men and women aged 30–54 years who lost 3.9 kg weight showed a SBP/DBP decrease of 2.9/2.3 mmHg over 18 months, with a stronger reduction in severely obese patients. In TOHP Phase II, individuals who lost at least 4.5 kg after 6 months and maintained their weight reduction over 30 months had the greatest BP decrease and a 65% reduction in the risk of developing hypertension [1472]. In the TAIM trial, on overweight and obese mild hypertensive patients, body weight and DBP decreased by 4.7 and 8.8 mmHg, respectively, after 6 months under hypocaloric diet compared with control groups under antihypertensive drug treatment, a low-sodium/high-potassium diet, a usual diet or placebo [1473]. In the TONE trial, moderate weight loss decreased the need for antihypertensive therapy by approximately 30% in older hypertensive patients on a single antihypertensive drug [1474]. The BP-lowering effects of weight reduction achieved by dietary approaches are also supported by meta-analyses [1475], and evidence is available that loss of body weight reduces sympathetic activity [368], while reversing abnormalities in natriuretic peptide regulation [1476,1477]. Thus, lifestyle interventions aimed at reducing body weight are recommended in patients with obesity and hypertension through low caloric diets and increased physical activity. Involvement in the treatment plan of dieticians may be helpful. A problem is, however, that even when concerned teams are made available and therapeutic plans are implemented, relatively few patients with obesity are able to sustain weight loss in the long-term.

20.1.3 Role of weight loss medications

Very few currently available weight loss medications have been specifically tested in obese hypertensive patients, having BP reduction as the primary goal. Newer weight loss drugs that have been evaluated for CV protection in large-scale trials on overweight and obese type 2 diabetic patients have not been shown to improve CV outcomes in nondiabetic patients with overweight or obesity. Therefore, the role of such medications in managing BP in obese hypertensive patients is unclear. A recent meta-analysis has shown that not all medications that reduce body weight improve BP control in patients with hypertension [373], although in one study combining orlistat with a hypocaloric diet was more effective than diet alone to achieve BP control in patients with obesity and hypertension [1478]. Furthermore, in other studies, low-dose topiramate/phentermine, which is not approved in Europe, reduced body weight and BP in obese hypertensive patients [1479,1480]. For other drugs, such as liraglutide or lorcaserin, BP responses have been modest or absent in the case of naltrexone/bupropion [373,1481–1483]. Once weekly treatment with the GLP-1 RA semaglutide decreased body weight more compared with daily liraglutide administration [1484]. BP decreased SBP/DBP by 2.8/4.5 mmHg more in the semaglutide compared with the liraglutide group [1484]. Seventy-two-week treatment with once weekly tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) GLP-1 RA lowered body weight in a dose-dependent fashion, with 20.9% body weight reduction at the highest 15 mg dose of the drug compared with 3.1% weight reduction under placebo [1332]. Compared with the placebo group, SBP in the pooled tirzepatide group decreased by 6.2 mmHg [1332]. It is important to mention that some antidiabetic agents favor weight loss [1485]. Metformin treatment is accompanied by a modest weight loss [1486,1487]. A consistent albeit moderate reduction in body weight has been also observed with SGLTi treatment. Overall, weight loss medications should not be primarily prescribed for the management of hypertension in patients with obesity. However, when prescribed for other reasons, BP reduction can be an added benefit depending on the drug class. Indeed, particularly GLP-1 RA and dual GIP/GLP-1 RA are important novel drugs that are approved or designated for approval for the treatment of patients with a BMI of at least 27 kg/m^2 but less than 30 kg/m^2 (overweight) and hypertension in addition to their approval in type 2 diabetes or obesity.

20.1.4 Role of bariatric surgery

Bariatric surgery comprises various procedures such as sleeve gastrectromy, Roux-en-Y gastric bypass or biliopancreatic diversion with the common goal of reducing body weight. Procedures differ in terms of weight reduction, adverse effects and weight-independent effects on gut hormones. The nonrandomized Swedish SOS study showed that weight reduction through bariatric surgery improves CV morbidity and mortality in men and in women with a BMI of at least 34 or 38 kg/m^2, respectively [1487]. A recent meta-analysis comprising 269 818 patients submitted to bariatric surgery and 1 270 086 control patients confirmed these findings [1488]. Bariatric surgery is also followed by a sustained reduction of metabolic and other risk factors, which improve overall CV risk profile [1486–1490]. A long-lasting reduction of sympathetic nerve activity [1491]

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and increased natriuretic peptide availability [1492,1493] may contribute to the beneficial effect on BP and risk. It has been remarked that long-term BP reduction following bariatric surgery is relatively modest for the large reduction in body weight [1488]. Along the same critical line, an analysis of SOS suggested that weight loss through bariatric surgery decreased the risk of hypertension only in the first few years following the procedure [1494]. However, the above-quoted meta-analysis has shown a substantial reduction in the incidence of hypertension in the bariatric surgery group [1488]. Furthermore, a more recent randomized trial in treated hypertensive patients with a BMI of 30–39.9 kg/m^2 has reported that compared with medical therapy, the Roux-en-Y gastric bypass surgery group required fewer antihypertensive medications to maintain BP below 140/90 mmHg for up to 3 years [1495] following surgery. In addition, after 1 year, no patients in the surgery group and 14.9% patients in the medical group exhibited treatment-resistant hypertension [19]. Thus, patients with obesity and hypertension who undergo bariatric surgery often appear to experience improvements in BP control, require fewer antihypertensive medications and have less risk to develop hypertension over time, although doubts still exist on whether the risk reduction persists indefinitely [1494]. Considering the risks associated with surgery and the limited amount of data, bariatric surgery should not be considered primarily for the management of hypertension. However, improved BP control appears to be an added benefit in patients with obesity submitted to bariatric surgery.

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Hypertension management in obesity

Recommendations and statements	CoR	LoE
In adults with elevated BP who are overweight or obese, weight reduction is recommended to reduce BP and improve CV outcomes.	I	A
Thiazide/Thiazide-like Diuretics and BBs have some unfavorable metabolic effects. However, since optimal BP control is the primary goal of antihypertensive treatment, combination therapy with these drug classes is frequently necessary and recommended.	I	A
Dual GIP/GLP-1 RA or GLP-1 RA should not be prescribed for BP control in patients with obesity.	III	C
Obese patients should not be referred to bariatric surgery for BP control.	III	C
Dual GIP/GLP-1 RA or GLP-1 RA or bariatric surgery lower BP indirectly in parallel with body weight reduction and contribute to BP control in obese patients.	II	B
In obese patients with diabetes and hypertension treatment with anti-diabetic drugs that reduce both body weight and BP could be preferred.	II	B

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20.2 Obstructive sleep apnea

Sleep disorders such as a reduction of sleep to <6 h per night [1496] are included in the list of risk factors for development of hypertension and increased CV risk. The most widely studied sleep disorder is OSA, which can be found in a considerable number of patients with difficult-to-treat or resistant hypertension [729], which favors this condition via multiple and complex pathophysiological mechanisms [1497]: hypoxia during night-time episodes of hypopnea and apnea, sympathetic overdrive, systemic vasoconstriction, oxidative stress and systemic inflammation [1498]. Hypertension mediated by OSA is

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often associated with MH, higher BP values during the night or nocturnal hypertension and a nondipping status [1499]. To reduce BP in patients with OSA, all major classes of antihypertensive drugs can be used. BP reduction has been reported also with the use of MRAs [1500]. Continuous positive airway pressure (CPAP) application has been shown to induce small reductions (about 3 mmHg for) in office and 24 h SBP, the 24 h BP reduction including day-time and night-time BP values [1501]. Patients that may benefit more from CPAP treatment have been reported to be younger than 60 years, with an uncontrolled BP before treatment initiation and with severe oxygen desaturation at baseline [1501]. The BP-lowering effect of CPAP can be seen also in patients with resistant hypertension and it has been found to be almost double for the nightime than to the daytime BP [1502], due to reduced sleep segmentation and improved intermittent hypoxia [1503]. Reduction of arterial stiffness, decrease of high-sensitive C-reactive protein, plasma cortisol and noradrenaline levels have also been associated with use of CPAP [757,1504,1505].

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20.3 Asthma

Hypertension and asthma are common diseases frequently encountered together in the same patient. Epidemiological studies indicate an increased prevalence of hypertension in asthmatic patients compared with patients without asthma [1506]. It has also been reported that hypertension is associated with augmented asthma severity, reduced lung function and reduced forced expiratory volume in 1 s (FEV1) as a marker of CV mortality, independent of the smoking history [1507]. The hypothesis has been advanced that the bidirectional relationship between hypertension and asthma can at least in part reflect underlying low-grade systemic inflammation, and an inverse relationship between C-reactive protein levels and decreased FEV1 has indeed been reported [1506]. The pathophysiological interplay between hypertension and asthma may also result from the concomitance of other comorbid conditions. A meta-analysis of prospective studies showed that a condition closely related to hypertension such as obesity is an important risk factor for asthma and asthma-related morbidity [1508,1509]. Obese patients with asthma experience more frequently severe exacerbations of the disease and a reduced response to asthma medications, possibly via an increased production of pro-inflammatory cytokines and systemic inflammation [1508,1509]. The OSA syndrome is another asthma-related factor associated with hypertension and systemic inflammation. OSA was found to be more prevalent in asthma patients as well as an independent risk factor for poor asthma control [1506,1508–1510]. A combination of genetic factors, age, emotional stress, diet and lifestyle characteristics also contribute to the hypertensive asthmatic phenotype and may predispose patients with asthma to hypertension [1506,1511,1512].

Patients with hypertension and asthma constitute a subgroup of patients in whom treatment of either condition is more difficult and the risk of developing CV events is elevated [4,1506,1513]. Lifestyle modifications appropriate to both conditions should be implemented, smoking cessation being of obvious primary importance. For the drug treatment of hypertension, CCBs appear to be particularly suitable, as they may favor bronchial smooth muscle relaxation. Among RAS blockers, ARBs should be preferred because of the risk of developing cough during treatment with ACEis, which may be particularly disturbing in asthmatic patients. It is recommended to avoid BBs for antihypertensive treatment in patients with asthma because the safety margin of these drugs is smaller than in chronic COPD, where BBs are safe [1514], although this is a controversial issue [1515]. Nevertheless, a cautious use of BBs in patients with compelling indications to balance individual benefits and risks appears reasonable. Finally, treatment of asthma with beta-adrenergic agonists and corticosteroids may induce adverse CV effects by increasing heart rate and BP [1506,1513].

20.4 Obstructive pulmonary disease

Hypertension is the most common comorbidity in patients with COPD and both comorbidities are independently associated with increased risk of CV events [1516]. Patients with COPD are characterized by the presence of chronic systemic inflammation, which plays a role also in the pathophysiology of comorbidities that are frequently associated with COPD [1516], including hypertension. In hypertension, COPD also promotes HMOD such as endothelial dysfunction, atherosclerosis and cardiorenal damage [1516]. A common CV risk factor that is a major cause of COPD, i.e. smoking, also contributes to BP elevation and CV risk in hypertension [1517,1518]. Management of hypertension in patients with COPD should consider the effects of antihypertensive drug classes on impaired respiratory function, adverse pulmonary outcomes, including not only COPD exacerbations but also overall CV outcome and mortality [4,1516]. Interactions between antihypertensive drugs and agents used for treating COPD such as bronchodilators and corticosteroids should also be taken into account, because of their possible pressor and tachycardic effects [1516]. In this regard, the general recommended strategy for antihypertensive drug treatment applies also to COPD. This applies also to BBs, the use of which is upgraded compared with previous guidelines [4], and treatment recommendations in general. While in the past, BBs were contraindicated for COPD patients, because of their bronchoconstrictive effects, this view has now changed. A systematic review and meta-analysis of 49 studies involving more than 670 000 patients indicated that treatment of patients with COPD and CVD with both ß1-selective and nonselective BBs significantly lowered heart rate (about 8 bpm) and reduced all-cause mortality as compared with COPD patients with no BB treatment. Additionally, use of ß1-selective BBs, but not of nonselective ones, reduced CODP exacerbations [1519]. Thus, in COPD patients, hypertension and CVD should be treated, if tolerated with more ß1-selective BBs, to reduce both mortality and COPD exacerbations (Table 16).

20.5 Gout and uric acid

The prevalence of hypertension in patients with gout is twice as high compared with patients without gout (36 versus 17%), while hyperuricemia (with or without gout) can be found in more than one out of four hypertensive patients [1520,1521].

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Furthermore, hypertension is independently predicted by greater serum uric acid levels [1522,1523] and their predictive role can be seen also in childhood and adolescence, while being almost completely lost in the older population as well as in patients with secondary hypertension and normal kidney function [1524]. Gout is clearly associated with an increased risk of CV events (including myocardial infarction and stroke) [1525] through mechanisms that are not extraneous to the pathophysiology of hypertension and its associated CV and kidney complications, because inflammation and oxidative stress are common drivers of both diseases [1526]. Prevention of gout by lowering serum uric acid with allopurinol or xanthine-oxidase inhibitors has been reported to be associated with a small BP reduction [1527–1530] and achievement of serum uric acid level <6.0 mg/dl are recommended by recent guidelines on gout treatment [1530]. Drugs used for the treatment of gout flares, i.e. colchicine, NSAIDs and corticosteroids, may negatively impact on BP values and control in hypertensive patients, which means that under these circumstances, both office and out-of office BP monitoring should be intensified. The recently reported preventive role of colchicine against atherosclerotic disease [1531], presumably via reduction of its contribution to inflammation and atherosclerosis, requires confirmation. This is required also for the CV-protective effect of reducing serum uric acid by antiuricemic agents, which has been suggested by earlier studies [1527,1529] but recently denied by a RCT with allopurinol in patients with CAD [1532,1533].

Antihypertensive drugs have a well known differential effect on serum uric acid. Serum uric acid level increases with the use of Thiazide/Thiazide-like and loop diuretics [1534]. ACEis, ARBs, CCBs and BBs have no effect, although a reduction of kidney excretion of uric acid has been reported for BBs [1535]. Among ARBs, losartan has been shown to reduce serum urate levels through an uricosuric effect, with some favorable implications for CV outcome [1536]. Together with CCBs, losartan has also been shown to reduce the incidence of gout in hypertensive patients, regardless of the BP level, in a large nested case–control study [1535]. In line with other guidelines [1530], these guidelines suggest to prescribe diuretics with caution in patients with gout but not to avoid them if diuretics are needed to achieve BP control. In general, physicians should try to use lower doses of diuretics because the effect of these drugs on serum uric acid is dose-related.

20.6 Immune-mediated inflammatory diseases

Immune-mediated inflammatory diseases, including diseases such as rheumatoid arthritis, psoriasic arthritis or lupus erythematosus, are associated with an increased prevalence of hypertension that is often underdiagnosed and poorly controlled [1537–1539]. The increase in CV risk associated with immune-mediated inflammatory diseases is only partially related to traditional CV risk factors and possibly attributable to inflammatory changes in the vasculature [1538]. The increase of the overall CV risk in patients with immune-mediated inflammatory diseases can be estimated by available risk calculators [1530].

20.6.1 Rheumatoid arthritis

Rheumatoid arthritis is associated with an increased risk of CV disease [1540,1541]. According to some reports, the prevalence of hypertension in the unselected rheumatoid arthritis population is not greater compared with nonrheumatoid arthritis controls [1542]. However, this has not been confirmed by other studies that included hypertension as a baseline covariate, which have found an increased prevalence of hypertension or higher BP values in rheumatoid arthritis [1543]. Hypertension was reported to contribute to CV risk similarly in rheumatoid arthritis and in the general population [1544], although this is not entirely in line with the relationship between the duration of the disease and the progression of organ damage [1545]. Most of the currently used disease-modifying antirheumatic drugs do not seem to have substantial effects on BP. However, several other agents used in the symptomatic treatment of rheumatoid arthritis patients appear to raise BP [1546]. Paradigmatically, NSAIDs and glucocorticoids raise BP [1520] and may cause clinically significant hypertension or impairment of BP control in treated hypertensive patients. BP should be lowered in rheumatoid arthritis as in the general population, preferentially with CCBs and RAS inhibitors because of the evidence of an overactive RAS [1547] in this disease. Underlying diseases should be managed by reducing inflammation and by avoiding high doses of NSAIDs [1520].

20.6.2 Psoriatic arthritis

Psoriatic arthritis is associated with an increased cardiometabolic risk leading to an excess of CV disease [1548]. Psoriasis is a common, chronic inflammatory disease of the skin and joints that affects 2–4% of the general adult population. Recent studies suggest that psoriasis, particularly if severe, may be an independent risk factor for atherosclerosis, myocardial infarction and stroke [1549]. Hypertension is prevalent in patients with psoriatic arthritis (20–25%) [1549] along with obesity and several metabolic abnormalities involving glucose and lipid profiles. In patients with psoriatic arthritis, BP should be lowered according to the general antihypertensive treatment recommendations, preferentially with RAS inhibitors and CCBs. BBs may trigger or worsen psoriasis and should be avoided if possible or carefully used in the presence of compelling indications [1550] (Table 16). Glucose control should be considered in patients with hypertension and psoriatic arthritis [1551].

20.6.3 Systemic lupus erythematosus

Patients with systemic lupus erythematosus have a higher burden of CV risk factors compared with the general population, and this is responsible for the high prevalence of premature CVD in the affected patients [1552]. CVD is an important cause of

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both morbidity and mortality in systemic lupus erythematosus resulting from a combination of factors with prothrombotic and/or atherogenic properties. In a recent meta-analysis, the relative risk of CVD was significantly elevated in patients with systemic lupus erythematosus compared with the general population [1553]. Studies differ as to the risk factors that are more frequently represented and prognostically relevant in the systemic lupus erythematosus population. A multivariate analysis identified age (relative risk 1.03), hypertension (1.71), smoking (1.48), diabetes (2.2) and dyslipidemia (2.18) as significant risk factors for CV events in this condition. This can help in the adoption of appropriate preventive measures, including BP control [1554]. Apart from small old uncontrolled studies [1555,1556], no trial targeting hypertension in systemic lupus erythematosus is available. The 10-year survival rate of systemic lupus erythematosus patients has significantly improved during the last half century, now standing at 92% [1557]. This improved prognosis is because of early recognition of milder cases and improvement in both specific and general medical care, e.g. treatment with immunosuppressive drugs, kidney replacement therapies and treatment of comorbidities, including hypertension.

20.7 Glaucoma in hypertension

Glaucoma is a leading cause of irreversible blindness affecting more than 60 million people worldwide [1558]. Primary open-angle glaucoma (POAG) is the most common type of glaucoma, accounting for more than 90% of all glaucoma cases [1559]. Normal tension glaucoma is a common form of POAG with no elevation of the intraocular pressure. Development and progression of glaucoma is influenced by complex interactions between arterial BP, intraocular pressure and ocular perfusion pressure. The mean ocular perfusion pressure is the difference between the pressure in the central retinal artery and vein [1560]. The central retinal arterial perfusion pressure can be determined by the mean arterial pressure value and the intraocular pressure [1560]. High BP may lead to high intraocular pressure with increased production of aqueous humor attributed to high ciliary blood flow and capillary pressure as well as low aqueous outflow due to increased episcleral venous pressure [1561,1562]. In contrast, low-BP, either spontaneous or due to antihypertensive therapy, may decrease ocular perfusion pressure, but this may result in ischemic damage of the optic nerve [1562–1565]. Accordingly, in patients with normal tension glaucoma, deterioration of the visual field may still progress despite an intraocular pressure in the normal range.

A systematic review and meta-analysis assessed the association between BP and POAG as well as intraocular pressure [1561]. Both SBP and DBP were positively associated with intraocular pressure, with a 0.26 and 0.17 mmHg increment per 10 and 5 mmHg increase in SBP and DBP, respectively. Hypertension was significantly associated with POAG in both cross-sectional [1561] and longitudinal studies [1566]. Additionally, a large population-based study including 41 235 hypertensive patients with glaucoma from a National Danish Registry found that initiation of antihypertensive treatment postponed the onsite of glaucoma by 2 years [1567].

Zhao *et al.* [1561] investigated the association of BP as a continuous variable with POAG and observed a J-curve relationship, indicating both low and high BP as risk factors for glaucoma. In this regard, it is important to know that intraocular pressure also varies according to change of the body position. In the supine position, and thus during sleep, an increase in intraocular pressure is observed leading to a decrease in ocular perfusion pressure [1564]. Nocturnal hypotension as recorded by ABPM strongly correlated with glaucoma progression [1568]. Further evidence showed that the link between nocturnal BP and glaucomatous optic neuropathy was driven by an adverse association of the nerve damage with extreme dipping, i.e. an excessive nocturnal BP reduction phenotype [1569]. In addition to circadian BP variations and body position, antihypertensive treatment can also influence ocular perfusion pressure. A study examining the timing of antihypertensive drug administration showed that patients with glaucoma taking antihypertensive drugs in the evening had lower nocturnal BP, more pronounced dipping, lower nocturnal ocular perfusion pressure and greater visual field loss [1570]. Moreover, different antihypertensive drugs may have a different impact on intraocular pressure and glaucoma. Use of BBs has been associated with a lower intraocular pressure [1571,1572] as well as a reduced risk of POAG [1573]. The reduced risk of POAG is in agreement with the well established intraocular pressure reduction by BBs through blockade of sympathetic nerve endings in the ciliary epithelium. This causes a fall in aqueous humor production and makes topical therapy with BBs a mainstay in glaucoma management [1574]. In this regard, it is worthwhile mentioning that topical treatment of glaucoma with BBs may also induce systemic effects, including side effects such as bradycardia, due to absorption of the drugs [1575]. RAS inhibitors have been associated with higher intraocular pressures [1571] and increased risk of POAG [1573]. However, in the above-mentioned National Danish Registry, all antihypertensive drugs, except vasodilators (e.g. hydralazine), delayed the progression of glaucoma [1567].

Taken together, not only hypertension but also low BP values, an extreme nocturnal dipping status and high 24 h BP variability leading to frequent BP peaks and dips (especially dips) are all associated with an increased risk of POAG. Therefore, in hypertensive patients with glaucoma the BP targets recommended for the general hypertensive population should be pursued with caution, and use should be made of ABPM to avoid low nocturnal BP, extreme dipping and thus glaucoma progression.

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Glaucoma and hypertension

Recommendations and statements	CoR	LoE
It is recommended that patients with hypertension >60 years old (or >40 years old in African Americans) may be screened for glaucoma.	II	C
In hypertensive patients with glaucoma, ABPM and closer ophthalmologic examinations should be associated with frequent BP measurements, including ABPM, particularly in patients with unexplained visual field deterioration.	I	C
In patients with glaucoma, both very low and very high BP should be avoided, particularly during the night.	I	B
In patients with glaucoma, bedtime administration of antihypertensive drugs should be avoided as it may increase the risk of excessive lowering of BP and thus visual field loss.	III	B
BBs, have been associated with lower intraocular pressure and decreased risk of primary open-angle glaucoma and maybe preferred in hypertensive patients with glaucoma.	II	B

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20.8 Hypertension oncology

20.8.1 Hypertension and its association with cancer

The association between hypertension and cancer is bidirectional with overlapping risk factors (e.g. unhealthy diet, alcohol intake, physical inactivity, smoking, increased BMI) and pathophysiological mechanisms (e.g. immunoinflammation and oxidative stress) involved in both conditions [1576,1577]. Particularly for renal cell carcinoma (RCC), hypertension has been proposed as an independent risk factor, although the estimated risk ratios range between a 2.5-fold increase in patients with grade 2 hypertension [1578] to an overall smaller risk estimate of 1.12-fold only [1579], while confounding cannot be completely excluded [1577]. A Mendelian randomization study found DBP to be an independent risk factor for RCC, while the role of SBP is less clear [1580]. The association between hypertension and other types of cancer is even less clear and a direct causative association is unproven [1576,1577]. The same applies to the potential role of antihypertensive drugs for cancer development as discussed in Section 11.10.10.3.

Due to its high prevalence, preexisting hypertension is the most common comorbidity in patients with cancer, particularly in older patients, in parallel with the high prevalence of hypertension in the old age (Section 3.3). Careful BP monitoring and hypertension management in cancer patients is recommended, because these patients are at risk of hypertension-related complications, including hypertension emergencies [1581] (Section 16.2), and long-term CV risk increases in cancer survivors [1576,1577].

20.8.2 Hypertension induced by cancer treatments

Data on incident hypertension in cancer trials are difficult to analyze due to differences in the definitions of hypertension used. The Common Terminology Criteria for Adverse Events (CTCAE) in cancer therapy uses a BP grading system with four grades starting in the normotensive range according to the definition of these guidelines. Grade 1 is defined by a SBP of 120–139 mmHg or a DBP of 80–89 mmHg [1582].

20.8.2.1 Hypertension induced by VEGF inhibitors

Anticancer drugs and adjunctive therapy used in oncology can induce de novo hypertension or contribute to worsening preexisting hypertension. BP elevation during therapy with various cancer drugs have been known for a long time. However, this problem has recently come to special attention due to the development of inhibitors of the vascular endothelial growth factor (VEGF), a pathway that causes some BP increase in virtually every patient [1576,1577]. Drugs

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TABLE 26. Hypertension induced by selected anticancer treatments

Drug class	Selected example drugs	Selected malignancies	Potential mechanisms	Hypertension incidences	Comments
VEGF inhibitors	Axitinib, Bevacizumab, Cabozantinib, Dasatinib, Lenvatinib, Nilotinib, Pazopanib, Ponatinib, Ramucirumab, Regorafenib, Sorafenib, Sunitinib, Tivozanib, Vandetanib	Renal, hepatocellular, thyroid, gastrointestinal stromal cancer	↑Endothelin-1 bioavailability ↓ NO bioavailability Oxidative stress Endothelial dysfunction Microvascular rarefication ↓Lymphangiogenesis Kidney injury	**20%-90%**	
Bruton TK inhibitors	Acalabrutinib, Ibrutinib	Chronic lymphocytic leukemia, mantle cell lymphoma	↓Heat shock protein ↓NO bioavailability	**71%**	Long-term effects
Platinum-based compounds	Carboplatin, Cisplatin, Oxaliplatin	Mesothelioma, testicular, bladder, gynaecological, colorectal, and lung cancers	↓NO bioavailability Endothelial dysfunction Kidney injury	**53%**	Long-term effects
Alkylating compounds	Busulfan, Cyclophosphamide, Ifosfamide	Haematologic and solid organ malignancies	↓VEGF bioavailability and vascular/kidney toxicity (Cyclophosphomide)	**36% in adults 15%-58% in children**	Possible confounding by concomitant use of glucocorticoids; long-term effects
Calcineurin inhbitors	Cyclosporin, Tacrolimus	After stem cell transplantation	↑Vasoconstriction (↑RAS and Endothelin-1) ↓NO bioavailability ↑SNS	**30%–60%**	Long-term effects
Proteasome inhibitors	Bortezomib, Carfilzomib	Multiple myeloma	↓NO bioavailability Endothelial dysfunction	**10%-32%**	
BRAF/MEK inhibitors	Binimetinib, Cobimetinib, Dabrafenib, Encorafenib, Trametinib, Vemurafenib	Melanoma, colorectal cancer	CD47 upregulation ↓cGMP, ↓NO Endothelial dysfunction	**19.5%**	
RET kinase inhibitors	Pralsetinib, Selparcatinib, Vandetanib	Thyroid, non–small cell lung cancer	CD47 upregulation ↓cGMP, ↓NO Endothelial dysfunction	**21%-43%**	
PARP inhibitors	Niraparib, Olaparib[a]	Breast, ovarian cancer	Inhibition of dopamine, norepinephrine, and serotonin re-uptake	**19%**	
mTOR inhibitors	Everolimus, Sirolimus	Renal cell, breast, PNET cancer	↓VEGF bioavailability	**No data**	
Androgen synthesis inhibitors	Abiraterone	Metastatic prostate cancer Prostate cancer	Mineralocorticoid activity of accumulated steroid precursors	**26%**	
Androgen receptor blockers	Enzalutamide	Metastatic prostate cancer	Unknown	**11%**	

Data are obtained from Cohen *et al.* [1577] and van Dorst *et al.* [1576]. BRAF indicates v-raf murine sarcoma viral oncogene homolog B1; CD47, cluster of differentiation 47; cGMP, cyclic guanosine monophosphate; ET-1, endothelin-1; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NO, nitric oxide; PARP, poly ADP ribose polymerase; PNET, primitive neuroectodermal tumor; RET, rearranged during transfection; SNS, sympathetic nervous system; TK, tyrosine kinase; VEGF, vascular endothelial growth factor.
[a]Olaparib: possible antihypertensive and cardioprotective effects.

targeting the VEGF pathway are used for the treatment of various cancers (e.g. renal, hepatocellular, thyroid, gastrointestinal stromal cancer) [1583] (Table 26). VEGF inhibitors include i.v. administered monoclonal antibodies (VEGF-A monoclonal antibody, bevacizumab; VEGF-R2 monoclonal antibody, ramucirumab; VEGF-R1/R2 fused to Fc portion of IgG1, aflibercept), or oral small-molecule receptor tyrosine kinase inhibitors (RTKIs) targeting the VEGF-R1-33 and other receptors which mediate the downstream cellular signaling pathways essential for tumor cell survival (Table 26) [1576,1583,1584]. All types of VEGF inhibitors increase BP [1584–1588] via multiple mechanisms that have a similarity with the pathophysiology of preeclampsia, including activation of the ET-1 pathway, decrease in NO bioavailability, capillary rarefaction with reduction in microvascular flow, activation of the renal epithelial amiloride-sensitive Na channel (ENaC) and increased salt-sensitivity. For this reason, use of low-dose aspirin, which is recommended for the prevention of preeclampsia (Section

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16.1) [1084–1086], has been also proposed for cancer patients who develop complications in response to VEGF inhibitor treatment [1578]. The effects of VEGF inhibitors on BP are classified as on-target effects because they reflect also anticancer treatment efficacy [1576]. Hypertension is the most commonly reported adverse event during VEGF inhibitor therapy, with a dose-dependent increase of BP, which is usually reversible and can become manifest within days from the initiation of the anticancer therapy [1585,1589], highlighting the importance of regular BP surveillance, at best with HBPM [1589]. Even though BP increases can be seen in virtually all patients treated with VEGF inhibitors, the incidence of hypertension is highly variable due to (i) the presence or absence of preexisting hypertension and control BP status; (ii) the variable between-drug potency to block the VEGF pathway and (iii) the large between-patient pharmacokinetic variability in patients treated with the same VEGF inhibitor [1584,1586,1590]. The highest incidence of hypertension was observed with the potent RTKI axitinib and the multikinase inhibitor lenvatinib, among whom 13 and 43%, respectively, developed severe hypertension [204,1590,1591]. The use of VEGF inhibitors is associated with an increased risk of incident and worsening HMOD and of other hypertension-related complications including LV dysfunction and HF, cardiac arrhythmias, kidney damage and both arterial and venous thrombotic events [204,1591]. Cardiac damage may lead to severe HF and cardiac death [1576,1592]. The risk of kidney complications includes acute kidney injury with thrombotic microangiopathy [1593] or glomerular damage leading to massive proteinuria [1576,1577,1594]. However, even though the relative risk of these adverse events is high compared to placebo and other anticancer drugs, the absolute risk increase of the aforementioned complications remains low during the time-frame of treatment with VEGF inhibitors.

20.8.2.2 Hypertension induced by other anticancer drugs

A list of additional anticancer drugs that can also induce hypertension is presented in Table 26 [1576,1577]. The list includes classic chemotherapeutic compounds such as cyclophosphamide and more recently developed therapies such as proteasome inhibitors (bortezomib, carfilzomib), poly ADP ribose polymerase (PARP) inhibitors (olaparib, niraparib) and Bruton's tyrosine kinase inhibitors (ibrutinib, acalabrutinib). The last class increases also the risk of AF and HF [204,1591]. The mechanism by which these therapies increase BP is most likely multifactorial and remains to be elucidated [1595]. It is still unclear whether immune check-point inhibitors (ICIs), which include monoclonal antibodies against the inhibitory programmed death-1 (PD-1) receptor or its ligand (PD-L1), and antibodies against the cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor, increase the risk of hypertension. Possibly they synergistically increase CV toxicity when combined with VEGF inhibitors [1595]. Abiraterone acetate is a CYP17A1 inhibitor that decreases androgen synthesis and is thus used in patients with progressive metastatic prostate cancer. This drug can also increase BP because of the inhibition of CYP17A1 upstream in the steroid synthesis at the level of adrenal glands, which leads to the synthesis of excessive amounts of 11-deoxycorticosterone via the counter-regulatory stimulation of ACTH release in response to a decrease in cortisol synthesis [1596]. The binding of 11-deoxycorticosterone to the mineralocorticoid receptor induces hypertension with hypokalemia, sodium and fluid retention and decreases the plasma levels of renin and aldosterone [1597] A low dose of prednisone is usually prescribed concomitantly with abiraterone to reduce the stimulation of ACTH release and may control the hypertension. If needed a MRA can be added [1598].

20.8.2.3 Hypertension induced by adjunctive therapies, radiotherapy or surgery

Adjunctive therapies with glucocorticoids, erythropoietin (EPO) to treat anemia and NSAIDs to treat pain and/or inflammation, can contribute to the development of hypertension or the worsening of hypertension in cancer patients. Radiotherapy to the neck and/or extensive neck dissection surgery can cause baroreflex failure (Section 14.10) leading to extreme BP variability with dramatic hypertensive surges, hypotensive episodes, and orthostatic hypotension in some patients [915–917]. In addition, abdominal radiotherapy has been associated with renal artery stenosis, which occasionally can cause renovascular hypertension [1598]. Moreover, during long-term FU, an increased risk for CV events has been noted in patients who have undergone radiotherapy for various malignancies including lymphoma, breast cancer and neck-cancer, for which radiation injury of the vasculature has been proposed as an underlying mechanism [1599].

20.8.3 Management of hypertension in cancer patients

20.8.3.1 BP monitoring and general management before start of cancer treatment

Before starting cancer therapy, BP control in patients with preexisting hypertension should be confirmed by appropriate office BP measurement as recommended in Section 4 and also include the use of out-of office (ABPM or HBPM) measurements whenever possible (Fig. 9). The use of HBPM is particularly important and should be encouraged with education on proper use (Section 4.7), because HBPM can play an important role for BP monitoring both during cancer treatment and during FU after cancer treatment. Furthermore, BP measurements should be also performed in patients without previously documented hypertension in order to exclude hypertension and to document the baseline BP values before patients are exposed to anticancer drugs that may induce hypertension (Table 26). Control of pain and anxiety before BP measurements requires special attention in cancer patients. Unfavorable changes of individual risk factor profiles (e.g. increased stress, incident depression, impairment of sleep, Table 2) and lifestyle factors (e.g. unhealthy diet, increased alcohol intake, Section 7) may have contributed to worsening of hypertension and BP control in cancer patients and should be addressed. Drug therapy should be intensified and adapted if needed (see below) according to the general recommended strategy (Fig. 12).

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Recommendations	CoR	LoR
Office BP measurement is recommended before the start of anticancer therapy in patients with or without prexisting hypertension, because anticancer drugs can cause acute BP increases and hypertension-related complications including hypertension emergencies.	I	B
Control of pain and anxiety before BP measurements requires special attention in cancer patients and is recommended.	I	C
The use of ABPM and HBPM whenever possible is recommended during active cancer treatment and during further follow-up if available, particularly in patients receiving anticancer drugs which can induce hypertension.	I	C
Hypertensive patients with cancer may be screened for HMOD (ECG, echocardiography, kidney function parameters, and evidence of heart failure) and CV risk before starting anticancer therapy.	II	C
In patients who are treated with cardiotoxic anticancer drugs, echocardiograhic evaluation at baseline, during anticancer treatment, and during follow-up is recommended.	I	C
BP monitoring after active cancer treatment and during long-term follow- up is recommended, because BP may drop when anticancer drugs are stopped, which may require backtitration or discontinuation of BP lowering drugs.	I	C
Cancer survivors have a higher risk to develop hypertension and other CV and renal complications and should be occasionally screened with BP measurements and informed about their increased CV risk.	I	C

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20.8.3.2 General BP-lowering therapy and management during cancer therapy

Patients with active cancer were regularly excluded from outcome-based RCTs in hypertension. Conversely, in cancer trials, patients with uncontrolled hypertension or elevated BP are commonly excluded. Consequently, no evidence from outcome-based RCTs is available to guide overall management and drug therapy for hypertension in patients with cancer. Mindful of these limitations, these guidelines recommend that, by extrapolation, the definition of hypertension, BP thresholds and targets, lifestyle interventions and drug treatment strategies recommended for the general hypertensive population should be also applied to cancer patients. In severely ill cancer patients, treatment of hypertension should be individualized according to symptoms, comorbidities and polypharmacy in a shared decision-making process. Although there is no general consensus, these guidelines recommend that the threshold for withholding anticancer therapy should be

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a SBP ≥180 mmHg and/or a DBP ≥110 mmHg [1577,1582]. Thus, initiation of anticancer therapy should not be deferred in patients with uncontrolled BP unless they are symptomatic or present with grade 3 hypertension. In these patients, measures to control BP and symptoms should be initiated first, ideally by a team-based multidisciplinary approach, to allow initiation of anticancer therapy as early as possible.

Some considerations on drug selection and use specific for cancer patients during active cancer treatment need to be emphasized:

1. Thiazide/Thiazide-like diuretics should be used only if needed for BP control and in patients with fluid retention. They should be used with caution, because they may (i) increase serum calcium concentration in patients with bone metastasis, (ii) further increase the risk of cardiac arrhythmias induced by some anticancer drugs because of prolongation of the QT interval by inducing hypokalemia, (iii) worsen SIADH-dependent hyponatremic states occurring in some cancer patients and (iv) worsen hypovolemic states or dehydration [204,1584,1600].
   A preferential use of a DHP-CCB in combination with a RAS blocker may, therefore, apply in many cancer patients (Fig. 12).
2. Use of non-DHP-CCBs, which are indicated for heart rate control in patients with contraindications or intolerance to BBs, is problematic and should be avoided in some cancer patients. This results from the evidence that non-DHP-CCBs (i) are moderate inhibitors of CYP3A4 or P-gp and interfere with the pharmacokinetics of some, but not all, anticancer drugs, e.g. oral RTKIs that are substrates of CYP3A4 or P-gp [1600,1601] and (ii) can worsen HF induced by cardiotoxic anticancer drugs due to their negative inotropic effects (Section 11.2.2). Nevertheless, this does not exclude their cautious use in cancer patients per se, e.g. in hypertensive patients with tachycardia who cannot tolerate BBs and in patients treated with anticancer drugs that do not show relevant pharmacokinetic interactions via P-gp or CYP3A4.

20.8.3.3 Treatment of hypertension induced by VEGF inhibitors

There are no data from RCTs that can help the prevention and/or treatment of de-novo hypertension induced by anticancer therapies, e.g. in response to VEGF inhibitor treatment. Nevertheless, sodium restriction may be helpful as a maximum intake of 4 g sodium per day in combination with dietary counseling has recently been shown to attenuate the VEGF inhibitor-induced BP rise by almost 50% in a small (pilot) study (16 patients) [1602]. In a retrospective cohort study involving 343 cancer patients that were treated with oral VEGF inhibitors (sorafenib, sunitinib, pazopanib, regorafenib, lenvatinib or cabozantinib), about half of the included patients exhibited significant BP increases (≥20 mmHg in SBP or ≥10 mmHg in DBP). Normotension at baseline and treatment with pazopanib identified as significant risk factors for this significant BP rise [1603]. Treatment with a CCB or RAS blocker (ACEi or ARB) effectively reduced SBP (−24.1 and −18.2 mmHg, respectively) and DBP (−12.0 and −11.0 mmHg, respectively) [1603]. In patients treated with VEGF inhibitors any BP-lowering therapy administered during the on-treatment periods must be carefully monitored, e.g. by HBPM, and reduced or even stopped as needed during the off-treatment periods because of the excess risk of hypotension.

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Management of hypertension in cancer patients

Recommendations	CoR	LoR
In patients with cancer, the same definition of hypertension, thresholds, targets, lifestyle interventions and drug treatment strategies are recommended as for the general hypertension population.	I	C
In patients with uncontroilled hypertension and BP values ≥180 mmHg for systolic and/or ≥110 mmHg for diastolic BP, it is not recommended to initiate anticancer therapy.	III	C
In patients with uncontrolled hypertension and BP values ≥180 mmHg for systolic and/or ≥110 mmHg for diastolic BP, measures to control BP and symptoms should be initiated by team-based multidisciplinary care to allow initiation of anticancer therapy as early as possible.	I	C
Thiazide/Thiazide-like diuretics may be used only if needed for BP control and in patients with fluid retention, because of their potential to cause unwanted effects in cancer patients including increases in serum calcium concentration in patients with bone metastasis, increased risk of cardiac arrhythmias due to prolonging the QT interval by inducing hypokalaemia, increase the risk of hyponatremia, and potential worsening of hypovolaemic states or dehydration.	II	C
Non-DHP CCBs should be avoided in cancer patients who are treated with anticancer drugs that are susceptible to pharmacokinetic interactions mediated by CYP3A4 and/or P-gp.	III	B
Hypertension induced by VEGF inhibitors may be treated with either RAS-inhibitors (ACEis or ARBs) or DHP-CCBs.	II	B
In severely ill cancer patients, treatment of hypertension should be individualised according to symptoms, co-morbidities and polypharmacy in a shared-decision making process.	I	C

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20.8.4 Follow-up and management of hypertension in cancer survivors

Long-term close FU of cancer patients after active cancer treatment is important. One reason is that, acute BP changes may occur in patients who were exposed to anticancer drugs that induce short-term and reversible BP increases, requiring backtitration or eventually discontinuation of any previous BP-lowering drugs to avoid hypotension. Another reason is that cancer patients with preexisting hypertension may have developed progression of previously existing HMOD or de-novo

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organ damages because of the cardiorenal toxicity of anticancer drugs. Thus, depending on the individual risk profile and phenotypes, FU should include monitoring of HMOD parameters (Fig. 6). Overall, BP monitoring during long-term FU, preferably by HBPM, is recommended, because long-term cancer survivors are at increased risk to develop hypertension, e.g. long-term survivors of cancer in childhood [1604], and CV events. Finally, patients who developed severe worsening of hypertension during anticancer therapy may have a secondary cause of hypertension as underlying disease and appropriate diagnosis to exclude or detect such forms may be considered in suspected cases (Section 6).

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20.9 COVID-19 and hypertension

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the coronavirus disease 2019 (COVID-19) pandemic, led to fundamental disruptions of many if not all aspects of people's lives. In the early acute setting [1605], but also during the first year [1606] of the pandemic, COVID-19 was associated with a substantial increase in mortality including fatal CV events such as stroke, ischemic heart disease, arrhythmias, HF, venous thromboembolism, cardiac arrest and acute kidney injury and failure. All these complications have a close association with hypertension. However, several more direct aspects of the relationship between COVID-19 and hypertension have emerged. Coexistence of hypertension and COVID-19 was not only one of the most common comorbidities in patients with COVID-19 [1607], but its coexistence with this infection was also associated with an increased risk of severe COVID-19 (defined as hospitalization or death) [1607,1608]. Hypertension was also reported to be an independent factor in a vulnerability score predicting severe or fatal COVID-19 developed from millions of people from Italy [1609]. In treated hypertensive patients, elevated SBP showed a dose–response relationship with severe COVID-19 [1610], even when age and CV comorbidities were taken into account [1611]. These are important observations, because the possible association between hypertension and COVID-19 in the initial phase was confounded by the high age of patients hospitalized with severe COVID-19 in parallel with the high prevalence of hypertension at that age [1611]. The most likely explanation supporting hypertension as a risk factor for the COVID-19 severity is that hypertension often causes subclinical HMOD in vital organs [216,276], which may reduce the body's defenses against severe infections. Another possibly additive explanation could be the detrimental role of several immunological dysregulations, which may be associated with hypertension [1612].

20.9.1 COVID-19 and RAS inhibitors

The findings that (i) SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry, and (ii) in experimental settings, treatment with ACEis and ARBs may lead to an upregulation of ACE2 expression [1613], generated the hypothesis that treatment with ACEis or ARBs could increase the infectivity and severity of the clinical course of COVID-19. This caused concern in health authorities and scientific societies, which feared that, neglecting the observation that ACE2 was found to have protective effects against lung injury in animal models [1613], patients might stop using these drugs in diseases for which they have a life-saving role, with a consequent increase of fatal or nonfatal CV events. However, large observational studies already made available in the early pandemic phase [1614,1615] consistently showed that treatment with RAS blockers did not affect the risk of COVID-19 infection, severe illness or mortality [1616], a conclusion confirmed by later meta-analyses of available studies [1617]. Minimal effects of RAS blockers in either direction on the course of COVID-19 were later shown by another much larger meta-analysis, which, however, additionally emphasized the limitations and bias of conclusions based on observational studies [1618]. This confirmed 'a posteriori' the recommendation issued in the early pandemic phase by several learned societies, including the ESH [1613], that patients treated with RAS inhibitors for hypertension, HF, CAD or other conditions should in general not discontinue this treatment. Unfortunately, as shown by a survey in ESH Excellence Centers, a sizeable number of patients did discontinue treatment, with possible, although never calculated, detrimental effects [1619].

20.9.2 COVID-19 lockdown and hypertension management

In an attempt to limit the infectious spread, diagnostic and therapeutic procedures related to hypertension were dramatically reduced during the first year of the COVID-19 pandemic, with the largest reduction during the first lockdown [1620]. This was also true for patients with severe hypertension [1621] and involved to a striking degree face-to-face consultations and clinic BP measurements [1622], followed by a decrease in medication adherence [1623]. In response, remote clinical management programmes, involving not only physicians, but also nurses and pharmacists, were developed [1624]. Such programmes, based on automatically transmitted standardized HBPM and evidence-based hypertension management algorithms, achieved some implementation during the pandemic [1624]. In fact, expanding the role of virtual management for hypertension may be regarded as an important favorable consequence of the pandemic in the field of hypertension (Section 21). With respect to practical antihypertensive treatment aspects, no consistent alterations in the choice of drugs and treatment strategies (including BP thresholds and targets for treatment) have been adopted in patients with COVID-19 because of lack of available evidence and appearing reasons to do so.

On top of the disruption in medical care for chronic diseases such as hypertension [1620], the COVID-19 pandemic caused potential changes in lifestyle factors and behaviors (physical activity, dietary patterns, alcohol consumption, smoking, emotional/psychologic stress, changes in sleep patterns and diurnal rhythms), as well as environmental changes (air pollution, environmental noise) likely to influence BP control and CV risk during and after the pandemic [17], in particular during its strict or less strict lockdown phases. A few changes such as reduced air pollution and noise exposure (due to less traffic) were potentially favorable, because air pollution and noise have been shown to have a pressor effect.

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However, most were probably detrimental. Indeed, a rise in office [1622,1625] and home [1626] BP, as well as an increase in the proportion of patients with uncontrolled hypertension [1626] has been observed during the pandemic, albeit not consistently in all studies [1627].

20.9.3 Vaccination against SARS-CoV-2 and hypertension

Vaccination against SARS-CoV-2 has clearly reduced the occurrence of myocardial infarction and stroke after COVID-19 [1628,1629]. These data should not be interpreted as to mean that the vaccine has a specific CV protective effect. The reduced incidence of CV events is rather attributable to the fact that the SARS-CoV-2 infection affects multiple organs and can by all accounts be considered a systemic rather than lung-restricted disease. No signal of a BP increase or consistent change has emerged from the RCTs evaluating the efficacy and safety of the vaccines [1630]. This seems to be in line with the results of pharmacovigilance databases and observational studies that the pooled estimated proportion of abnormal/increased BP after vaccination was only 3.2% [1631], but in the absence of randomized data, no reliable conclusion is possible. Short-term BP changes such as stressor-related BP responses and white-coat effects may have played some role.

20.9.4 Long COVID-19 and hypertension

Regarding the persistent CV symptoms several months after COVID-19, i.e. Long-COVID, the CV system is frequently affected [1611] and preexisting hypertension may be a modest risk factor [1632,1633]. Hypertension may be among the more common reasons for medical consultations after COVID-19. However, long-term follow-up studies, and more data, in general, are needed to shed more light on this important issue [1634,1635].

21. FOLLOW-UP

21.1 Importance of follow-up

The FU of hypertensive patients is crucial not only to ascertain achievement of BP control but also to support lifestyle modifications, assess drug adherence and medication side effects and to adapt therapy and check for development or changes in HMOD (Fig. 21). In this context, three main questions need to be addressed: (i) how often patients should be seen, (ii) what needs to be checked and (iii) who and which setting should be involved in the management of patients during FU, in addition or alternatively to office re-visits. Unfortunately for each of these questions, available studies are scarce. Nevertheless, these guidelines acknowledge their importance for patients' FU and address them in some detail below. According to some recommendations after the initiation of drug therapy, patients need to be evaluated monthly until BP control is achieved [97,1361]. However, three large observational studies and one small RCT suggest that FU visits with shorter intervals (every 2 weeks) result in earlier and more common BP control rates [1636–1639]. It seems obvious that during the treatment titration phase, the frequency of the visits should not be subjected to rigid rules but differ according to BP phenotypes and response to treatment. Other obvious parameters that affect the frequency of FU visits are severity of hypertension, presence and type of HMOD, CVD or CKD as well as other comorbidities. Return visits have been reported to be more than twice more common in patients with ≥3 comorbidities compared with patients with fewer or no comorbidities [1640]. A BP reduction is slower with monotherapy than with dual-drug combinations, with which a reduction in BP levels is expected within 1–2 weeks, although a further smaller progressive BP decline may continue for few more weeks.

Once the BP target is reached, a visit interval of a few months seems reasonable. No difference was detected in BP control between FU visits at 3 and 6 months intervals in one study [1641], thus favoring a twice or four times a year visit frequency during the first year after treatment initiation for the majority of hypertensive patients. A 3-month time interval is in line with the results of a large observational study in 90 000 hypertensive patients that revealed that when the time to return visit exceeded 2.7 months, the risk of CV events was increased by 18% [651]. After the first year, two or even one FU visit per year seems a reasonable frequency, if medical conditions are stable, BP control appears to be consistent (based on information from HBPM whenever possible) and patients are not affected by major treatment-related problems. Patients should be made aware that office and out-of-office BP values tend to be a few mmHg lower during the summer than during the winter months [1642,1643], due to differences in indoor and outdoor temperature as well as to other factors [1642,1644–1646].

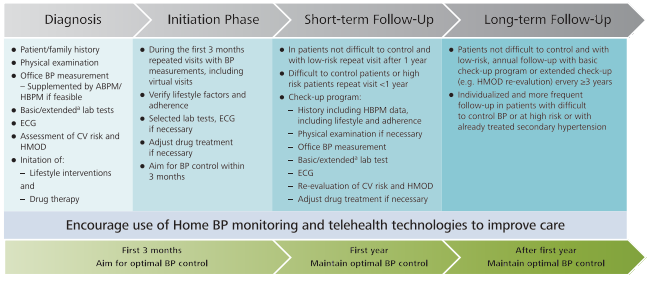


FIGURE 21 Suggested follow-up in patients with hypertension.

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Usually, lower BP values in the summer do not pose specific problems to the patient but may require a supplementary medical visit. If lower BP values are associated with dizziness or fatigue, patients may be advised to modestly downtitrate drug treatment, especially diuretics.

Another useful bit of information is that BP increases under conditions of hypobaric hypoxia due to a number of factors, including sympathetic activation [1647]. Patients with grade 2 and 3 hypertension and poor BP control by treatment should avoid exposure to altitudes above 2500 m from sea level. Vacationing at lower altitudes does not appear to pose BP problems to hypertensive patients, although BP checks before and during exposure to altitude appears advisable. Possible impairment of blood oxygenation and other problems may extend the risk of hypobaric hypoxia to lower altitude levels in older patients or patients with respiratory or CV diseases [1647].

Obviously, during the FU visits, BP measurements according to the recommendations of the guidelines are of fundamental importance. BP measurements should be extended to ABPM whenever indicated and feasible, at intervals usually longer than those for office BP measurements. HBPM can be advised not only before visits but also on a more regular basis as a useful tool to verify consistency of BP control as well as to improve adherence to treatment. During visits, there should be collection of the most recent medical history, including questions addressing lifestyle interventions, tolerability of drug therapy and any changes of comorbidities and comedications, including intake of over-the-counter medicines. A new physical examination should usually be dispensed with, if the medical course before the re-visit was inconspicuous. Standard laboratory investigations, electrolytes (serum potassium) and kidney function are among the parameters that should be monitored most frequently together with serum cholesterol, the lipid profile, blood glucose and other parameters based on the individual drug treatment strategies and comorbidities. Re-assessment of HMOD should be carried out according to the considerations made in Section 5.5. HMOD assessment is important, as progression or regression of HMOD at FU visits has a major influence on management strategies and scheduling of further FU visits.

During long-term FU, visits may be also carried out by nonphysician healthcare professionals, such as qualified nurses or pharmacists. This approach has been adopted in some European and other countries, depending on the local organization of health resources and is supported by the results of RCTs, observational studies and meta-analyses, which point towards similar BP reductions, when treatment is handled by primary care physicians, nurses or pharmacists [1648–1651]. An important contribution in this direction may be provided by tele-health technologies in combination with patient empowerment. Further development of this approach can be expected to make an important contribution to FU management in hypertension in the future [138].

21.2 Adherence

21.2.1 Definitions

Adherence is defined as the extent to which a person's behavior, such as taking a medication, following a diet or executing lifestyle changes, corresponds with agreed prescriptions or oral recommendations from a healthcare provider. Persistence defines the length of time between the initiation of treatment and the last dose immediately preceding its discontinuation [478,1652]. To this end, adherence reflects a punctuated assessment of a patient's alignment with the prescribed treatment, whilst persistence is an illustration of adherence to the prescribed therapy over a longer period. Because of negative connotations, compliance is not the most appropriate term to use when referring to patients following of therapeutic recommendations from healthcare providers [1652].

21.2.2 Prevalence of nonadherence and associated burden

The estimates of the prevalence of nonadherence to antihypertensive treatment vary across studies depending on (i) the method used to assess adherence, (ii) the country/healthcare system where the research was undertaken and (iii) the clinical characteristics of hypertensive patients recruited. In general, nonadherence rates are higher in low-income and middle-income countries than in westernized societies [617] and in patients with difficult-to-manage hypertension (e.g. suboptimal BP control) compared with those from the general hypertensive population [662,674]. In a large sample of patients from the general population who were treated with antihypertensive drugs, only approximately one-fourth were adherent (a prescription coverage for ≥75% of the follow-up) [613]. On average, approximately one in three to four hypertensive patients are nonadherent to antihypertensive treatment, based on direct biochemical analysis of bodily fluids [613,662,663]. Nonpersistence is one of the most common cause of poor adherence in hypertension particularly among newly treated patients [478,1653]. In newly treated patients from Italy, about 36% did not renew the initial prescription of antihypertensive medications a second time [1654]. There is a strong correlation between the extent of nonadherence to antihypertensive treatment and the magnitude of BP elevation, based on both office BP measurements and 24 h ABPM [659]. Nonadherence is associated with several adverse CV outcomes, including LVH [1655], microalbuminuria [1656], myocardial infarction, stroke, HF [1657,1658], CKD [1659,1660], hospitalization rates, all-cause mortality [1661], reduced quality of life and overall increased healthcare costs [478]. CV hospitalization and death are also closely related to treatment discontinuation [477] and the relationship between adherence and clinical outcomes is apparent in both men and women [1024], younger and older patients [476] as well as patients with different levels of comorbidities and mortality risk [510]. For this reason, the 2018 ESC/ESH guidelines put a particularly strong emphasis on the detection and management of nonadherence to BP-lowering therapy [4], and this is mirrored in both the AHA/ACC guidelines [160] and the ISH guidelines [32]. Emphasis on adherence is recognized as one of the areas of convergence between European and American guidelines [1662].

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21.2.3 Methods to detect nonadherence to antihypertensive treatment

The ideal method of detection of nonadherence should be to prove the ingestion and provide information on how frequently this occurs over time because adherence is a dynamic process, i.e. it can vary considerably from one period to another. Today, none of the available methods fulfils these two criteria. Relying on the physician's impressions derived from interviews is convenient but is associated with a significantly biased assessment leading to an overestimation of adherence. Adherence questionnaires do not fulfil all the validity and reliability test criteria [1663] and show generally very poor/no relationship with BP control and CV outcomes [1664]. Directly observed administration of BP-lowering medications (usually followed by BP monitoring) can be informative but is not practical in most healthcare settings (expensive, operationally challenging) and cannot take into account the variable nature of adherence over time. It can be also clinically hazardous (severe BP drops have been reported in patients following witnessed intake of medicines) [1665]. Checking prescription refill records is inexpensive and may provide information on patients' persistence with their antihypertensive treatment, particularly in the context of healthcare systems in which all or almost all prescriptions are registered and centrally stored [476]. However, collecting a prescription is not equivalent to taking a medication, and thus this approach overestimates adherence. Electronic drug monitoring using sensors that register an act of opening a medication-dispensing container/blister pack is generally very accurate and provides detailed information upon both timing and frequency of adherence as well as persistence on treatment [680]. However, the costs, the risk of intentional/unintentional dose removal from the container without ingestion and the unfeasibility of the method for numerous antihypertensive medications represent important limitations. Biochemical detection of antihypertensive medications and/or their metabolites in bodily fluids provides direct and objective confirmation of drug intake. Yet, this method is costly, does not account for day-to-day variability in adherence and is not immune to toothbrush adherence effect (increased adherence before visits) [478,1666]. Self-reported adherence is usually overestimated and should not be routinely used in clinical practice. However, an affirmative confirmation of nonadherence is generally informative. Digitally tagged pills are not currently available in clinical practice and have a very high cost.

21.2.4 Etiology of nonadherence to antihypertensive treatment

WHO multidimensional adherence model classifies barriers to nonadherence into several categories, including: (i) health system (communication with a healthcare provider, low satisfaction with pharmacy services or problems with drug reimbursements); (ii) therapy-related (side-effects, complexity of drug regime or interference with daily routine); (iii) disease-related (severity of symptoms, lack of symptoms or presence of comorbidities); (iv) patient-related (low self-efficacy or inaccurate beliefs about medications) and (v) socioeconomic status-related (poverty, lack of family support or unemployment) [1667]. The causes of nonadherence to antihypertensive treatment largely maps onto these above dimensions. Unintentional is more common than intentional nonadherence [1668] and in some countries, access to healthcare and cost of medications are becoming an increasingly important contributor to nonadherence in hypertensive patients [138,616]. The generally asymptomatic nature of hypertension is likely to augment the risk of nonadherence when compared with CV conditions known to produce symptoms when treatments are not followed. For example, chronic HF is associated with much lower rates of nonadherence than hypertension [1669], and better adherence to antihypertensive treatment was reported in patients with a history of hospitalization because of CV or renal events [620]. No difference in adherence has been reported between brand name drugs and generics [1670], while the number of prescribed antihypertensive medications has been shown to act as a key determinant of nonadherence to BP-lowering treatment [674]. In contrast, class of antihypertensive treatment is not a consistent determinant of nonadherence to antihypertensive treatment, although persistence is higher with some antihypertensive drugs than with others [674]. Algorithms that use demographic and simple clinical data are not yet sensitive or specific enough to predict nonadherence to antihypertensive treatment, as drug adherence is a very dynamic and poorly predictable process. Overall, nonadherence to antihypertensive treatments has a multifactorial, complex background and there is a large variation in the causes of nonadherence to BP-lowering treatment among patients.

21.2.5 When and how to screen for nonadherence

Screening for nonadherence to antihypertensive treatment should be part of the routine assessment of effectiveness of BP-lowering drugs [4] and should be checked (i) at every clinical appointment, (ii) prior to escalation of antihypertensive treatment [32], (iii) prior to screening for secondary hypertension [32] and (iv) when resistant hypertension is suspected [32,1671]. Screening for nonadherence to antihypertensive treatment should also be considered in patients who are taking two antihypertensive medications and have an inadequate BP response to this treatment [4,664]. Objective indirect or direct methods (review of pharmacy records, electronic monitoring devices, directly witnessed intake of medication and biochemical detection of medicine in urine) are generally preferred over subjective methods of diagnosing nonadherence to antihypertensive treatment [32]. In lower resource settings, where these tests are not available, confirmation of nonadherence (but not of 'adherence') by a patient can be informative. Lack of an expected response to antihypertensive treatment, such as no BP improvement with multiple antihypertensive drugs, tachycardia, despite treatment with beta-blockers, heart rate-limiting effects with some CCBs or lack of hair growth in patients using minoxidil, increase the probability of nonadherence, in particular when combined with information on the most established risk factors of nonadherence such as polypharmacy or the occurrence of side-effects.

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Screening for nonadherence to BP-lowering therapy improves the diagnostic approach and treatment decisions almost in all hypertensive patients. Indeed, in patients with suboptimal BP control (e.g. resistant hypertension), a confirmation of nonadherence to antihypertensive treatment (i) substantiates a diagnosis of pseudoresistant hypertension, (ii) explains the cause of resistance to treatment, (iii) helps to avoid unnecessary treatment escalations and expensive additional investigations and (iv) reduces the healthcare costs [1672]. A confirmation of adherence to antihypertensive treatment in such patients justifies undertaking additional diagnostic tests (e.g. to exclude secondary hypertension) and suggests that a change in antihypertensive treatment may be necessary. In patients with satisfactory BP control, a confirmation of nonadherence to antihypertensive treatment allows a de-escalation of antihypertensive treatment while results consistent with adherence to therapy provide a positive reinforcement of the effectiveness of this treatment [478].

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21.2.6 Management of nonadherence to antihypertensive treatment

Management of nonadherence to antihypertensive treatment should be tailored to the individual modifiable drivers of nonadherence in each patient. There is not a single universal strategy that could help to manage nonadherence in all hypertensive patients. To this end, a confirmation of nonadherence to antihypertensive treatment should be followed by a nonjudgmental discussion between a patient and a healthcare professional (as partners) [674,1666,1672,1673]. This should lead to understanding the barriers to adherence to antihypertensive treatment. The therapeutic strategies to consider, in combination or alone, are: (i) simplification of treatment (e.g. reduction in the number of antihypertensive medications or pills/tablets with a preference for long-acting and once-daily administration systems) [617,678], (ii) single-pill combinations [618,652,678], (iii) reminders and electronic monitoring [617], (iv) elimination of medications that cause side-effects or are unnecessary [478], (v) financial incentives [617] and (vi) addressing incorrect beliefs about hypertension and BP-lowering therapy [617], family and social support [617], repeated adherence testing [617,663] and matching therapy with daily routines [478]. Collaboration with other healthcare providers in the context of team-based care [1674] and the development of virtual management of hypertension based on HBPM [62,1675].

Nonadherence to antihypertensive therapy

Recommendations and statements	CoR	LoE
Screening for non-adherence to treatment is recommended in all patients with apparent resistant hypertension.	I	B
Consider screening for non-adherence patients who are on combination treatment (i.e. at least 2 drugs) and have an inadequate BP response to this treatment.	II	C
Check adherence prior to screening for secondary hypertension.	I	C
Physicians should collect information on adherencen mindful that all methods have limitations.	I	C
Use of single pill combinations to improve adherence and persistence to antihypertensive treatment is generally recommended.	I	B
Several strategies can be considered to improve adherence and a multidimensional team-based care approach is recommended.	I	C

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21.3 Clinical inertia

Clinical inertia in hypertension management can be divided into (i) diagnostic inertia, i.e. failure of the physician or another health-care provider to detect a BP elevation in the patient and (ii) therapeutic inertia, i.e. failure of the physician to start or modify drug treatment (drug change, dose change or drug addition) in the presence of BP values above the recommended target [1676]. There is little information on the contribution of diagnostic inertia to the fraction of the hypertensive population unaware of its high BP status. On the other hand, evidence is available that therapeutic inertia significantly contributes to the low rate of BP control that characterizes treated hypertension in real life [530,1677,1678]. In a Dutch study on 530 564 individuals followed by general practitioners, 10% ($n = 64\,000$) of the hypertensive population was found to have uncontrolled BP because of therapeutic inertia [1679]. Greater percentages have been reported in other studies, in which uncontrolled BP in the absence of appropriate drug titration has been directly determined or indirectly inferred from

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questionnaires [1680–1684]. The factors associated with therapeutic inertia have also been investigated and found to include the doctor's feeling that the measured BP does not reflect the patient's true BP, deferment of the decision to future visits, hope for an effect of lifestyle changes or fear of adverse effects [1685]. Therapeutic inertia has also been consistently associated with a limited SBP increase, older age and BP values moderately above target [1682,1684]. Finally, a very common type of inertia involves failure of the physician to use combinations of antihypertensive drugs in most patients. In a large study on the populations of Belgium and Luxemburg, about 50% of the patients were found to be on monotherapy after 8 years of treatment [1681]. Similarly, in a population of northern Italy, only 36% of patients starting antihypertensive drug monotherapy moved to drug combination after 3 years of treatment [608]. In the same population, long-term antihypertensive monotherapy has been recently found to extend to about two-thirds of the patients, largely independently of the demographic and clinical conditions and with few changes in three cohorts spaced over a 6-year period [615]. Prevalence of antihypertensive monotherapy is shared by several European countries [613]. This is an example of large-scale therapeutic inertia because BP control requires more than one antihypertensive drugs in the vast majority of patients [954,1686]. It is important to know that therapeutic inertia is also reported in the setting of clinical trials in which, despite specific treatment protocols and regular verification of the planned BP targets, a number of patients do not complete the planned treatment titration and thus fail to reach BP control [610]. Importantly, the adverse effects of therapeutic inertia usually extend beyond an uncontrolled BP and include lack of control of associated risk factors.

Although only few studies have addressed the question of how to limit doctor's inertia, a few suggestions can be made. The most important step is obviously to improve doctors' knowledge of the increased CV risk associated with hypertension, whatever the age, gender and protective effects of adequate BP reductions, a goal that needs dissemination of treatment guidelines. Patients' knowledge and empowerment as well as home BP measurements are also important to provide appropriate and timely feed-backs to the doctor, with perhaps a further help of telemetric transmission of the home BP measurements [1687]. A CV prevention strategy combining three approaches has been shown to improve BP control and to reduce therapeutic inertia in a large group of hypertensive patients in the USA [1688]. More frequent visits and simpler uptitration treatment strategies can also be considered. Incentives based on the number of patients achieving BP control has also been proposed [1689]. It should be noted that in some cases, therapeutic inertia is caused by patients' reluctance to increase the number and/or doses of the drugs or to the doctor's need to depart from the average guidelines recommendations in a number of individual patients. In this case, therapeutic inertia is only apparent [1690].

There are potential solutions to overcome clinical inertia in the management of hypertension. They can be classified as not only educational (i.e. improve knowledge), clinical (i.e. improve screening and detection of uncontrolled BP) and therapeutical but also organizational (improved FU). Most of the time they are directed to the physician but improving a patient's attitude can also contribute to fighting clinical inertia [478].

21.4 Patient empowerment

In order to follow a health-care plan and reach therapeutic targets, involving the patient is strongly recommended both initially and at every step of FU [941]. Factors such as poor health literacy or lack of education can directly affect the quality of care, thus patient information and sharing medical decisions are the first steps of a patient-centered approach. This empowerment process (i.e. giving the power to the patient to be active in managing his/her medical condition) is a key factor for success. These approaches are based on behavioral and motivational strategies. They offer a good chance to improve management of high BP by enhancing adherence to drugs or lifestyle modifications but also more generally to achieve a healthy lifestyle, as these approaches have been validated for the management of other CV risk factors (smoking cessation, weight loss, moderation in alcohol intake, increased physical activity and consumption of a healthy diet). Although high-quality evidence supports empowerment and cognitive interventions in reducing BP [1688,1691], the level of evidence and impact of shared medical decision on BP control is low [1692].

Discrepancy between physician and patient expectations can lead to behavioral changes affecting BP control. In this situation, interventions such as goal setting, provision of feedback, self-monitoring, FU, motivational interviewing, and promotion of self-sufficiency are effective, and effectiveness is better when the interventions are combined rather than promoted individually (lower level of evidence) [136,1693]. The use of telemedicine and mobile health technologies (Section 21.6) when the patient is at home can be of help for not only promoting self-monitoring and self-sufficiency but also for improving health and well being. The physician–patient interaction needs to be framed within a team-based care approach involving the healthcare system, professionals and a multidisciplinary group of health providers (Section 21.8), leading to a comprehensive patient-centered plan of care. These approaches need to be personalized and cultural, social and economic context variables need to be considered.

21.5 Follow-up of low-risk hypertensive patients and deprescribing

The therapeutic management of low-risk hypertensive patients is perceived to differ from intermediate/high-risk patients, not only because monotherapy can be more frequently used as first-line (although the present guidelines recommend initial two-drug SPCs to also be used in most of these patients) but also because it may seem rational to assume that the FU of low-risk patients should be less close, as BP levels are lower and no significant comorbidities may exist. However, even these patients might benefit from closer FU visits, and more so in the initial period of therapy, because they are at high risk of nonpersistence on treatment. In a retrospective study of almost 3000 patients younger than 40 years of age and with incident hypertension, it was found that during a 2-year FU period, BP control rates were higher with shorter visit intervals [1694].

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In some low-risk hypertensive patients in whom treatment is accompanied by effective BP control for an extended period, it may be possible to reduce the number and/or dosage of drugs. This may particularly be the case if BP control is accompanied by healthy lifestyle changes such as weight loss, exercise habit and a low-fat and low-salt diet, which minimizes environmental pressor influences. A reduction of medications should be made gradually, and the patient's BP should be checked frequently because reappearance of hypertension is frequent and can occur at variable time intervals, i.e. not only within days or weeks but also possibly after many months, because of the slow re-development of structural arteriolar changes that favor a BP elevation [681]. Patients with a high CV risk, HMOD or previous accelerated hypertension should not have their treatment withdrawn. Patients with high-normal BP or WCH frequently have additional risk factors and may also exhibit asymptomatic HMOD with a prevalence that, for WCH, is intermediate between normotensive and sustained hypertensive individuals [1015,1695–1699]. Thus, even when untreated, they should be scheduled for regular (at least annual) FU visits to measure office BP, as well as to check the CV risk profile. At annual visits, recommendations on lifestyle changes, which represent the most frequent recommended treatment in many of these patients, should be reinforced. In WCH patients, annual measurements should include not only office BP but also out-of office BP and assessment of HMOD, because in these patients, there is evidence of a greater risk of development of new HMOD and sustained hypertension [216].

21.6 Use of telemedicine and tele-health technologies

The advent of new technologies has allowed use of internet-based interactive digital interventions (tele-health) and health-related mobile applications that can also be installed on smartphones. This enables, at least in perspective, virtual care of hypertension [138]. The COVID-19 pandemic highlighted the role of remote management of chronic conditions and greatly contributed to the familiarization of both patients and physicians with these new technologies [17,138].

Interactive digital interventions include behavioral aids and promotional material for hypertension self-management. Several studies and meta-analyses suggest that these interventions are associated with better patient education, greater BP reduction and even reduced CV outcomes [1700–1702]. Mobile applications include the assessment of heart rate, thereby recognizing AF, sleep quality, physical activity and even cuff-less BP measurement [62,1703]. Transmission of HBPM, or even additional data obtained by physician are under investigation by many studies, including those promoted by ESH [1704,1705]. At present, it is premature to reach a conclusion on the benefits of these technologies, and the virtual management approach in general. Nevertheless, favorable data on home BP telemonitoring have been obtained. A meta-analysis of 46 RCTs in about 14 000 hypertensive patients revealed that home BP telemonitoring is associated with significant BP reduction and improved BP control [1706]. Similar results were reported by others [138,1707] including a study during the COVID-19 pandemic [1627].

21.7 Challenges of long-term follow-up

Hypertension requires lifelong therapy. Therefore, long-term FU is needed, and a proper FU organization is essential. Strategies for FU organization depend on the specialty of the treating physicians (e.g. primary or specialist care i.e. cardiologists, internists, nephrologists, etc.), the setting of the care (private office, hypertension clinic, hospital unit), and the resources available. In practice, the vast majority of hypertensive patients are taken care of by primary or family physicians and only a small percentage is seen and followed by specialists and, even more rarely, by hypertension centers. Hypertensive patients are also not candidates for hospitalization except for hypertension emergencies or when a hypertension-related clinical complication occurs. Ideally, complete electronic health records should be available for each patient and all information regarding the initial evaluation and lifelong management should be included, i.e. the records should incorporate demographic information, medical history, lifestyle habits, clinical findings, comorbidities, HMOD, concomitant medications, side effects of medications, laboratory results and hospital records. In several European countries, very little of this integrated information is made available for a number of reasons, including strict privacy rules that do not consent the sharing of clinical data. Nevertheless, physicians involved in long-term hypertension FU should build patients' records that include crucial information, such as the trajectories of office and, if available, the out-of-office BP profile, the history of the treatment strategies and of their inconveniences, the CV risk factor profile, the diagnoses at discharge from hospital and the HMOD dynamic status.

21.8 Role of general physician, pharmacies and team-based care

Physicians in primary care, i.e. general and family physicians, play a pivotal role in hypertension management. However, primary care workload has increased markedly over the last decades and appears to be close to or to have reached the saturation point in many countries. A key component of this workload is the diagnosis and management of long-term chronic conditions, among which hypertension-related consultations play an important role. It is likely that the hypertension-related fraction of this workload will further increase because the prevalence of hypertension is increasing, and lower BP targets make antihypertensive treatment more complex and medical visits more frequently needed. In order to avoid this problem, it is of fundamental importance that medical visit time should not be shortened. Visit times are already too short and frequently even below the time needed to properly measure BP. Attention should rather be directed to healthcare plans that carefully quantify the 'time needed to treat' by primary or specialist care physicians, including the one necessary for management of hypertension [1708], and to provide the necessary personnel accordingly. Alternative models of hypertension care, in which other health professionals participate, may also be tested and implemented. In this context, favorable

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results have been obtained by adopting care models that are different from the current one. A substantial increase in the rate of BP control as assessed over a 3-year FU has been reported by a Chinese study in which the care model was based on cost elimination, home BP measurements and home BP visits [1709]. An improvement of BP control and CV risk has been reported by use of a healthcare model, which involved primary care physicians but was led by nonphysician health workers [1710]. The evaluation of hypertension care by pharmacists has shown that BP control can be improved [1711,1712] and that community pharmacies may offer proximity and accessibility to the majority of the population in many countries, including individuals who would otherwise not seek medical advice. Community pharmacies may also be suitable places to provide health education on hypertension management [1713], which is essential for long-term treatment of largely asymptomatic diseases. In Europe, there are about 160 000 community pharmacies, with an estimated 46 million citizens visiting a pharmacy every day [1714–1721], and available evidence supports a favorable role for them in the detection and control of hypertension and CV risk factors [1722]. Finally, hypertensive patients may be followed by healthcare teams that provide the expertise and cooperation of different medical specialists and other healthcare professionals. This may offer substantial benefits, provided that each team member has a clear and specific role. Team-based interventions can significantly reduce physicians' workload and have been associated with significantly greater BP reductions and enhanced BP control rates compared with usual care [1719,1723]. Participation of nurses in healthcare teams with a role that goes far beyond BP measurements and includes instrumental examinations, nonpharmacological and pharmacological treatment delivery and explanations of the nature of the clinical condition and the rationale of the medical decisions (already successfully implemented in several European countries) may be of special importance.

21.9 Hypertension clinics

Outpatient Hypertension Units are available in most large hospitals and can offer a high-quality care to a considerable number of hypertensive patients, including patients with complicated hypertension, resistant hypertension or suspected secondary hypertension. The importance of these centers can be illustrated by the Hypertension Excellence Centers that have been established by ESH throughout Europe, fulfilling prespecified criteria regarding the ability to provide multidisciplinary services and offer high-quality inpatient and outpatient care [1724]. These centers are also contributing to clinical hypertension research, and thereby contributing to the advances of knowledge in the field [1620,1725].

21.10 Health risks at workplace

Industrialization and globalization have highlighted the role of occupational medicine reviving the previous concept of 'blue collar' and 'white collar' hypertension. Several occupational factors have been associated with hypertension and CVD and should be given attention to physicians responsible for hypertensive patients during FU. Long working hours have been associated with unhealthy lifestyles, obesity and physical inactivity [410,1726], i.e. factors that are implicated in BP elevation and CV events. Recent meta-analyses revealed that shift work is associated with increased risk of incident hypertension [1727], which is more evident in night workers compared with rotational shift workers [1728]. Occupational physical inactivity has also been associated with increased risk of incident hypertension [1726], and this is the case for sedentary occupations as well [1729]. Job-related stress is another important contributing factor to a BP elevation. In a recent report including 63 800 employees from the Dutch LifeLines Cohort Study, higher levels of job strain were associated with higher BP and increased risk of incident hypertension [1730]. The aforementioned occupational risk factors are usually interconnected and may act synergistically. Indeed, a recent epidemiological study revealed that the risk for hypertension was greater in workers with high job strain and physical inactivity [117]. Recently, several meta-analyses have unveiled an increased risk of hypertension with high occupational noise exposure in line with a similar effect of environmental noise. The increased risk varies from marginal (8%) [1731] to substantial (155%) [16], highlighting the complexity of the association and the necessity of standardization in future studies. Both job-related stress and shift work have been associated with increased CV risk [1732]. The recent COVID-19 pandemic uncovered another occupational hazard, i.e. the unemployment fear that may also adversely impact on BP and CV events. The WHO emphasizes the workplace as a priority setting for promotion of health and wellbeing, including provision of a safe and healthy physical and psychosocial work environment. Evidence concerning health promotion in the workplace suggests that health promotion programmes are effective when interventions address both individual and environmental influences [1733].

21.11 Patient organizations

Patient organizations are becoming increasingly important for chronic diseases. They are nonprofit organizations formed by patients or those who care for them. Although they were initially created mainly to provide patients with support and advice (e.g. Alcoholics Anonymous), their role is constantly expanding. An advocacy role aiming not only to reach public awareness but also to exert political pressure has been attained with large campaigns in mass and social media as well as with the inclusion of organization representatives on official advisory and decision-making boards. In some cases, patient organizations are even actively involved in research and clinical trials and operate to guide future research towards their needs. The structure and the size of patient organizations vary significantly between diseases and geographic regions. Large patient organizations for hypertension exist in a few European countries (e.g. Germany and France) but unlike for other diseases (HF, CKD or diabetes mellitus) they are absent or only nominally active in other countries. This has negative implications, because patient organizations may help patients to better share their experience with others and better cope

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with the multiple problems posed by a chronic disease. An example is the involvement of patients in programmes that evaluate the role of renal denervation as a therapeutic intervention in hypertension [773]. A future role of patient organizations may also be their participation in the elaboration of guidelines to which they would offer a wider perspective.

Hypertension management during follow-up

Recommendations and statements	CoR	LoE
Patient follow-up is recommended as a crucial part of hypertension management, to assess BP control, the need of lifestyle and drug treatment changes, to identify HMOD and necessary risk factor modifications and to check adherence.	I	C
During the first three months after treatment initiation, where lifestyle interventions and drug treatment strategies to achieve BP control are implemented, it is recommended that physician visits (including virtual care visits) should take place every month or even more frequently, depending on hypertension grade, CV risk, previous unsuccessful attempts to achieve BP control and other factors suggesting antihypertensive treatment difficulties.	I	C
After the end of the titration phase, when BP is controlled, less frequent visits may be necessary, although data on the best visit intervals are not available, annual visits are recommended to favor physician-patient relationship and adherence. More frequent visits should be considered in patients in which BP control was more difficult during the titration phase and in patients at high CV risk.	I	C
Follow-up visits should collect standard measurements of office BP, update of medical history (side effects of treatment in particular) and physical examination. Frequency of laboratory examinations should depend on the clinical condition and risk level of the patient. To collect ECG and blood test data at annual intervals appears reasonable in low risk patients. Adherence should be checked at each visit.	I	C
ABPM may be included in the follow-up examinations whenever possible.Yearly intervals may appear reasonable but frequency will depend on the hypertension grade, BP variability between visits and the BP phenotypes in previous ABPM recordings.	II	C

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Use of HBPM, ideally by using automatic electronic devices allowing automated storage and asynchronous data transfer to care providers with mobile phone, personal computer or internet link or cloud-based connectivity, is strongly encouraged. HBPM data are useful for prompting physician visits where changes in treatment and overall management should be decided.	I	C
It is recommended that HMOD should be also checked periodically. In patients without preexisting HMOD subsequent checks can be done at longer intervals, e.g every 3 years. In patients with pre-existing HMOD, checks should be done more frequently, depending on the type of HMOD, sensitivity to change detection or HMOD-related symptoms.	I	C
The use of novel telehealth technologies and virtual care possibilties are recommended to improve hypertension management during follow-up.	I	C

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22. GAPS IN EVIDENCE AND FUTURE OPPORTUNITIES

As mentioned in Section 1, the present guidelines have placed RCTs at the top of the evidence on which to base the recommendations on hypertension management. This acknowledges a fundamental advantage of this research approach, i.e. the indentical composition or at least close similarity of the compared groups at baseline and thus the possibility to safely ascribe their FU differences to the intervention studied. However, RCTs have limitations, and their adoption over almost 60 years has not been able to provide an answer to many important clinical problems posed by a BP elevation. For example, RCTs can last no more than a small fraction of the life expectancy of most hypertensive patients, which means that the current recommendation of life-long hypertension treatment is necessarily based on extrapolation from much shorter time data. Recommendations in very old (>85 years of age) and young people pose unsurmountable difficulties because RCTs, have never been done at these extreme ages. Whether BP-lowering interventions (drug-based or device-based) lead to patient protection in resistant hypertension is unknown and this is the case also for BP reduction in common conditions such as MH and WCH. Even the popular use of ABPM and HBPM is not validated by any trial in which traditional office BP-guided treatment is compared with out-of-office BP-guided treatment or the two intervention strategies together are compared with one or the other intervention strategy alone. Furthermore, even when RCTs are available, the transferability of their results to clinical practice can be problematic because RCTs are conducted with a superior level of expertise and in an environment that guarantees fewer errors, a much better treatment adherence [1734] and a lower therapeutic inertia than in real-life practice. The gaps between the two situations are particularly evident in the assessment of drug tolerability, usually considerably more optimistic when initially investigated in trials than when later addressed by real-word studies, in which context even previously unsuspected side effects may emerge. Hypertension management as well as management of diabetes, dyslipidemia and other chronic diseases can now count gain important information from additional research approaches [476], which were previously downgraded due to a greater risk of bias due to confounding. Local, regional and even national registries, administrative or health utilization databases extended on regional or national level and extensive biobank data, all covering long periods of time (up to 20 years) are now available and suitable data sources for addressing problems unaddressed by trials. Originally available in the United States and run by public health organizations or medical insurance companies, these databases are now available in most European countries, where they can collect data from large proportions of or even the entire population, which in Europe, has the advantage of a greater residential stability than in the United States. Additional advantages over RCTs are that (i) compared with the relative homogeneity of trial data, these databases reflect the real-world patient heterogeneity, thereby offering better options for the development of precision or individualized medicine and (ii) their results can be obtained at reduced cost and much more quickly than in trials. Quick data collection is an especially important advantage, as experienced with the recent COVID-19 pandemic, during which collection of trial data was unfeasible and responses to important public health questions by trials unavailable. Future use of

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Table 27. Gaps in the evidence

Epidemiology and risk
- Association between BP levels in children and adolescents and the risk for clinical CV and kidney outcomes
- Trajectories of BP and hypertension phenotypes throughout life and their association with CV and kidney outcomes
- The optimal SBP and DBP level at different time points in life
- Predictive ability and therapeutic responsiveness of HMOD
- Incremental benefit of more advanced risk estimation (SCORE2 => HMOD => vascular imaging/polygenic risk scores)
- Incremental accuracy of risk estimation by use of short and long term BP variability
Diagnostic procedures
- Benefits of screening
- Optimal interval for reassessment of BP in nonhypertensive patients
- Does the incremental prognostic ability of ABPM and HBPM substantially improve diagnosis and treatment?
- Association of ABPM and HBPM with CV and kidney outcomes by serial ABPM and HBPM measurements
- Validity and application of cuffless BP measurement devices
- Optimal BP measurement methods and interpretation of BP values in AF
Treatment strategies
- Optimal time-point and BP level to initiate treatment in young patients
- Optimal and safe BP thresholds and targets in very old and frail patients
- Office vs out-of-office guided treatment on clinical outcomes
- BP thresholds and targets in low-to moderate risk individuals
- BP thresholds and targets in specific patient groups (LVH, ISH, CKD, people aged 80 years or older)
- BP thresholds and targets using ABPM and HBPM
- Treatment effect on clinical outcomes in MH and WCH
- BP- vs HBPM- guided antihypertensive treatment
- Effect of nocturnal BP reduction by treatment on clinical outcomes
- Effect of lifestyle interventions of CV outcomes
- Strategies to implement lifestyle recommendations effectively
- Choice of first-line antihypertensive agent and sequence of titration from a population and individual level perspective
- Effectiveness and implementation strategies for individualized antihypertensive treatment
- Effect of device-based therapy (RDN) on CV and kidney outcomes
- Effect of drug treatment of true resistant hypertension on CV and kidney events
- Effects of down-titration and treatment withdrawal in different clinical settings
Follow-up
- Optimal timing and frequency of follow-up
- Optimal BP measurement modality (OBP, HBPM, ABPM) for follow-up
- The role of cuff-less devices for monitoring
- Effect of distance monitoring and digital alert systems on clinical outcomes
- Evaluation of, and interventions to improve, adherence

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these approaches will be facilitated by statistical methods that allow equalization of compared groups at baseline or sophisticated testing for unmeasured confounders. As the temporal length of these bases is now considerable, future studies will more and more frequently be able to compare treatment data within individuals, with a substantial reduction of the confounding associated with comparisons of nonrandomized groups of patients [472]. Lastly, regional- and nationwide administrative and clinical databases may now be used as a foundation for register-based RCTs, combining many advantages related to recruitment, follow-up and generalizability from observational studies with the unbiased estimates derived from an experimental design [1735]. Several contributions of real-word research to present knowledge of hypertension epidemiology, diagnosis and treatment have been mentioned in the present guidelines and considered for the guideline recommendations. These contributions will grow in the future and will thus have to be taken into progressively greater consideration by physicians in their update of research progress and knowledge on hypertension. Although complex and somewhat controversial, this growth will include the analysis of big real-word datasets data by the machine learning and artificial intelligence approaches [1735,1736]. Machine learning aims at processing complex databases automatically by methods that make use of highly sophisticated statistics in order to develop new diagnostic and treatment algorithms [1737]. Artificial intelligence takes the analysis further by including analytical processes specific of human-related decision steps. This approach extends to a large variety of human activities and in hypertension has produced promising results for an improvement of the ability to predict the risk of incident hypertension and future organ damage [1738,1739]. Promising results have also been obtained on the possibility to personalize antihypertensive treatment [1740,1741–1743]. Improved prediction of future hypertension and HMOD development by these approaches would be of particular importance, because of the possibility to focus intensive preventive treatment on people at greater risk (Table 27).

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Conflicts of interest

There are no conflicts of interest.

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