Guidelines

2020 International Society of Hypertension global hypertension practice guidelines

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Abbreviations: ABI, ankle–brachial index; ABPM, ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; ARB, angiotensin AT-1 receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; BP, blood pressure; CAD, coronary artery disease; CCBs, calcium channel blockers; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DHP-CCB, dihydropyridine calcium channel blocker; DM, diabetes mellitus; DRI, direct renin inhibitor; eGFR, estimated glomerular filtration rate; ESC-ESH, European Society of Cardiology–European Society of Hypertension; HBPM, home blood pressure measurement; HDL, high-density lipoprotein; HELLP, heamolysis, elevated liver enzymes and low platelets; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIC, high-income countries; HIIT, high-intensity interval training; HMOD, hypertension-mediated organ damage; IMT, intima–media thickness; IRD, inflammatory rheumatic disease; ISH, International Society of Hypertension; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LMIC, low and middle-income countries; LV, left ventricular; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; PWV, pulse wave velocity; RAAS, renin–angiotensin–aldosterone system; RAS, renin–angiotensin system; RCT, randomized control trials; SNRI, selective norepinephrine and serotonin reuptake inhibitors; SPC, single pill combination therapy; SRI, serotonin reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; s-UA, serum uric acid; T4, thyroxin 4; TG, Triglycerides; TIA, transient ischemic attack; TMA, thrombotic micro-angiopathy; TSH, thyroid stimulating hormone; TTE, two-dimensional transthoracic echocardiogram; UACR, urinary albumin creatinine ratio

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SECTION 1: INTRODUCTION

Context and purpose of this guideline

Statement of remit: To align with its mission to reduce the global burden of raised blood pressure (BP), the International Society of Hypertension (ISH) has developed worldwide practice guidelines for the management of hypertension in adults, aged 18 years and older. The ISH Guidelines Committee extracted evidence-based content presented in recently published extensively reviewed guidelines and tailored ESSENTIAL and OPTIMAL standards of care in a practical format that is easy-to-use particularly not only in low-resource settings but also in high-resource settings- by clinicians, but also nurses and community health workers, as appropriate. Although distinction between low-resource and high-resource settings often refers to high (HIC) and low-income and middle-income countries (LMIC), it is well established that in HIC, there are areas with low-resource settings, and vice versa.

Herein optimal care refers to evidence-based standard-of-care articulated in recent guidelines [1,2] and summarized here, whereas essential standards recognize that optimal standards would not always be possible. Hence, essential standards refer to minimum standards of care. To allow specification of essential standards of care for low-resource settings, the Committee was often confronted with the limitation or absence in clinical evidence, and thus applied expert opinion.

In the Guidelines, differentiation between optimal and essential standards were not always possible, and were made in sections where it was most practical and sensible. The Guidelines Committee is also aware that some recommended essential standards may not be feasible in low-resource settings, for example, out-of-office BP measurements, the requirement of multiple visits for the diagnosis of hypertension, or advising the use of single pill combination therapy. Although challenging to implement, these guidelines may aid in local initiatives to motivate policy changes and serve as an instrument to drive local improvements in standards of care. Every effort should be made to achieve essential standards of care to reduce hypertension-induced cardiovascular morbidity and mortality.

Motivation: Raised BP remains the leading cause of death globally, accounting for 10.4 million deaths per year [3]. When reviewing global figures, an estimated 1.39 billion people had hypertension in 2010 [4]. However, BP trends show a clear shift of the highest BPs from high-income to low-income regions [5], with an estimated 349 million with hypertension in HIC and 1.04 billion in LMICs [4].

The large disparities in the regional burden of hypertension are accompanied by low levels of awareness, treatment, and control rates in LMIC, when compared with HIC. In response to poor global awareness for hypertension (estimated 67% in HIC and 38% in LMIC) [4], the ISH launched a global campaign to increase awareness of raised BP, namely the May Measurement Month initiative [6,7].

Despite several initiatives, the prevalence of raised BP and adverse impact on cardiovascular morbidity and mortality are increasing globally, irrespective of income [4,5]. It is, therefore, critical that population-based initiatives are applied to reduce the global burden of raised BP, such as salt-reduction activities and improving the availability of fresh fruit and vegetables. To improve the management of hypertension, the ISH has published in 2014 with the American Society of Hypertension, Clinical Practice Guidelines for the Management of Hypertension in the Community (see Section 11: Resources). Recently, we have observed a recent flurry of updated evidence-based guidelines arising mainly from high-income regions and countries, including the United States of America [2], Europe [1], United Kingdom [8], Canada [9], and Japan [10]. New developments include redefining hypertension [2], initiating treatment with a single pill combination therapy [1], advising wider out-of-office BP measurement [2,10], and lower BP targets [1,2,8,11,12].

Low-income and middle-income regions often follow the release of guidelines from high-income regions closely, as their resources and health systems to develop and implement local guidelines remain challenging. In Africa, only 25% of countries have hypertension guidelines [13], and in many instances, these guidelines are adopted from those of high-income regions. However, the adoption of guidelines from high-income regions are sometimes impractical as low-resource settings are confronted with a substantial number of obstacles including severe lack of trained healthcare professionals, unreliable electricity in rural clinics, low access to basic office BP devices and limited ability to conduct basic recommended diagnostic procedures and poor access to affordable high-quality medications. In both low-income and high-income regions, the ambiguities of latest guidelines are often met with confusion among health care providers, anxiety among patients [14], and they resulted in a call for global

TABLE 1. Classification of hypertension based on office blood pressure measurement

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal BP	<130	and	<85
High-normal BP	130–139	and/or	85–89
Grade 1 Hypertension	140–159	and/or	90–99
Grade 2 Hypertension	≥160	and/or	≥100

TABLE 2. Criteria for hypertension based on office blood pressure, ambulatory blood pressure, and home blood pressure measurement

		SBP/DBP (mmHg)
Office BP		≥140 and/or ≥90
ABPM	24h average	≥130 and/or ≥80
	Day time (or awake) average	≥135 and/or ≥85
	Night time (or asleep) average	≥120 and/or ≥70
HBPM		≥135 and/or ≥85

harmonization [15]. Guidelines from high-income regions may thus not fit global purpose [16].

Guideline development process: The 2020 ISH Global Hypertension Practice Guidelines were developed by the ISH Hypertension Guidelines Committee based on evidence criteria, (a) to be used globally; (b) to be fit for application in low-resource and high-resource settings by advising on essential and optimal standards; and (c) to be concise, simplified, and easy to use. They were critically reviewed and evaluated by numerous external hypertension experts from HIC and LMIC with expertise in the optimal management of hypertension and management in resource-constraint settings. These guidelines were developed without any support from industry or other sources.

Composition of the International Society of Hypertension Hypertension Guidelines Committee and Selection of External Reviewers: The ISH Hypertension Guidelines Committee was composed of members of the ISH Council; they were included on the basis of the following: specific expertise in different areas of hypertension; previous experience with the generation of hypertension guidelines, as well as representation of different regions of the world. A similar strategy was followed concerning the selection of external reviewers with particular consideration of representatives from LMICs.

SECTION 2: DEFINITION OF HYPERTENSION

- In accordance with most major guidelines, it is recommended that hypertension be diagnosed when a person's SBP in the office or clinic is ≥140 mmHg and/or their DBP is ≥90 mmHg following repeated examination (see below, Section 3). Table 1 provides a classification of BP based on office BP measurement, Table 2 provides ambulatory and home BP values used to define hypertension; these definitions apply to all adults (>18 years old). These BP categories are designed to align therapeutic approaches with BP levels.
- High-normal BP is intended to identify individuals who could benefit from lifestyle interventions and who would receive pharmacological treatment if compelling indications are present (see Section 9).
- Isolated systolic hypertension defined as elevated SBP (≥140 mmHg) and low DBP (<90 mmHg) is common in young and in elderly people. In young individuals, including children, adolescents and young adults, isolated systolic hypertension is the most common form of essential hypertension. However, it is also particularly common in the elderly, in whom it reflects stiffening of the large arteries with an increase in pulse pressure (difference between SBP and DBP).
- Individuals identified with confirmed hypertension (Grade 1 and Grade 2) should receive appropriate pharmacological treatment.
- Details of home BP, office BP, and ambulatory BP measurement techniques are addressed in Section 3.

SECTION 3: BLOOD PRESSURE MEASUREMENT AND DIAGNOSIS OF HYPERTENSION

ESSENTIAL

Hypertension diagnosis: office blood pressure measurement

- The measurement of BP in the office or clinic is most commonly the basis for hypertension diagnosis and follow-up. Office BP should be measured according to recommendations shown in Table 3 and Fig. 1 [1,2,17,18].

TABLE 3. Recommendations for office blood pressure measurement

Conditions	• Quiet room with comfortable temperature. • Before measurements: Avoid smoking, caffeine and exercise for 30 min; empty bladder; remain seated and relaxed for 3 – 5 min. • Neither patient nor staff should talk before, during and between measurements.
Positions	• Sitting: Arm resting on table with mid-arm at heart level; back supported on chair; legs uncrossed and feet flat on floor ***(Figure 1)***.
Device	• Validated electronic (oscillometric) upper-arm cuff device. Lists of accurate electronic devices for office, home and ambulatory BP measurement in adults, children and pregnant women are available at www.stridebp.org. [22] (see also ***Section 11:*** Resources) • Alternatively use a calibrated auscultatory device, (aneroid, or hybrid as mercury sphygmomanometers are banned in most countries) with 1st Korotkoff sound for systolic blood pressure and 5th for diastolic with a low deflation rate [22].
Cuff	• Size according to the individual's arm circumference (smaller cuff overestimates and larger cuff underestimates blood pressure). • For manual auscultatory devices the inflatable bladder of the cuff must cover 75 – 100 % of the individual's arm circumference. For electronic devices use cuffs according to device instructions.
Protocol	• At each visit take 3 measurements with 1 min between them. Calculate the average of the last 2 measurements. If BP of first reading is <130/85 mmHg no further measurement is required
Interpretation	• Blood pressure of 2 – 3 office visits ≥ 140/90 mmHg indicates hypertension.

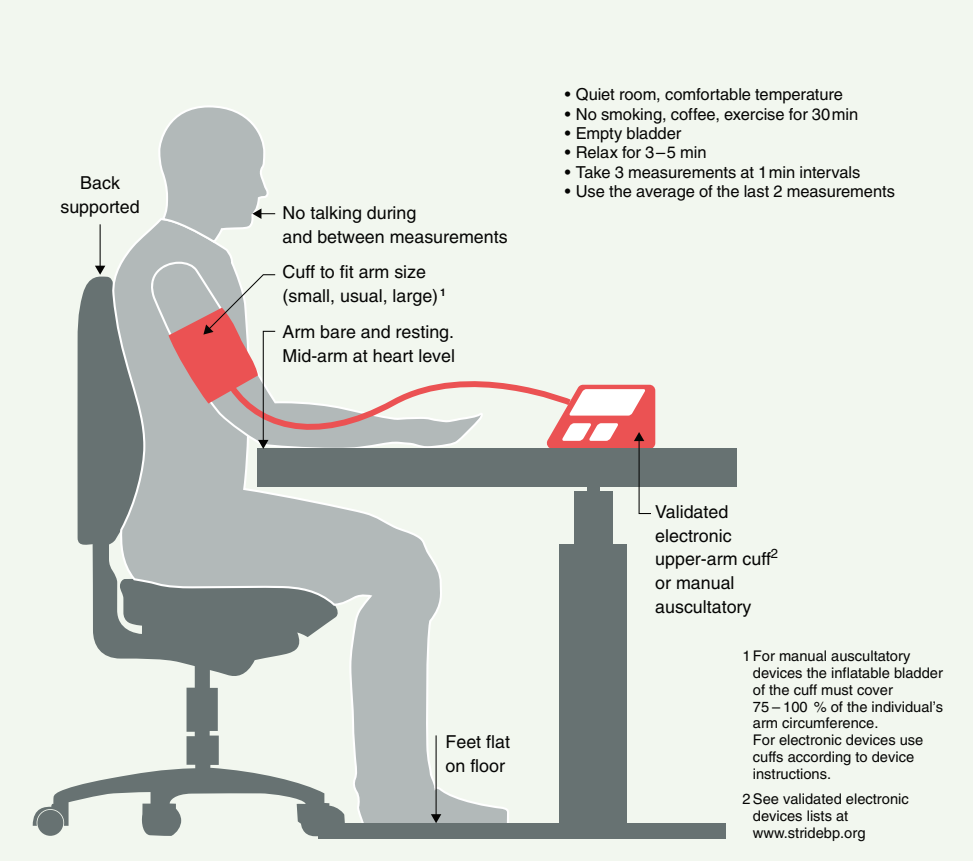

FIGURE 1 How to measure blood pressure.

- Whenever possible, the diagnosis should not be made on a single office visit. Usually two to three office visits at 1–4-week intervals (depending on the BP level) are required to confirm the diagnosis of hypertension. The diagnosis might be made on a single visit, if BP is ≥180/110 mmHg and there is evidence of cardiovascular disease (CVD) [1,2,17,18].
- The recommended patient management according to office BP levels is presented in Table 4.
- If possible and available, the diagnosis of hypertension should be confirmed by out-of-office BP measurement (see below) [1,2,19–21].

TABLE 4. Blood pressure measurement plan according to office blood pressure levels

Office blood pressure levels (mmHg)		
<130/85	130-159/85-99	>160/100
Remeasure within 3 years (1 year in those with other risk factors)	If possible confirm with out-of-office blood pressure measurement (high possibility of white coat or masked hypertension). Alternatively confirm with repeated office visits	Confirm within a few days or weeks

OPTIMAL

Hypertension diagnosis: office blood pressure measurement

- **Initial evaluation**: measure BP in both arms, preferably simultaneously. If there is a consistent difference between arms >10 mmHg in repeated measurements, use the arm with the higher BP. If the difference is >20 mmHg consider further investigation.
- **Standing blood pressure**: measure in treated hypertensive patients after 1 min and again after 3 min when there are symptoms suggesting postural hypotension and at the first visit in the elderly and people with diabetes.
- **Unattended office blood pressure**: multiple automated BP measurements taken while the patient remains alone in the office provide more standardized evaluation but also lower BP levels than usual office measurements with uncertain threshold for hypertension diagnosis [17,18,23,24]. Confirmation with out-of-office BP is again needed for most treatment decisions.

Hypertension diagnosis: out-of-office blood pressure measurement

- Out-of-office BP measurements [by patients at home or with 24-h ambulatory blood pressure monitoring (ABPM)] are more reproducible than office measurements, more closely associated with hypertension-induced organ damage and the risk of cardiovascular events and identify the white-coat and masked hypertension phenomena (see below).
- Out-of-office BP measurement is often necessary for the accurate diagnosis of hypertension and for treatment decisions. In untreated or treated subjects with office BP classified as high-normal BP or grade 1 hypertension (systolic 130–159 mmHg and/or diastolic 85–99 mmHg), the BP level needs to be confirmed using home or ambulatory BP monitoring (Table 5) [1,2,17–21].
- Recommendations for performing home and ambulatory BP measurement are presented in Table 5.

TABLE 5. Clinical use of home and ambulatory blood pressure monitoring

	Home blood pressure monitoring	24-hour ambulatory blood pressure monitoring
Condition	As for office blood pressure *(see above)*.	Routine working day.
Position	As for office BP *(see above)*.	Avoid strenuous activity. Arm still and relaxed during each measurement.
Device	Validated electronic (oscillometric) upper- arm cuff device (www.stridebp.org, and Section 11: Resources)	
Cuff	Size according to the individual's arm circumference	
Measurement protocol	**Before each visit to the health professional:** • 3 – 7-day monitoring in the morning (before drug intake if treated) and the evening. • Two measurements on each occasion after 5 min sitting rest and 1 min between measurements. **Long-term follow-up of treated hypertension:** • 1 – 2 measurements per week or month.	• 24-hour monitoring at 15 – 30 min intervals during daytime and nighttime. • At least 20 valid daytime and 7 nighttime BP readings are required. If less, the test should be repeated.
Interpretation	• Average home blood pressure after excluding readings of the first day ≥ 135 or 85 mmHg indicates hypertension.	• 24-hour ambulatory blood pressure ≥ 130/80 mmHg indicates hypertension (primary criterion). • Daytime (awake) ambulatory blood pressure ≥ 135/85 mmHg and nighttime (asleep) ≥ 120/70 mmHg indicates hypertension

White-coat and masked hypertension

- The use of office and out-of-office (home or ambulatory) BP measurements identifies individuals with white-coat hypertension, who have elevated BP only in the office (nonelevated ambulatory or home BP), and those with masked hypertension, who have nonelevated BP in the office but elevated BP out of the office (ambulatory or home) [1,2,17–21,25–27]. These conditions are common among both untreated subjects and those treated for hypertension. About 10–30% of subjects attending clinics because of high BP have white-coat hypertension and 10–15% have masked hypertension.
- **White-coat hypertension**: these subjects are at intermediate cardiovascular risk between normotensives and sustained hypertensive patients. The diagnosis needs confirmation with repeated office and out-of-office BP measurements. If their total cardiovascular risk is low and there is no hypertension-mediated organ damage (HMOD), drug treatment may not be prescribed. However, they should be followed with lifestyle modification, as they may develop sustained hypertension requiring drug treatment [1,2,17–21,25–27].
- **Masked hypertension**: these patients are at similar risk of cardiovascular events as sustained hypertensive patients. The diagnosis needs confirmation with repeated office and out-of-office measurements. Masked hypertension may require drug treatment aiming to normalize out-of-office BP [1,2,17–21,25–27].

SECTION 4: DIAGNOSTIC/CLINICAL TESTS

ESSENTIAL

Medical history

Patients with hypertension are often asymptomatic; however, specific symptoms can suggest secondary hypertension or hypertensive complications that require further investigation. A complete medical and family history is recommended and should include [1]:

- **Blood pressure**: new onset hypertension, duration, previous BP levels, current and previous antihypertensive medication, other medications/over-the counter medicines that can influence BP, history of intolerance (side-effects) of antihypertensive medications, adherence to antihypertensive treatment, previous hypertension with oral contraceptives or pregnancy.
- **Risk factors**: personal history of CVD [myocardial infarction, heart failure, stroke, transient ischemic attacks (TIA)], diabetes, dyslipidemia, chronic kidney disease (CKD), smoking status, diet, alcohol intake, physical activity, psychosocial aspects, history of depression. Family history of hypertension, premature CVD, (familial) hypercholesterolemia, diabetes.
- **Assessment of overall cardiovascular risk**: in line with local guidelines/recommendations (see risk scores in Section 11 at the end of the document).
- **Symptoms/signs of hypertension/co-existent illnesses**: chest pain, shortness of breath, palpitations, claudication, peripheral edema, headaches, blurred vision, nocturia, haematuria, dizziness.
- **Symptoms suggestive of secondary hypertension**: muscle weakness/tetany, cramps, arrhythmias (hypokalemia/ primary aldosteronism), flash pulmonary edema (renal artery stenosis), sweating, palpitations, frequent headaches (pheochromocytoma), snoring, daytime sleepiness (obstructive sleep apnea), symptoms suggestive of thyroid disease (see Section 10 for full list of symptoms).

Physical examination

A thorough physical examination can assist with confirming the diagnosis of hypertension and the identification of HMOD and/or secondary hypertension and should include:

- **Circulation and heart**: pulse rate/rhythm/character, jugular venous pulse/pressure, apex beat, extra heart sounds, basal crackles, peripheral edema, bruits (carotid, abdominal, femoral), radiofemoral delay.
- **Other organs/systems**: enlarged kidneys, neck circumference >40 cm (obstructive sleep apnea), enlarged thyroid, increased BMI/waist circumference, fatty deposits, and coloured striae (Cushing's disease/syndrome).

Laboratory investigations and ECG

- **Blood tests**: sodium, potassium, serum creatinine, and estimated glomerular filtration rate (eGFR). If available, lipid profile and fasting glucose.
- **Urine test:** dipstick urine test.
- **12-lead ECG:** detection of atrial fibrillation, left ventricular hypertrophy (LVH), ischemic heart disease.

OPTIMAL

Additional diagnostic tests

Additional investigations whenever indicated can be undertaken to assess and confirm suspicion of HMOD, co-existent diseases, or/and secondary hypertension.

Imaging techniques

- **Echocardiography**: LVH, systolic/diastolic dysfunction, atrial dilation, aortic coarctation.
- **Carotid ultrasound**: plaques (atherosclerosis), stenosis.
- **Kidneys/renal artery and adrenal imaging**: ultrasound/renal artery Duplex; CT-angiography/MR-angiography: renal parenchymal disease, renal artery stenosis, adrenal lesions, other abdominal pathology.
- **Fundoscopy**: retinal changes, hemorrhages, papilledema, tortuosity, nipping.
- **Brain CT/MRI**: ischemic or hemorrhagic brain injury because of hypertension.

Functional tests and additional laboratory investigations

- **Ankle–brachial index**: peripheral (lower extremity) artery disease.
- **Further testing for secondary hypertension if suspected**: aldosterone–renin ratio, plasma free metanephrines, late-night salivatory cortisol or other screening tests for cortisol excess.
- **Urinary albumin/creatinine ratio**
- **Serum-Uric Acid (s-UA) levels**
- **Liver function tests**

SECTION 5: CARDIOVASCULAR RISK FACTORS

Diagnostic approach

- More than 50% of hypertensive patients have additional cardiovascular risk factors [28,29].
- The most common additional risk factors are diabetes (15–20%), lipid disorders [elevated low density lipoprotein-cholesterol (LDL-C) and triglycerides (30%)], overweight-obesity (40%), hyperuricemia (25%) and metabolic syndrome (40%), as well as unhealthy lifestyle habits (e.g. smoking, high alcohol intake, sedentary lifestyle) [28–30].
- The presence of one or more additional cardiovascular risk factors proportionally increases the risk of coronary, cerebrovascular, and renal diseases in hypertensive patients [1].

ESSENTIAL

- An evaluation of additional risk factors should be part of the diagnostic workup in hypertensive patients particularly in the presence of a family history of CVD.
- **Cardiovascular risk should be assessed in all hypertensive patients by** easy-to-use scores based on BP levels and additional risk factors according to a simplified version of the approach proposed by ESC-ESH Guidelines (Table 6) [1].
- A reliable estimate of cardiovascular risk can be obtained in daily practice by including:
- **Other risk factors**: age (>65 years), sex (men > women), heart rate (>80 beats/min), increased body weight, diabetes, high LDL-C/TG, family history of CVD, family history of hypertension, early onset menopause, smoking habits, psychosocial or socio-economic factors. **HMOD**: LVH (LVH with ECG), moderate–severe CKD (CKD; eGFR <60 ml/min/1.73 m^2), any other available measure of organ damage. **Disease**: previous coronary heart disease (CHD), HF, stroke, peripheral vascular disease, atrial fibrillation, CDK stage 3+.

- The therapeutic strategy must include lifestyle changes, BP control to target, and the effective treatment of the other risk factors to reduce the residual cardiovascular risk.
- The combined treatment of hypertension and additional cardiovascular risk factors reduces the rate of CVD beyond BP control.

TABLE 6. Simplified classification of hypertension risk according to additional risk factors, hypertension-mediated organ damage, and previous disease[a]

Other risk factors, HMOD, or disease	High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP ≥160 DBP ≥100
No other risk factors	Low	Low	Moderate – High
1 or 2 risk factors	Low	Moderate	High
≥3 risk factors	Low – Moderate	High	High
HMOD, CKD grade 3, diabetes mellitus, CVD	High	High	High

[a]Example based on a 60-year-old male patient. Categories of risk will vary according to age and sex.

Other additional risk factors

- Elevated serum uric acid (s-UA) is common in patients with hypertension and should be treated with diet, urate-influencing drugs (losartan, fibrates, atorvastatin) or urate-lowering drugs in symptomatic patients [gout with s-UA >6 mg/dl (0.357 mmol/l)].
- An increase in cardiovascular risk must be considered in patients with hypertension and chronic inflammatory diseases, chronic obstructive pulmonary disease (COPD), psychiatric disorders, psycho-social stressors where an effective BP control is warranted [1].

SECTION 6: HYPERTENSION-MEDIATED ORGAN DAMAGE

Definition and role of hypertension-mediated organ damage in hypertension management

Hypertension-mediated organ damage (HMOD) is defined as the structural or functional alteration of the arterial vasculature and/or the organs it supplies that is caused by elevated BP. End organs include the brain, the heart, the kidneys, central and peripheral arteries, and the eyes.

While assessment of overall cardiovascular risk is important for the management of hypertension, additional detection of HMOD is unlikely to change the management of those patients already identified as high risk (i.e. those with established CVD, stroke, diabetes, CKD, or familial hypercholesterolemia). However, it can provide important therapeutic guidance on 1) management for hypertensive patients with low or moderate overall risk through re-classification because of presence of HMOD, and 2) preferential selection of drug treatment based on the specific impact on HMOD [1].

Specific aspects of hypertension-mediated organ damage and assessment

- **Brain:** TIA or strokes are common manifestations of elevated BP. Early subclinical changes can be detected most sensitively by MRI and include white matter lesions, silent microinfarcts, microbleeds, and brain atrophy. Due to costs and limited availability, brain MRI is not recommended for routine practice but should be considered in patients with neurologic disturbances, cognitive decline, and memory loss.
- **Heart**: a 12-lead ECG is recommended for routine workup of patients with hypertension and simple criteria (Sokolow–Lyon index: SV1+RV5 ≥35 mm, Cornell index: SV3+RaVL >28 mm for men or >20 mm for women and Cornell voltage duration product: >2440 mm·ms) are available to detect presence of LVH. Sensitivity of ECG-LVH is very limited and a two-dimensional transthoracic echocardiogram (TTE) is the method of choice to accurately assess LVH [left ventricular mass index (LVMI): men >115 g/m^2;

women >95 g/m^2] and relevant parameters including LV geometry, left atrial volume, LV systolic and diastolic function, and others.

- **Kidneys:** kidney damage can be a cause and consequence of hypertension and is best assessed routinely by simple renal function parameters (serum creatinine and eGFR) together with investigation for albuminuria [dipstick or urinary albumin creatinine ratio (UACR) in early morning spot urine].
- **Arteries**: three vascular beds are commonly assessed to detect arterial HMOD: 1) the carotid arteries through carotid ultrasound to detect atherosclerotic plaque burden/stenosis and intima–media thickness (IMT); 2) the aorta by carotid—femoral pulse wave velocity (PWV) assessment to detect large artery stiffening; and the lower extremity arteries by assessment of the ankle–brachial index (ABI). Although there is evidence to indicate that all three provide added value beyond traditional risk factors, their routine use is currently not recommended unless clinically indicated, that is, in patients with neurologic symptoms, isolated systolic hypertension, or suspected peripheral artery disease, respectively.
- **Eyes**: fundoscopy is a simple clinical bedside test to screen for hypertensive retinopathy although interobserver and intraobserver reproducibility is limited. Fundoscopy is particularly important in hypertensive urgencies and emergencies to detect retinal haemorrhage, microaneurysms, and papilledema in patients with accelerated or malignant hypertension. Fundoscopy should be performed in patients with grade 2 hypertension, ideally by experienced examiners or alternative techniques to visualize the fundus (digital fundus cameras) where available.

ESSENTIAL

The following assessments to detect HMOD should be performed routinely in all patients with hypertension:
- serum creatinine and eGFR
- dipstick urine test
- 12-lead ECG

OPTIMAL

All other techniques mentioned above can add value to optimize management of hypertension in affected individuals and should be considered wherever clinically indicated and available. Serial assessment of HMOD (LVH and albuminuria) to monitor regression with antihypertensive treatment may be helpful to determine the efficacy of treatment in individual patients but this has not been sufficiently validated for most measures of HMOD.

SECTION 7: EXACERBATORS AND INDUCERS OF HYPERTENSION

Background

Several medications and substances may increase BP or antagonize the BP-lowering effects of antihypertensive therapy in individuals (Table 7). It is important to note that the individual effect of these substances on BP can be highly variable with greater increases noted in the elderly, those with higher baseline BP, using antihypertensive therapy or with kidney disease.

ESSENTIAL **OPTIMAL**

- Screen all patients (with hypertension and those at risk for hypertension) for substances that may increase BP or interfere with the BP-lowering effect of antihypertensive medications.
- Where appropriate, consider reducing or eliminating substances that raise BP. If these substances are required or preferred, then treat BP to target regardless. (see resource [31] on possible antihypertensive therapies that target mechanisms underlying the raised BP induced by these substances).

TABLE 7. Drug/substance exacerbators and inducers of hypertension

Drug/substance [32–43]	Comments on specific drugs and substances[a]
Nonsteroidal Antiinflammatory Drugs (NSAIDs)	No difference or an increase of up to 3/1 mmHg with celecoxib 3/1 mmHg increase with nonselective NSAIDs No increase in blood pressure with aspirin NSAIDs can antagonize the effects of RAAS inhibitors and beta blockers
Combined oral Contraceptive pill	6/3 mmHg increase with high doses of estrogen (>50 μg of estrogen and 1–4 μg progestin)
Antidepressants	2/1 mmHg increase with SNRI (selective norepinephrine and serotonin reuptake inhibitors) Increased odds ratio of 3.19 of hypertension with tricyclic antidepressant use No increases in blood pressure with SSRI (selective serotonin reuptake inhibitors)
Acetaminophen	Increased relative risk of 1.34 of hypertension with almost daily acetaminophen use
Other medications	Steroids Antiretroviral therapy: inconsistent study findings for increased blood pressure Sympathomimetics: pseudoephedrine, cocaine, amphetamines Antimigraine serotonergics Recombinant human erythropoeitin Calcineurin inhibitors Antiangiogenesis and kinase inhibitors 11β-hydroxysteroid dehydrogenase type 2 inhibitors
Herbal and other Substances [44,45]	Alcohol, Ma-huang, Ginseng at high doses, Liquorice, St. John's Wort, Yohimbine

[a]Average increase in blood pressure or risk of hypertension. However, the effect of these medications/substances on blood pressure may highly vary between individuals.

TABLE 8. Lifestyle modifications

Salt reduction	There is strong evidence for a relationship between high salt intake and increased blood pressure [47]. Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods, such as soy sauce, fast foods, and processed food including breads and cereals high in salt.
Healthy diet	Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products, and reducing food high in sugar, saturated fat and trans fats, such as DASH diet (http://www.dashforhealth.com) [48]. Increase intake of vegetables high in nitrates known to reduce BP, such as leafy vegetables and beetroot. Other beneficial foods and nutrients include those high in magnesium, calcium, and potassium, such as avocados, nuts, seeds, legumes, and tofu [49].
Healthy drinks	Moderate consumption of coffee, green, and black tea [50]. Other beverages that can be beneficial include Karkadé (Hibiscus) tea, pomegranate juice, beetroot juice, and cocoa [49].
Moderation of alcohol consumption	Positive linear association exists between alcohol consumption, blood pressure, the prevalence of hypertension, and CVD risk [51]. The recommended daily limit for alcohol consumptions is two standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking.
Weight reduction	Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used [52]. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations [53,54].
Smoking cessation	Smoking is a major risk factor for CVD, COPD, and cancer. Smoking cessation and referral to smoking cessation programs are advised [55].
Regular physical activity	Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension [56–58]. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 min on 5–7 days per week or HIIT (high intensity interval training), which involves alternating short bursts of intense activity with subsequent recovery periods of lighter activity. Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on 2–3 days per week.
Reduce stress and induce mindfulness	Chronic stress has been associated to high blood pressure later in life [59]. Although more research is needed to determine the effects of chronic stress on blood pressure, randomized clinical trials examining the effects of Transcendental Meditation/mindfulness on blood pressure suggest that this practice lowers blood pressure [60]. Stress should be reduced and mindfulness or meditation introduced into the daily routine.
Complementary, alternative or traditional medicines	Large proportions of hypertensive patients use complementary, alternative, or traditional medicines (in regions, such as Africa and China) [61,62] yet large-scale and appropriate clinical trials are required to evaluate the efficacy and safety of these medicines. Thus, use of such treatment is not yet supported.
Reduce exposure to air pollution and cold temperature	Evidence from studies support a negative effect of air pollution on blood pressure in the long-term [63,64].

SECTION 8: TREATMENT OF HYPERTENSION

8.1. Lifestyle modifications

Healthy lifestyle choices can prevent or delay the onset of high BP and can reduce cardiovascular risk [46]. Lifestyle modification is also the first line of antihypertensive treatment. Modifications in lifestyle can also enhance the effects of antihypertensive treatment. Lifestyle modifications should include the following (Table 8) [47–64].

Seasonal blood pressure variation [65]

BP exhibits seasonal variation with lower levels at higher temperatures and higher at lower temperatures. Similar changes occur in people travelling from places with cold to hot temperature, or the reverse. A meta-analysis showed average BP decline in summer of 5/3 mmHg (systolic/diastolic). BP changes are larger in treated hypertensive patients and should be considered when symptoms suggesting overtreatment appear with temperature rise, or BP is increased during cold weather. BP below the recommended goal should be considered for possible down-titration, particularly if there are symptoms suggesting overtreatment.

8.2. Pharmacological treatment

Contemporary data from over 100 countries [66,67] suggest that on average, <50% of adults with hypertension receive BP-lowering medication, with few countries performing better than this and many worse. This is despite the fact that a difference in BP of 20/10 mmHg is associated with a 50% difference in cardiovascular risk [68].

The pharmacological treatment strategies recommended here (Figs. 2–4) are largely compatible with those made in the most recent United States [2] and European guidelines [1,8].

8.3. Adherence to antihypertensive treatment

Background

Adherence is defined as to the extent to which a person's behaviours, such as taking a medication, following a diet or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider [74]. Non-adherence to antihypertensive treatment affects 10–80% of hypertensive patients and is one of the key drivers of suboptimal BP control [75–77]. Poor adherence to antihypertensive treatment correlates with the magnitude of BP elevation and is an indicator of poor prognosis in hypertensive patients [78–81]. The etiology of nonadherence to antihypertensive treatment is multifactorial and includes causes associated with the healthcare system, pharmacological therapy, the disease, patients, and their socioeconomic status [74].

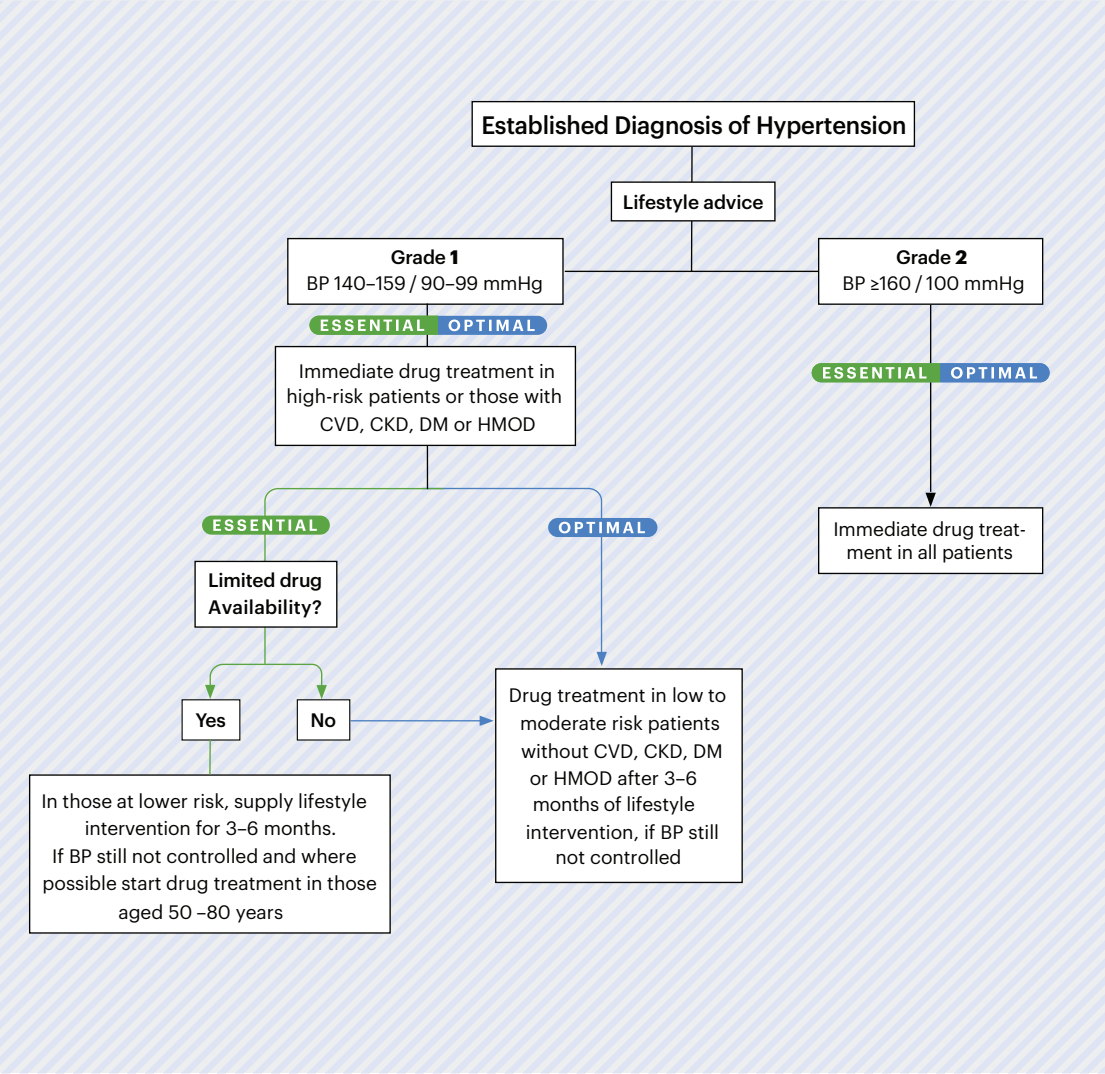

FIGURE 2 Pharmacological treatment of hypertension: general scheme. See Table 2 (Section 2) for equivalent BP levels based on ambulatory or home BP recordings.

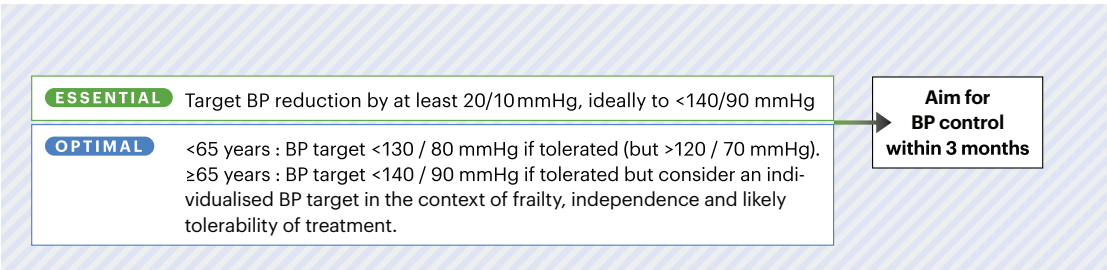

FIGURE 3 Office blood pressure targets for treated hypertension.

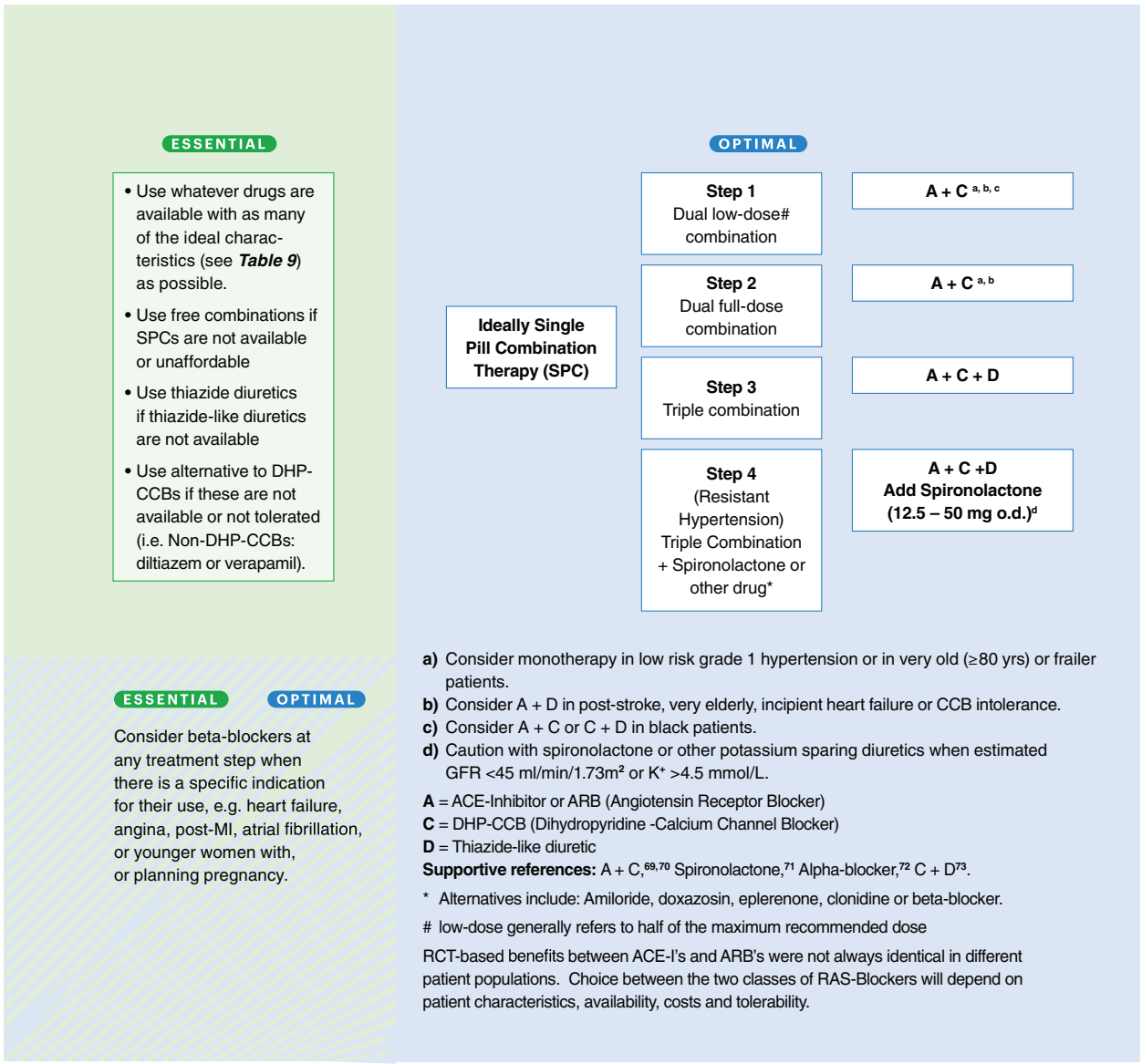

FIGURE 4 ISH core drug-treatment strategy. Data from [69–73]. Ideal characteristics of drug treatment (see Table 9).

TABLE 9. Ideal characteristics of drug treatment

1. Treatments should be evidence-based in relation to morbidity/mortality prevention.
2. Use a once-daily regimen, which provides 24 h blood pressure control.
3. Treatment should be affordable and/or cost-effective relative to other agents.
4. Treatments should be well-tolerated.
5. Evidence of benefits of use of the medication in populations to which it is to be applied.

Recommendations: adherence to antihypertensive therapy

ESSENTIAL OPTIMAL

- Evaluate adherence to antihypertensive treatment as appropriate at each visit and prior to escalation ofantihypertensive treatment.
- Consider the following strategies to improve medication adherence [82–87].
  - a reducing polypharmacy – use of single pill combinations
  - b once daily dosing over multiple times per day dosing
  - c linking adherence behaviour with daily habits
  - d providing adherence feedback to patients
  - e home BP monitoring
  - f reminder packaging of medications
  - g empowerment-based counselling for self-management
  - h electronic adherence aids such as mobile phones or short messages services
  - i multidisciplinary health care team approach (i.e. pharmacists) to improve monitoring for adherence

OPTIMAL

- Objective indirect (i.e. review of pharmacy records, pill counting, electronic monitoring devices) and direct (i.e. witnessed intake of medications, biochemical detection of medications in urine or blood) are generally preferred over subjective methods to diagnose nonadherence to antihypertensive treatment [80,85].
- The most effective methods for management of nonadherence require complex interventions that combine counselling, self-monitoring, reinforcements, and supervision.

SECTION 9: COMMON AND OTHER COMORBIDITIES AND COMPLICATIONS OF HYPERTENSION

Background

- Hypertensive patients have several common and other comorbidities that can affect cardiovascular risk and treatment strategies.
- The number of comorbidities increases with age, with the prevalence of hypertension and other diseases.
- Common comorbidities include coronary artery disease (CAD), stroke, CKD, heart failure, and COPD.
- Uncommon comorbidities include rheumatic diseases and psychiatric diseases.
- Uncommon comorbidities are largely underestimated by guidelines and frequently treated with drugs often self-prescribed and possibly interfering with BP control.
- Common and uncommon comorbidities should be identified and managed according to available evidence.

Common comorbidities and complications

Hypertension and coronary artery disease (CAD)

- A strong epidemiological interaction exists between CAD and hypertension that accounts for 25–30% of acute myocardial infarctions [88].
- Lifestyle changes are recommended (smoking cessation, diet, and exercise).
- BP should be lowered if ≥140/90 mmHg and treated to a target <130/80 mmHg (<140/80 in elderly patients).
- RAS-blockers, beta-blockers irrespective of BP levels ±calcium-channel blockers (CCBs) are first-line drugs in hypertensive patients [1].
- Lipid-lowering treatment with an LDL-C target <55 mg/dl (1.4 mmol/l) [89].
- Antiplatelet treatment with acetyl salicylic acid is routinely recommended [1].

Hypertension and previous stroke

- Hypertension is the most important risk factor for ischemic or hemorrhagic stroke [90].
- Stroke can be largely prevented by BP control.
- BP should be lowered if ≥140/90 mmHg and treated to a target <130/80 mmHg (<140/80 in elderly patients) [1].
- RAAS blockers, CCBs, and diuretics are first-line drugs [1].
- Lipid-lowering treatment is mandatory with a LDL-C target <70 mg/dl (1.8 mmol/l) in ischemic stroke [1].
- Antiplatelet treatment is routinely recommended for ischemic but not hemorrhagic stroke and should be carefully considered in patients with hemorrhagic stroke only in the presence of a strong indication [1].

Hypertension and heart failure (HF)

- Hypertension is a risk factor for the development of heart failure with reduced ejection fraction (HFrEF), and with preserved ejection fraction (HFpEF). Clinical outcome is worse and mortality is increased in the hypertensive patients with HF [2].
- Lifestyle changes are recommended (diet and exercise).
- Treating hypertension has a major impact on reducing the risk of incident heart failure and heart failure hospitalization. BP should be lowered if ≥140/90 mmHg and treated to a target <130/80 mmHg but >120/70 mmHg.
- RAS blockers, beta-blockers, and mineralocorticoid receptor antagonists are all effective in improving clinical outcome in patients with established HFrEF, whereas for diuretics, evidence is limited to symptomatic improvement [1]. CCBs are indicated on in case of poor BP control.
- Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan) is indicated for the treatment of HFrEF as an alternative to ACE inhibitors or ARBs also in hypertensive populations. The same treatment strategy can be applied to patients with HFpEF even if the optimal treatment strategy is not known [91].

Hypertension and chronic kidney disease (CKD)

- Hypertension is a major risk factor for the development and progression of albuminuria and any form of CKD [92].
- A lower eGFR is associated with resistant hypertension, masked hypertension, and elevated night-time BP values [92].
- The effects of BP-lowering on renal function (and albuminuria) are dissociated from cardiovascular benefit [1].
- BP should be lowered if ≥140/90 mmHg and treated to a target <130/80 mmHg (<140/80 in elderly patients) [1].
- RAS blockers are first-line drugs because they reduce albuminuria in addition to BP control. CCBs and diuretics (loop-diuretics if eGFR <30 ml/min/1.73 m^2) can be added [1].
- eGFR, microalbuminuria, and blood electrolytes should be monitored [1].

Hypertension and chronic obstructive pulmonary disease (COPD)

- Hypertension is the most frequent comorbidity in patients with COPD.
- BP should be lowered if ≥140/90 mmHg and treated to a target <130/80 mmHg (<140/80 in elderly patients).
- Lifestyle changes (smoking cessation) are mandatory [93].
- Environmental (air) pollution should be considered and avoided if possible [93].
- The treatment strategy should include an Angiotensin AT_1-Receptor Blocker (ARB) and CCB and/or diuretic, whereas beta blockers (β_1-receptor selective) may be used in selected patients (e.g. CAD, HF).
- Additional cardovascular risk factors should be managed according to cardiovascular risk profile.

HIV/AIDS

- People living with HIV are at increased cardiovascular risk [40].
- There may be a drug interaction with CCB under most of the antiretroviral therapies.
- Hypertension management should be similar to the general hypertensive populations.

Management of comorbidities:

ESSENTIAL OPTIMAL

- In addition to BP control, the therapeutic strategy should include lifestyle changes, body weight control and the effective treatment of the other rick factors to reduce the residual cardiovascular risk [1].
- Lifestyle changes as in Table 8.
- LDL-cholesterol should be reduced according to risk profile: 1) >50 % and <70 mg/dl (1.8 mmol/l) in hypertension and CVD, CKD, diabetes mellitus or no CVD and very high-risk; 2) >50% and <100 mg/dl (2.6 mmol/l) in high-risk patients; 3) <115 mg/dl (3mmol/l) in moderate-risk patients [1,89].
- Fasting serum glucose levels should be reduced below 126 mg/dl (7 mmol/l) or HbA1c below 7% (53 mmol/mol) [1].
- s-UA should be maintained below 6.5 mg/dl (0.387mmol/l) [<6 mg/dl (0.357 mmol/l) in patients with gout] [94].
- Antiplatelet therapy should be considered in patients with CVD (secondary prevention only) [95].

Diabetes

- BP should be lowered if ≥140/90 mmHg and treated to a target <130/80 mmHg (<140/80 in elderly patients) [96].
- The treatment strategy should include a renin–angiotensin system (RAS) inhibitor [and a calcium channel blocker (CCB) and/or thiazide-like diuretic].
- The treatment should include a statin in primary prevention if LDL-C >70 mg/dl (1.8 mmol/l) (diabetes with target organ damage) or >100 mg/dl (2.6 mmol/l) (uncomplicated diabetes).
- The treatment should include glucose and lipid lowering as per current guidelines (see Resources, Section 11).

Lipid disorders

- BP should be lowered as done in the general population, preferentially with RAS-inhibitors (ARB, ACE-I) and CCBs [97].
- Statins are the lipid-lowering treatment of choice with or without ezetimibe and/or PCSK9 inhibitor (in the optimal setting) [98].
- Serum triglyceride lowering should be considered if >200 mg/dl (2.3 mmol/l) particularly in patients with hypertension and diabetes mellitus. Possible additional benefits using fenofibrate in low HDL/high triglyceride subgroup.

Metabolic syndrome (MS)

- Patients with hypertension and MS have a high-risk profile.
- The diagnosis of MS should be made by separate evaluation of single components.
- The treatment of MS is based on changes in lifestyle (diet and exercise).
- The treatment of hypertension and MS should include BP control as in the general population and treatment of additional risk factors based on level and overall cardiovascular risk (SCORE and/or ASCVD calculator).

Other comorbidities

(see Table 10)

Hypertension and inflammatory rheumatic diseases (IRD)

- IRD (rheumatoid arthritis, psoriasis–arthritis, etc.) are associated with an increased prevalence of hypertension under diagnosed and poorly controlled [99,100].
- IRD show an increase in cardiovascular risk only partially related to cardiovascular risk factors [99].
- Rheumatoid arthritis is predominant among IRD.
- The presence of IRD should increase one step of cardiovascular risk [99].
- BP should be lowered as in the general population, preferentially with RAS-inhibitors (evidence of an overactive RAAS system [100]) and CCBs.
- Underlying diseases should be effectively treated by reducing inflammation and by avoiding high doses of NSAIDs.
- Lipid-lowering drugs should be used according to cardiovascular risk profile (SCORE/ASCVD calculator) also considering the effects of biologic drugs [100].

TABLE 10. Outline of evidence-based management of other comorbidities and hypertension

Additional comorbidity	Recommended Drugs	Warning
Rheumatic disorders	• RAS-inhibitors and CCBs ± Diuretics • Biologic drugs not affecting blood pressure should be preferred (where available)	High doses of NSAIDs
Psychiatric disorders	• RAS-inhibitors and diuretics • Beta-blockers (not metoprolol) if drug-induced tachycardia (antidepressant, antipsychotic drugs). • Lipid-lowering drugs/antidiabetic drugs according to risk profile	Avoid CCBs if orthostatic hypotension (SRIs)

Hypertension and psychiatric diseases

- The prevalence of hypertension is increased in patients with psychiatric disorders and in particular depression [101,102].
- According to guidelines, psychosocial stress and major psychiatric disorders increase the cardiovascular risk.
- Depression has been associated with cardiovascular morbidity and mortality, suggesting the importance of BP control [101].
- BP should be lowered as in the general population, preferentially with RAS-inhibitors and diuretics with a lesser rate of pharmacological interactions under antidepressants. CCBs and alpha$_1$-blockers should be used with care in patients with orthostatic hypotension [e.g. serotonin reuptake inhibitors (SRI's)].
- The risk of pharmacologic interactions, ECG abnormalities and postural BP changes must be considered.
- Beta-blockers (not metoprolol) should be used in presence of drug-induced tachycardia (antidepressant drugs, antipsychotic drugs) [103].
- Additional risk factors should be managed according to cardiovascular risk profile (SCORE/ASCVD calculator, see Section 11, Resources).

SECTION 10: SPECIFIC CIRCUMSTANCES

10.1. Resistant hypertension

Background

Resistant hypertension is defined as seated office BP >140/90 mmHg in a patient treated with three or more antihypertensive medications at optimal (or maximally tolerated) doses including a diuretic and after excluding pseudoresistance (poor BP measurement technique, white-coat effect, nonadherence, and suboptimal choices in antihypertensive therapy) [104,105] as well as the substance/drug-induced hypertension and secondary hypertension [79]. Resistant hypertension affects around 10% of hypertensive individuals, has a negative impact on well-being [106] and increases the risk of coronary artery disease, chronic heart failure, stroke, end-stage renal disease, and all-cause mortality [107]. Approximately 50% of patients diagnosed with resistant hypertension have pseudoresistance rather than true resistant hypertension [104,105,108].

Recommendations:

ESSENTIAL

- If seated office BP >140/90 mmHg in patients managed with three or more antihypertensive medications at optimal (or maximally tolerated) doses including a diuretic, first exclude causes of pseudoresistance (poor BP measurement technique, white-coat effect, nonadherence, and suboptimal choices in antihypertensive therapy), and substance-induced increases in BP.
- Consider screening patients for secondary causes as appropriate (refer to Section 10.2).
- Optimize the current treatment regimen including health behaviour change and diuretic-based treatment (maximally tolerated doses of diuretics, and optimal choice of diuretic: use of thiazide-like rather than thiazide diuretics, and initiation of loop diuretics for eGFR <30 ml/min/1.73 m^2 or clinical volume overload) [109].
- Add a low dose of spironolactone as the fourth line agent in those whose serum potassium is <4.5 mmol/l and whose eGFR is >45 ml/min/1.73 m^2 to achieve BP targets [8,71,110]. If spironolactone is contraindicated or not tolerated, amiloride, doxazosin, eplerenone, clonidine, and beta-blockers are alternatives, or any available antihypertensive class not already in use [1,111–114].

OPTIMAL

- Resistant hypertension should be managed in specialist centres with sufficient expertise, and resources necessary to diagnose and treat this condition [115].

10.2. Secondary hypertension [116–121]

Background

A specific cause of secondary hypertension can be identified in 5–10% of hypertensive patients (Table 11). Early diagnosis of secondary hypertension and the institution of appropriate targeted treatment have the potential to cure hypertension in some patients or improve BP control/reduce the number of prescribed antihypertensive medications in others. The most common types of secondary hypertension in adults are renal parenchymal disease, renovascular hypertension, primary aldosteronism, chronic sleep apnea, and substance/drug-induced.

Recommendations:

ESSENTIAL

- Consider screening for secondary hypertension in 1) patients with early-onset hypertension (<30 years of age) in particular in the absence of hypertension risk factors (obesity, metabolic syndrome, familial history, etc.), 2) those with resistant hypertension, 3) individuals with sudden deterioration in BP control, 4) hypertensive urgency and emergency, 5) those presenting with high probability of secondary hypertension based on strong clinical clues.
- In patients with resistant hypertension, investigations for secondary hypertension should generally be preceded by exclusion of pseudoresistant hypertension and drug/substance-induced hypertension.
- Basic screening for secondary hypertension should include a thorough assessment of history, physical examination (see clinical clues), basic blood biochemistry (including serum sodium, potassium, eGFR, TSH) and dipstick urine analysis.

OPTIMAL

- Further investigations for secondary hypertension (additional biochemistry/imaging/others) should be carefully chosen based on information from history, physical examination, and basic clinical investigations.
- Consider referring for further investigation and management of suspected secondary hypertension to a specialist centre with access to appropriate expertise and resources.

10.3. Hypertension in pregnancy [122–126]

Hypertension in pregnancy is a condition affecting 5–10% of pregnancies worldwide. Maternal risks include placental abruption, stroke, multiple organ failure (liver, kidney), disseminated vascular coagulation. Fetal risks include intrauterine growth retardation, preterm birth, intrauterine death. Hypertension in pregnancy includes the following conditions:

- **Pre-existing hypertension**: starts before pregnancy or <20 weeks of gestation, and lasts >6 weeks postpartum combined with proteinuria.
- **Gestational hypertension**: starts >20 weeks of gestation, and lasts <6 weeks postpartum.
- **Pre-existing hypertension with superimposed gestational hypertension** with proteinuria.
- **Pre-eclampsia**: hypertension with proteinuria [>300 mg/24 h or ACR >30 mg/mmol (265 mg/g)]. Predisposing factors are pre-existing hypertension, hypertensive

TABLE 11. Features of secondary hypertension

Secondary hypertension	Clinical history and physical examination	Basic biochemistry and urine analysis	Further diagnostic tests
Renal parenchymal disease	• Personal/familial history of CKD	• Proteinuria, hematuria, leukocyturia on dipstick urine analysis • Decreased estimated GFR	• Kidney ultrasound
Primary aldosteronism	• Symptoms of hypokalemia (muscle weakness, muscle cramps, tetany)	• Spontaneous hypokalemia or diuretic-induced hypokalemia on blood biochemistry (50–60% of patients are normokalemic). • Elevated plasma aldosterone–renin activity ratio	• Confirmatory testing (e.g. intravenous saline suppression test) • Imaging of adrenals (adrenal computed tomography) • Adrenal vein sampling
Renal artery stenosis	• Abdominal bruit • Bruits over other arteries (i.e. carotid and femoral arteries) • Drop in estimated GFR >30% after exposure to ACE-inhibitors/ARBs • For suspected atherosclerotic RAS, history of flash pulmonary edema or history of atherosclerotic disease or presence of cardiovascular risk factors • For suspected fibromuscular dysplasia, young women with onset of hypertension <30 years	• Decrease in estimated GFR	• Imaging of renal arteries (duplex ultrasound, abdominal computed tomography or magnetic resonance angiograms depending on availability and patient's level of renal function)
Pheochromocytoma	• Headaches • Palpitations • Perspiration • Pallor • History of labile hypertension	• Increased plasma levels of metanephrines • Increased 24-h urinary fractional excretion of metanephrines and catecholamines	• Abdominal/pelvic computational tomography or MRI
Cushing's syndrome and disease	• Central obesity • Purple striae • Facial rubor • Signs of skin atrophy • Easy bruising • Dorsal and supraclavicular fat pad • Proximal muscle weakness	• Hypokalemia • Increased late night salivary cortisol	• Dexamethasone suppression tests [118] • 24 h urinary free cortisol • Abdominal/pituitary imaging
Coarctation of the aorta	• Higher blood pressure in upper than lower extremities • Delayed or absent femoral pulses		• Echocardiogram • Computational tomography angiogram • Magnetic resonance angiogram
Obstructive sleep apnea	• Increased BMI • Snoring • Daytime sleepiness • Gasping or choking at night • Witnessed apneas during sleep • Nocturia		• Home sleep apnea testing (e.g. level 3 sleep study) • Overnight polysomnography testing
Thyroid disease	• Symptoms of hyperthyroidism: heat intolerance, weight loss, tremor, palpitations • Symptoms of hypothyroidism: cold intolerance, weight gain, dry brittle hair	• TSH, Free T4	

disease during previous pregnancy, diabetes, renal disease, first or multiple pregnancy, autoimmune disease (SLE). Risks are fetal growth restriction, pre-term birth.

- **Eclampsia**: hypertension in pregnancy with seizures, severe headaches, visual disturbance, abdominal pain, nausea and vomiting, low urinary output: immediate treatment and delivery required.
- **HELLP Syndrome**: Hemolysis, Elevated Liver enzymes, Low Platelets: Immediate treatment and delivery required.

Blood pressure measurement in pregnancy

ESSENTIAL Office BP measurement following general guidelines. Take office BP measurement using a manual auscultatory device, or an automated upper-arm cuff device which has been validated specifically in pregnancy and pre-eclampsia (list of validated devices at www.stridebp.org).

OPTIMAL ABPM or home BP monitoring using devices validated specifically in pregnancy and pre-eclampsia to evaluate white coat hypertension, diabetes mellitus, nephropathy.

Investigation of hypertension in pregnancy

ESSENTIAL

Urine analysis, full blood count, liver enzymes, hematocrit, serum creatinine, and s-UA. Test for proteinuria in early pregnancy (pre-existing renal disease) and second half of pregnancy (pre-eclampsia). A dipstick test >1+ should be followed up with UACR in a single spot urine; UACR <30 mg/mmol excludes proteinuria.

OPTIMAL

Ultrasound of kidneys and adrenals, free plasma metanephrines (if clinical features of pheochromocytoma); Doppler ultrasound of uterine arteries (after 20 weeks of gestation is useful to detect those at higher risk of gestational hypertension, pre-eclampsia, and intrauterine growth retardation).

Prevention of pre-eclampsia:

Women at high risk (hypertension in previous pregnancy, CKD, autoimmune disease, diabetes, chronic hypertension), or moderate risk (first pregnancy in a woman >40, pregnancy interval >10 years, BMI >35 kg/m^2, family history of pre-eclampsia, multiple pregnancies): 75–162 mg aspirin at weeks 12–36. Oral calcium supplementation of 1.5–2 g/day is recommended in women with low dietary intake (<600 mg/day).

Management of hypertension in pregnancy

Mild hypertension: drug treatment at persistent BP >150/95 mmHg in all women.

Drug treatment at persistent BP >140/90 mmHg in gestational hypertension, pre-existing hypertension with superimposed gestational hypertension; hypertension with subclinical HMOD at any time during pregnancy. First choices: Methyldopa, beta-blockers (labetalol), and dihydropyridine-calcium channel blockers (DHP-CCBs) [nifedipine (not capsular), nicardipine). Contraindicated: RAS Blockers (ACE-I, ARB, direct renin inhibitors (DRI)] because of adverse fetal and neonatal outcomes.

Severe hypertension: At BP >170 mmHg systolic and/or >110 mmHg diastolic: immediate hospitalization is indicated (emergency). Treatment with intravenous labetalol (alternative intravenous nicardipine, esmolol, hydralazine, urapidil), oral methyldopa or DHP-CCBs [nifedipine (not capsular) nicardipine]. Add magnesium (hypertensive crisis to prevent eclampsia). In pulmonary edema: Nitroglycerin intravenous infusion. Sodium-nitroprusside should be avoided because of the danger of fetal cyanide poisoning with prolonged treatment.

Delivery in gestational hypertension or pre-eclampsia: at week 37 in asymptomatic women. Expedite delivery in women with visual disturbances, haemostatic disorders.

Blood pressure postpartum: if hypertension persists, any of recommended drugs except methyldopa (postpartum depression).

Breastfeeding: all antihypertensives excreted into breast milk at low concentrations. Avoid atenolol, propranolol, nifedipine (high concentration in milk). Prefer long-acting CCBs. Refer to prescribing information.

Long-term consequences of gestational hypertension: increased risk of hypertension and CVD (stroke, ischemic heart disease) in later life.

ESSENTIAL Lifestyle adjustment

OPTIMAL Lifestyle adjustment and annual checkups (BP, metabolic factors)

10.4. Hypertensive emergencies

Definition of hypertensive emergencies and their clinical presentation

A hypertensive emergency is the association of substantially elevated BP with acute HMOD. Target organs include the retina, brain, heart, large arteries, and the kidneys [127]. This situation requires rapid diagnostic workup and immediate BP reduction to avoid progressive organ failure. Intravenous therapy is usually required. The choice of antihypertensive treatment is predominantly determined by the type of organ damage. Specific clinical presentations of hypertensive emergencies include:

Malignant hypertension: severe BP elevation (commonly >200/120 mmHg) associated with advanced bilateral retinopathy (hemorrhages, cotton wool spots, papilledema).

Hypertensive encephalopathy: severe BP elevation associated with lethargy, seizures, cortical blindness, and coma in the absence of other explanations.

Hypertensive thrombotic microangiopathy: severe BP elevation associated with haemolysis and thrombocytopenia in the absence of other causes and improvement with BP lowering therapy.

Other presentations of hypertensive emergencies include: severe BP elevation associated with cerebral hemorrhage, acute stroke, acute coronary syndrome, cardiogenic pulmonary edema, aortic aneurysm/dissection, and severe pre-eclampsia and eclampsia.

Patients with substantially elevated BP who lack acute HMOD are not considered a hypertensive emergency and can typically be treated with oral antihypertensive therapy [128].

Clinical presentation and diagnostic workup

The clinical presentation of a hypertensive emergency can vary and is mainly determined by the organ (s) acutely affected. There is no specific BP threshold to define a hypertensive emergency.

Symptoms include: headaches, visual disturbances, chest pain, dyspnoea, neurologic symptoms, dizziness and more unspecific presentations.

Medical history: pre-existing hypertension, onset and duration of symptoms, potential causes [nonadherence with prescribed antihypertensive drugs, lifestyle changes, concomitant use of BP-elevating drugs (NSAIDS, steroids, immune-suppressants, sympathomimetics, cocaine, anti-angiogenic therapy)].

ESSENTIAL **Thorough physical examination:** cardiovascular and neurologic assessment. Laboratory analysis: haemoglobin, platelets, creatinine, sodium, potassium, lactate dehydrogenase (LDH), haptoglobin, urinalysis for protein, urine sediment. **Examinations:** fundoscopy, ECG.

OPTIMAL Additional investigations may be required and indicated depending on presentation and clinical findings and may be essential in the context: Troponins (chest pain), chest X-ray (congestion/fluid overload), transthoracic echocardiogram (cardiac structure and function), CT/MRI brain (cerebral hemorrhage/stroke), CT-angiography thorax/abdomen (acute aortic disease). Secondary causes can be found in 20–40% of patients presenting with malignant hypertension [118] and appropriate diagnostic workup to confirm or exclude secondary forms is indicated.

Diagnostic tests and acute therapeutic management

The overall therapeutic goal in patients presenting with hypertensive emergencies is a controlled BP reduction to safer levels to prevent or limit further hypertensive damage while avoiding hypotension and related complications. There is a lack of randomized controlled trial data to provide clear cut guidance on BP targets and times within which these should be achieved. Most recommendations are based on expert consensus. The type of acute HMOD is the main determinant of the preferred treatment choice. The timeline and magnitude of BP reduction is strongly dependent on the clinical context. For example, acute pulmonary edema and aortic dissection require rapid BP reduction, whereas BP levels not exceeding 220/120 mmHg are generally tolerated in acute ischemic stroke for certain periods. Table 12 provides a general overview of timelines and BP targets as well as preferred antihypertensive drug choices with most common clinical presentations. Availability of drugs and local experience with individual drugs are likely to influence the choice of drugs. Labetalol and nicardipine are generally safe to use in all hypertensive emergencies and should be available wherever hypertensive emergencies are being managed. Nitroglycerine and nitroprusside are specifically useful in hypertensive emergencies including the heart and the aorta.

Specific situations

Sympathetic hyperreactivity: If intoxication with amphetamines, sympathomimetics or cocain is suspected as cause of presentation with a hypertensive emergency, use of benzodiazepines should be considered prior to specific antihypertensive treatment. Phentolamine, a competitive alpha-receptor blocking agent and clonidine, a centrally sympatholytic agent with additional sedative properties are useful if additional BP-lowering therapy is required. Nicardipine and nitroprusside are suitable alternatives.

TABLE 12. Hypertensive Emergencies Requiring Immediate blood pressure lowering

Clinical presentation	Timeline and target BP	First line treatment	Alternative
Malignant hypertension with or without TMA or acute renal failure	Several hours, MAP −20% to −25%	Labetalol Nicardipine	Nitroprusside Urapidil
Hypertensive encephalopathy	Immediate, MAP −20% to −25%	Labetalol Nicardipine	Nitroprusside
Acute ischaemic stroke and BP >220 mmHg systolic or >120 mmHg diastolic	1 h, MAP −15%	Labetalol Nicardipine	Nitroprusside
Acute ischaemic stroke with indication for thrombolytic therapy and BP >185 mmHg systolic or >110 mmHg diastolic	1 h, MAP −15%	Labetalol Nicardipine	Nitroprusside
Acute hemorrhagic stroke and systolic BP >180 mmHg	Immediate, systolic 130 < BP < 180 mmHg	Labetalol Nicardipine	Urapidil
Acute coronary event	Immediate, SBP <140 mmHg	Nitroglycerine Labetalol	Urapidil
Acute cardiogenic pulmonary edema	Immediate, SBP <140 mmHg	Nitroprusside or Nitroglycerine (with loop diuretic)	Urapidil (with loop diuretic)
Acute aortic disease	Immediate, SBP <120 mmHg and heart rate <60 bpm	Esmolol and Nitroprusside or Nitroglycerine or nicardipine	Labetalol or Metoprolol
Eclampsia and severe pre-eclampsia/HELLP	Immediate, SBP <160 mmHg and DBP <105 mmHg	Labetalol or nicardipine and magnesium sulphate	

Adapted from [127].

Pheochromocytoma: the adrenergic drive associated with pheochromocytoma responds well to phentolamine. Beta-blockers should only be used once alpha-blockers have been introduced to avoid acceleration of hypertension. Urapidil and nitroprusside are additional suitable options.

Pre-eclampsia/eclampsia: see section 10.3 'Hypertension in pregnancy'.

Follow-up

Patients who experienced a hypertensive emergency are at increased risk of cardiovascular and renal disease [129,130]. Thorough investigation of potential underlying causes and assessment of HMOD is mandatory to avoid recurrent presentations with hypertensive emergencies. Similarly, adjustment and simplification of antihypertensive therapy paired with advice for lifestyle modification will assist to improve adherence and long-term BP control. Regular and frequent follow-up (monthly) is recommended until target BP and ideally regression of HMOD has been achieved.

10.5. Ethnicity, race, and hypertension

Hypertension prevalence, treatment, and control rates vary significantly according to ethnicity. Such differences are mainly attributed to genetic differences, but lifestyle and socioeconomic status possibly filters through into health behaviours, such as diet – which appear to be major contributors.

Populations from African descent

- Black populations, whether residing in Africa, the Caribbean, USA or Europe, develop hypertension and associated organ damage at younger ages, have a higher frequency of resistant and night-time hypertension, and a higher risk of kidney disease [131], stroke, heart failure, and mortality [132], than other ethnic groups.
- This increased cardiovascular risk may be because of physiological differences including a suppressed RAAS [133,134], altered renal sodium handling [135], increased cardiovascular reactivity [136], and early vascular aging (large artery stiffness) [137].
- Management of hypertension:
  - Wherever possible, annual screening for hypertension is advised for adults 18 years and older.
  - Lifestyle modification should place additional focus on salt restriction, increased intake of vegetables and fruits (potassium intake), weight management, and reducing alcohol intake.
  - First-line pharmacological therapy is recommended as a single pill combination including a thiazide-like diuretic with CCB or CCB with ARB (see Sections 8 and 12) [71,138].
  - Among RAS-inhibitors, ARBs may be preferred as angioedema is about three times more likely to occur with ACE inhibitors among black patients [139].

Populations from Asia

- Ethnic-specific characteristics are recognized for East Asian populations. Hypertensive patients have a greater likelihood of salt-sensitivity accompanied with mild obesity. When compared with Western populations, East Asian people present a higher prevalence of stroke (particularly hemorrhagic stroke), and non-ischemic heart failure [1].
- Morning hypertension and night-time hypertension [140] are also more common in Asia, compared with European populations.
- South Asian populations originating from the Indian subcontinent have a particularly high risk for cardiovascular and metabolic diseases, including CAD and type 2 DM. With large hypertensive populations residing in India and China, clinical trials in these populations are required to advise whether current treatment approaches are ideal [141,142].
- Management of hypertension:
  - South East Asia: standard treatment as indicated in these guidelines is advised, until more evidence becomes available [138].

SECTION 11: RESOURCES

- **2018 European Society of Cardiology/European Society of Hypertension Guidelines** (Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; **36**: 1953–2041). These

comprehensive and evidence-based guidelines form a complete detailed resource.

- **2017 ACC/AHA/AAPA/ABC/ACPM/AGS/AphA/ASH/ASPC/NMA/PCNA Guidelines** (Whelton PK, Carey RM, Aronow WS, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High blood pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017; **71**:e13–e115]. The Guidelines from the United States of America, which attracted much comment on redefining hypertension, is very comprehensive and evidence-based, and largely in agreement with the 2018 European guidelines.
- Weber MA, Poulter NR, Schutte AE, *et al*. Is it time to reappraise blood pressure thresholds and targets? **Statement from the International Society of Hypertension** – a global perspective. *Hypertension* 2016; **68**:266–268.
- **Clinical Practice Guidelines for the Management of Hypertension in the Community**: A Statement by the American Society of Hypertension and the International Society of Hypertension. [Weber MA, Schiffrin EL, White WB et al. *The Journal of Clinical Hypertension* 2014; **16**:14–26].
- **NICE Guideline:** Hypertension in adults: diagnosis and management. Published: 28 August 2019. Available at: www.nice.org.uk/guidance/ng136
- **The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019).** *Hypertens Res* 2019; **42:**1235–1481. Available at: https://doi.org/10.1038/s41440-019-0284-9
- **2018 Chinese Guidelines for Prevention and Treatment of Hypertension** – A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. Liu LS, Wu ZS, Wang JG, Wang W. *J Geriatr Cardiol* 2019;**16**: 182–241.
- **Guidelines on the management of arterial hypertension and related comorbidities in Latin America** Task Force of the Latin American Society of Hypertension. *J Hypertens* 2017; **35**:1529–1545.
- **2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk**. Mach F, Baigent C, Catapano AL et al. *Eur Heart J* 2020; **41**:111–188 doi:10.1093/eurheartj/ehz455.
- **2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD:** The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). Cosentino F, Peter J, Grant PJ, Aboyans V, *et al. Eur Heart J* 2020;**41**:255–323. Available at: https://doi.org/10.1093/eurheartj/ehz486
- **The HOPE Asia Network** contributes largely to evidence for this region: Kario K *et al*. HOPE Asia (Hypertension Cardiovascular Outcome Prevention and Evidence in Asia) Network. The HOPE Asia Network for "zero" cardiovascular events in Asia. *J Clin Hypertens* 2018; **20**:212–214.
- **World Health Organization, HEARTS Technical Package:** [https://www.who.int/cardiovascular_diseases/hearts/en/]: The HEARTS package contains free modules (in English, French, Spanish and Russian) on e.g. Healthy-lifestyle counselling; Risk based charts, but particularly for Team-based care which is particularly relevant in low resource settings where task-sharing is highly relevant. Available at: https://apps.who.int/iris/bitstream/handle/10665/260424/WHO- NMH-NVI-18.4-eng.pdf;jsessionid=7AC6EC215FEB390CBD93898B69C4705C?sequence=1
- **Cardiovascular Risk Scores:** Several scoring systems are available. Some are based only on European populations, for example, SCORE.
  a. **SCORE:** http://www.heartscore.org/en_GB/access The following scores also take ethnicity into account.
  b. **QRISK2:** https://qrisk.org/2017/index.php
  c. **ASCVD:** https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/
- **World Heart Federation Roadmap to the Management and Control of Raised blood pressure** provides guidance on achieving the target of a relative reduction of the prevalence of raised blood pressure by 25% by 2025: https://www.world-heart-federation.org/cvd-roadmaps/whf-global-roadmaps/hypertension/.
- On the basis of this Roadmap, an Africa-specific roadmap was also developed: [Dzudie A, Rayner B, Ojji D, Schutte AE, et al. Roadmap to achieve 25% hypertension control in Africa by 2025. *Global Heart* 2018; **13**:45–59]

Listings of validated electronic blood pressure devices that were independently assessed for accuracy:

- **STRIDE BP:** https://stridebp.org/
- **British and Irish Hypertension Society:** https://bihsoc.org/bp-monitors/
- **German Hypertension Society:** https://www.hochdruckliga.de/messgeraete-mit-pruefsiegel.html
- **Hypertension Canada:** https://hypertension.ca/hypertension-and-you/managing-hypertension/measuring-blood-pressure/devices/
- **Japanese Society of Hypertension:** http://www.jpnsh.jp/com_ac_wg1.html

Blood pressure management in pediatric populations:

- Flynn JT, Kaelber DC, Baker-Smith CM, *et al*. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017; **140**: e20171904.
- Lurbe E, Agabiti-Rosei E, Cruickshank JK, *et al*. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens* 2016; **34**:1887–1920.
- Xi B, Zong X, Kelishadi R, Hong YM, *et al*. Establishing international blood pressure references among non-overweight children and adolescents aged 6 to 17 years. *Circulation* 2016; **133**:398–408.
- Dong Y, Ma J, Song Y, Dong B, *et al*. National blood pressure reference for Chinese Han children and adolescents aged 7 to 17 years. *Hypertension* 2017; **70**:897–890.

SECTION 12: HYPERTENSION MANAGEMENT AT A GLANCE

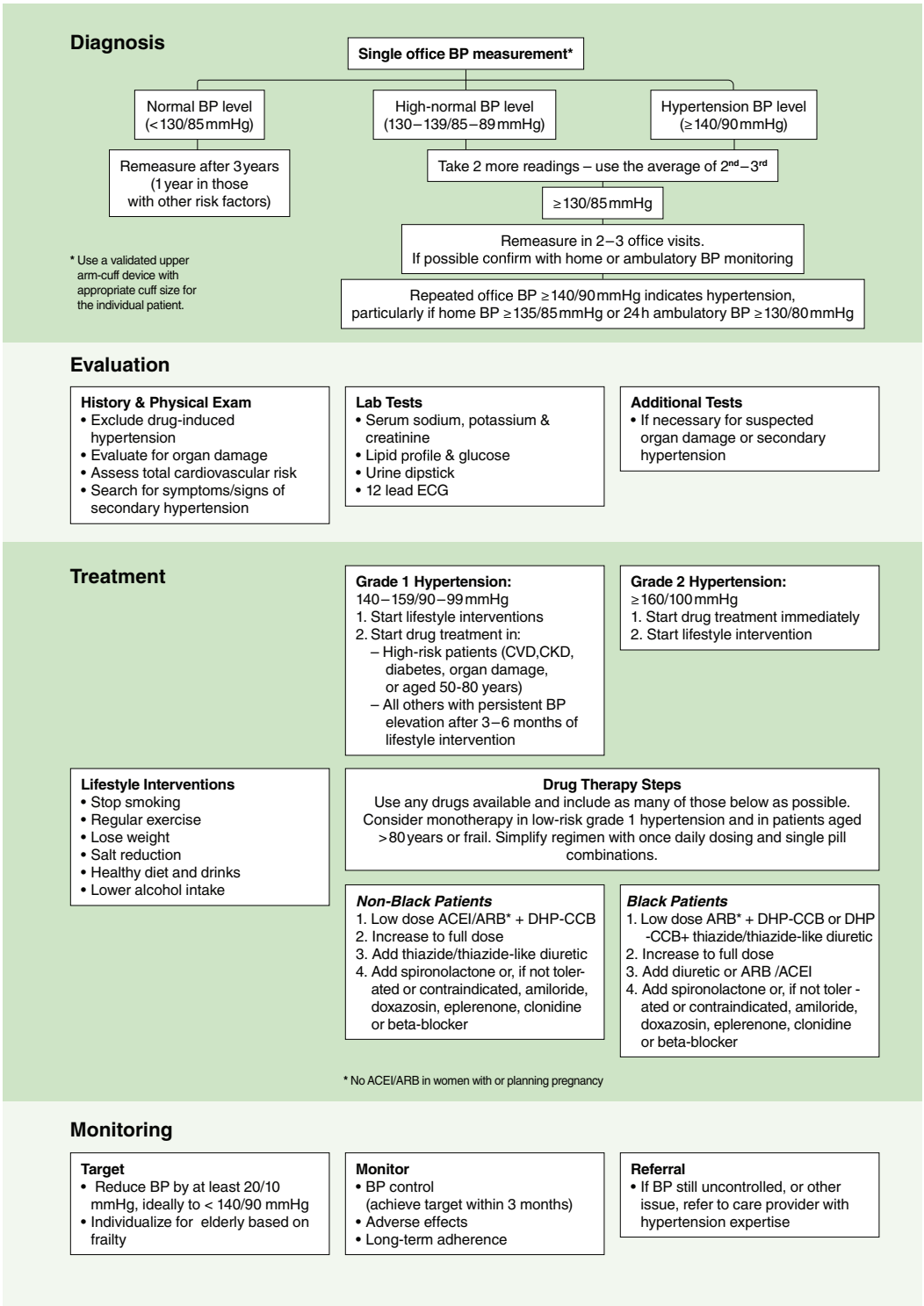

FIGURE 5 International Society of Hypertension 2020: ESSENTIAL recommendations (minimum standards of care).

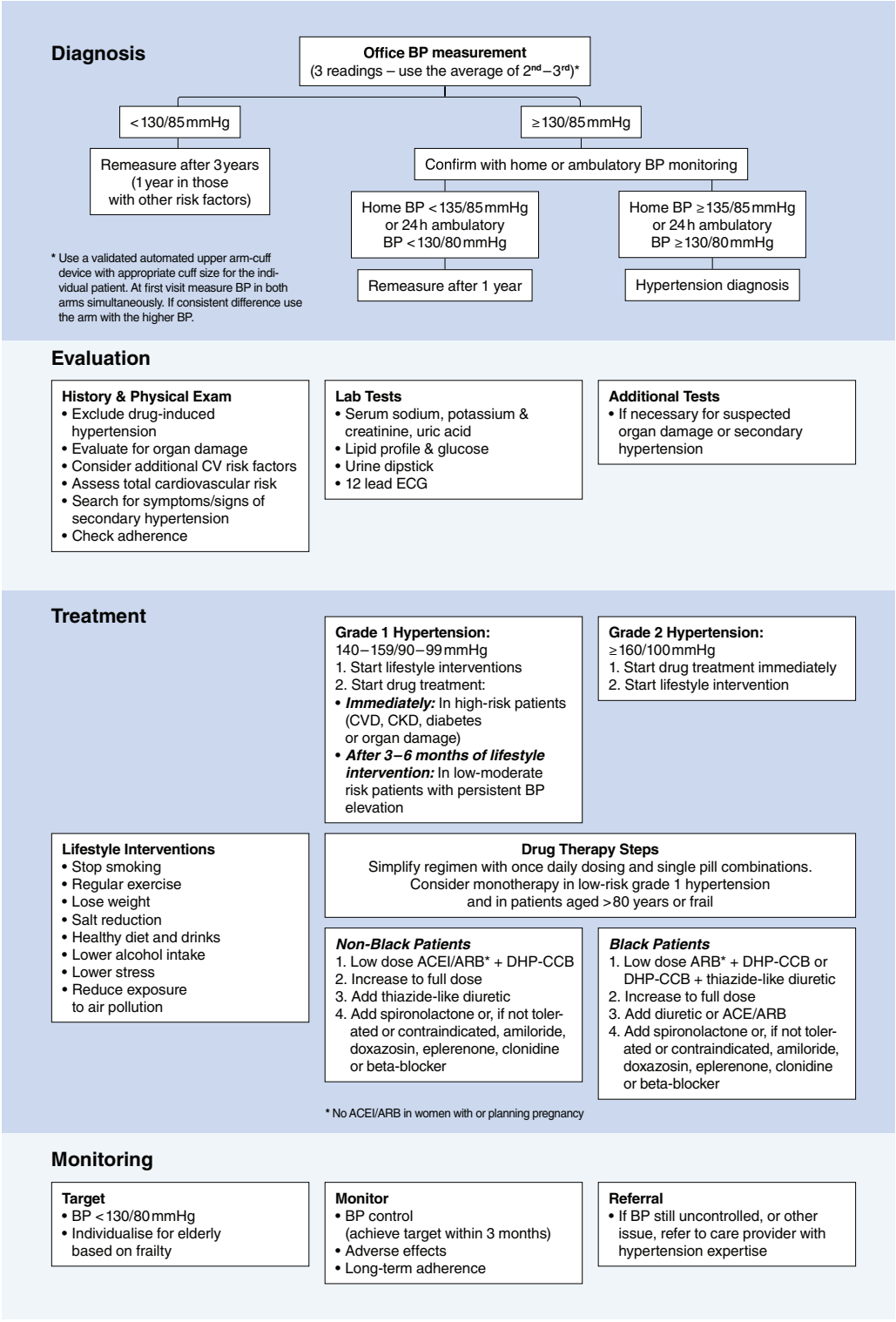

FIGURE 6 International Society of Hypertension 2020: OPTIMAL recommendations (evidence-based standards of care).

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