STATE UNIVERSITY OF MEDICINE AND PHARMACY
NICOLAE TESTEMITANU

COURSE OF CARDIOLOGY

CHEF OF COURSE **LIVIU GRIB**

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2013 ESH/ESC Guidelines for the management of arterial hypertension

Eur Heart J, 2013; 34: 2159-2219
J Hypertens, 2013; 31: 1281-1357
Blood Pressure, 2013: 193-278

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Epidemiological aspects

- Based on 21 reports from the last decade the prevalence of hypertension appears to be around 30-45% of the general population, with a steep increase with ageing.

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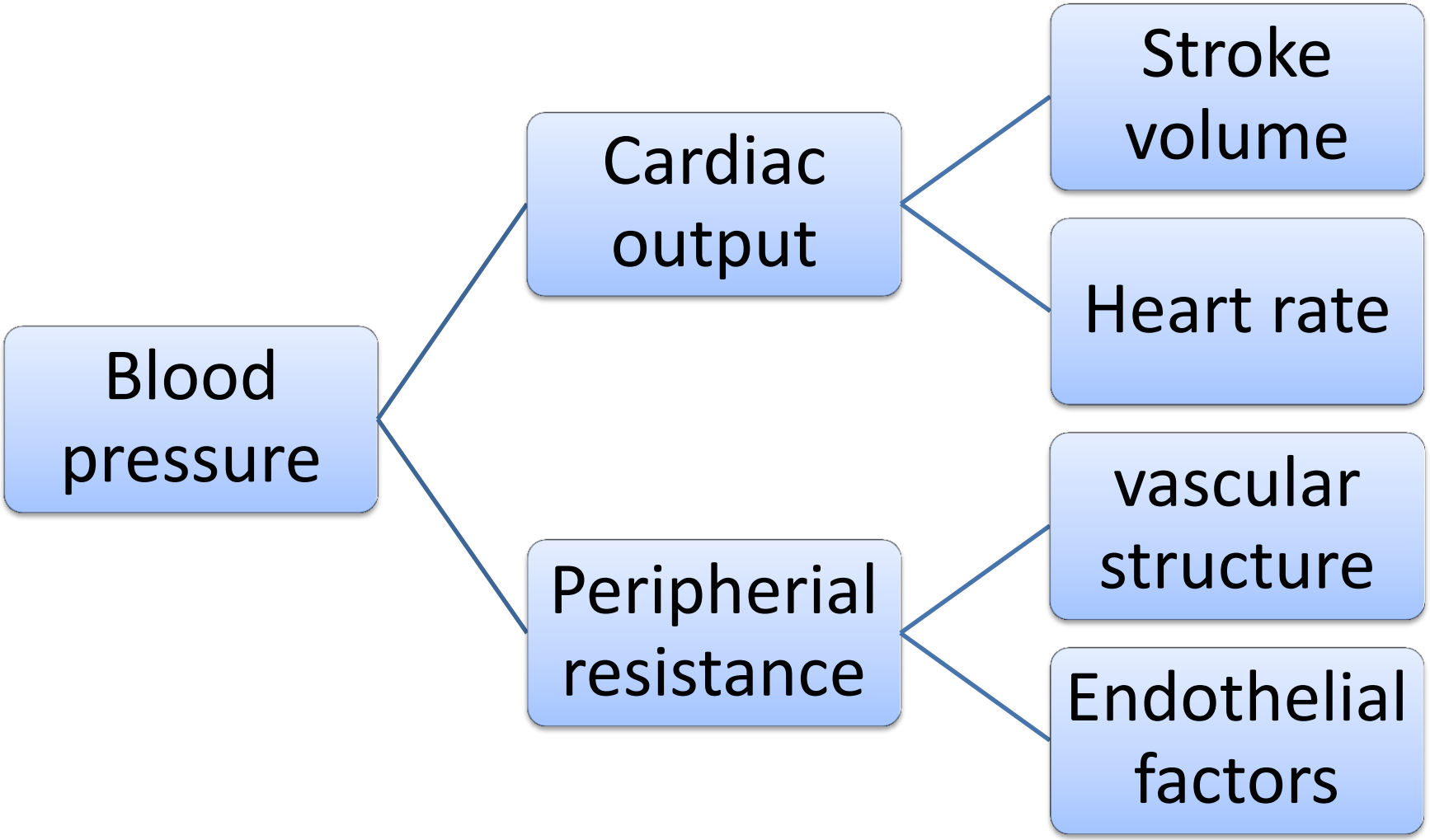
Definition

- **Hypertension** - persistent increase of blood pressure ≥ 140 mmHg systolic and ≥ 90 mmHg diastolic blood pressure in untreated patients.

Blood pressure

- The maximum blood pressure (systolic)occurs during systolic contraction of the left ventricle, and lowest blood pressure (diastolic) occurs during relaxation of the left ventricle.
- **Blood pressure** is determined by the **cardiac output** and **peripherial resistense**
- blood pressure depends on the heart, blood vesssels, extracellular fluid volume, the central and peripherial nervous system, kidneys, and circulating humoral factors

Blood pressure



Blood pressure

- Stroke volume (L/min) depends on intravascular volum, which in turn is regulated by the kidneys as well as myocardial contraction; depends on preload, afterload and contractility.
- Miocardial contraction is a complex process and depends on:
- the intrinsic cardiac condaction system, membrane transport, and cellular events, including influx of calcium
- effects of humoral substances, such as catecholamines and thyroxine, and sympathetic and parasympaphetic regulation of heart rate

Blood pressure

- The peripherial resistens is a complex integrated function, which depends on a number of factors including:

- neurohumoral substance,
- baroreflexes,
- sympathetic nervous system,
- endothelial factors,
- electolytes (sodium, potassium, calcium...,
- volume,
- intracellular events mediated by receptors and signal transduction.

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Diagnostic evaluation

- **The initial diagnostic evaluation of the patient with hypertension should:**
  - confirm the diagnosis of hypertension,
  - assess CV risk, asymptomatic organ damage and concomitant clinical conditions, and
  - detect causes of secondary hypertension.

- **The diagnostic evaluation requires:**
  - medical history, including family history,
  - physical examination, including careful BP measurement,
  - laboratory investigations and diagnostic tests.

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Diagnostic evaluation

Office blood pressure measurement

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Diagnostic evaluation
Office blood pressure measurement (1)

- At least two BP measurements are taken, spaced 1-2 min apart, after the patient has been sitting for 3-5 min, with additional measurements if the first two are quite different.
- Automated recording of multiple BP readings with the patient seated in an isolated room might be considered.

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Diagnostic evaluation
Office blood pressure measurement (2)

- In case of a consistent systolic BP difference of >10 mmHg between arms*, the arm with the higher BP values should be used.
- BP is taken 1 and 3 min after standing in elderly subjects, diabetic patients and in other conditions in which orthostatic hypotension may be frequent or suspected. Orthostatic hypotension* is defined as a reduction in systolic BP of ≥20 mmHg or in diastolic BP of ≥10 mmHg within 3 min of standing.
- Heart rate* should be assessed after the 2nd BP measurement.

* It is of note that all 3 variables independently predict CV risk

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Definition and classification of office blood pressure levels

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Definitions and Classification of Office Blood Pressure Levels (mmHg)

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

The BP category is defined by the highest level of BP, whether systolic or diastolic.

Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.

Office BP is the average of at least 2 BP measurements (with a validated device), spaced 1-2 min apart, after the patient has been sitting for 3-5 min, on at least 2 visits.

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Diagnostic evaluation

Out-of-office BP measurement: ambulatory and home blood pressure

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Diagnostic evaluation
Out-of-office BP measurement (1)

- The major advantage of out-of-office BP monitoring is that it provides a large number of BP measurements away from the medical environment, which represents a more reliable assessment of the actual BP than office BP.

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Diagnostic evaluation
Out-of-office BP measurement (2)

- ABPM and HBPM provide somewhat different information on the subject's BP status and risk, and the two methods should be regarded as complementary, rather than competitive or alternative.

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Definitions of hypertension by office and out-of-office blood pressure levels (mmHg)

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

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Diagnostic evaluation
Ambulatory BP: Prognostic significance of daytime and night-time BP

- Studies that accounted for daytime and night-time BP in the same statistical model found that night-time BP is a stronger predictor of morbidity and mortality than daytime BP.

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Diagnostic evaluation

White-coat and masked hypertension

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Definitions according to office BP and out-of-office BP (daytime ambulatory or home BP)

		Office BP (mmHg)	
		SBP <140 **and** DBP <90	SBP ≥140 **or** DBP ≥90
Daytime ABP or home BP (mmHg)	SBP <135 **and** DBP <85	True normotension (NT)	White-coat hypertension (WCHT)
	SBP ≥135 **or** DBP ≥85	Masked hypertension (MHT)	Sustained hypertension (SHT)

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Diagnostic evaluation
WCHT: Prevalence and determinants

- Based on population-based studies, the overall prevalence of WCHT averages about 13% (range: 9-16%) in the population and about 32% (range: 25-46%) among hypertensive patients in these surveys.
- Factors related to the prevalence of WCHT:
  - **higher prevalence:** older age, female gender, non-smoking, no organ damage, grade 1 hypertension,
- It is recommended that the diagnosis of WCHT be confirmed within 3 to 6 months.

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Diagnostic evaluation
Masked HT: Prevalence, determinants, organ damage and prognosis

- Based on population-based studies, the overall prevalence of masked hypertension averages about 13% (range: 10-17%).
- Factors related to the higher prevalence of masked HT: younger age, male gender, smoking, alcohol consumption, exercise-induced hypertension, physical activity, anxiety, job stress, obesity, diabetes, chronic kidney disease, family history of hypertension, high normal BP.
- Meta-analyses indicate that the incidence of CV events is about two times higher than in true normotension and is similar to the incidence in sustained hypertension.

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Clinical indications for out-of-office BP measurement for diagnostic purposes (1)

Clinical indications for HBPM or ABPM

- Suspicion of white-coat hypertension:
  - grade I hypertension in the office,
  - high office BP in individuals without asymptomatic organ damage and at low total CV risk.
- Suspicion of masked hypertension:
  - high normal BP in the office,
  - normal office BP in individuals with asymptomatic organ damage or at high total CV risk.
- Identification of white-coat effect in hypertensive patients.
- Considerable variability of office BP over the same or different visits.
- Autonomic, postural, post-prandial, siesta- and drug-induced hypotension.
- Elevated office BP or suspected pre-eclampsia in pregnant women.
- Identification of true and false resistant hypertension.

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Clinical indications for out-of-office BP measurement for diagnostic purposes (2)

Specific indications for ABPM

- Marked discordance between office BP and home BP.
- Assessment of dipping status.
- Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, chronic kidney disease, or diabetes.

incidence of cardiovascular events was higher in absence of dipping / reverse dippers

Night-time dipping pattern:

Category	Night/day ratio
Absence of dipping	> 1.0
Mild dipping	> 0.9 and ≤ 1.0
Dipping	> 0.8 and ≤ 0.9
Extreme dipping	≤ 0.8

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Assessment of cardiovascular risk

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Recommendations on cardiovascular risk assessment

Recommendations	Class	Level
In asymptomatic subjects with hypertension but free of CV disease, chronic kidney disease, and diabetes, total CV risk stratification using the SCORE model is recommended as a minimal requirement.	I	B
As there is evidence that asymptomatic organ damage predicts CV death independently of SCORE, a search for organ damage should be considered, particularly in individuals at moderate risk.	IIa	B
It is recommended that decisions on treatment strategies depend on the initial level of total CV risk.	I	B

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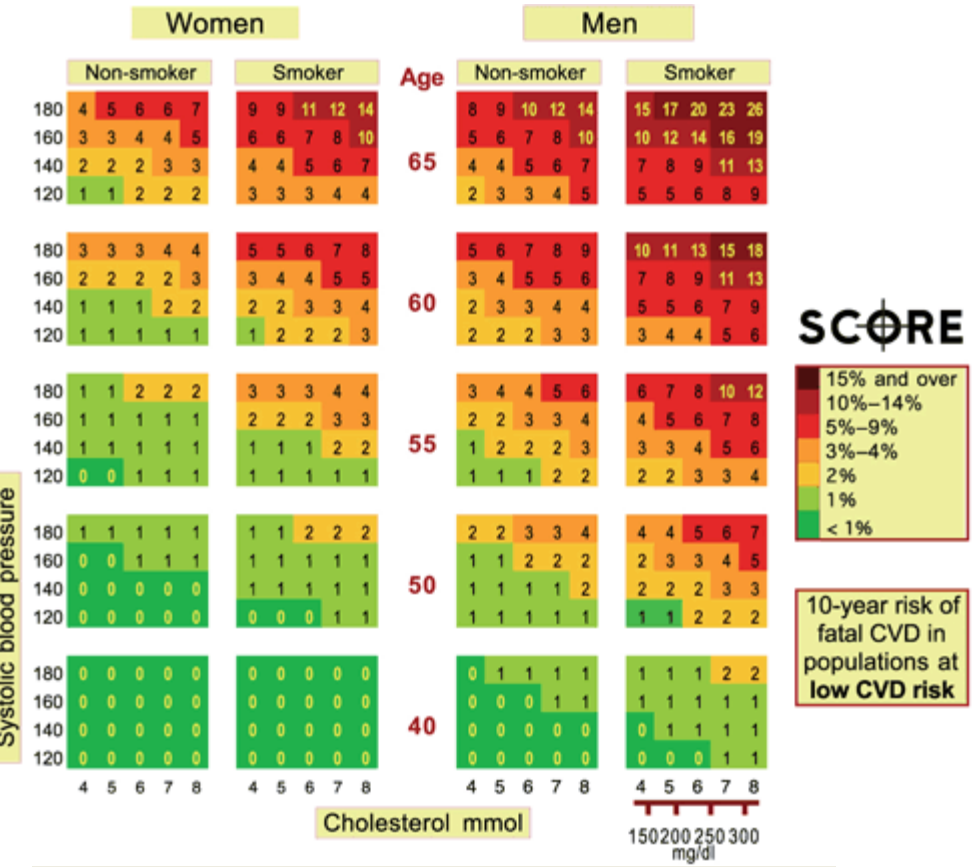
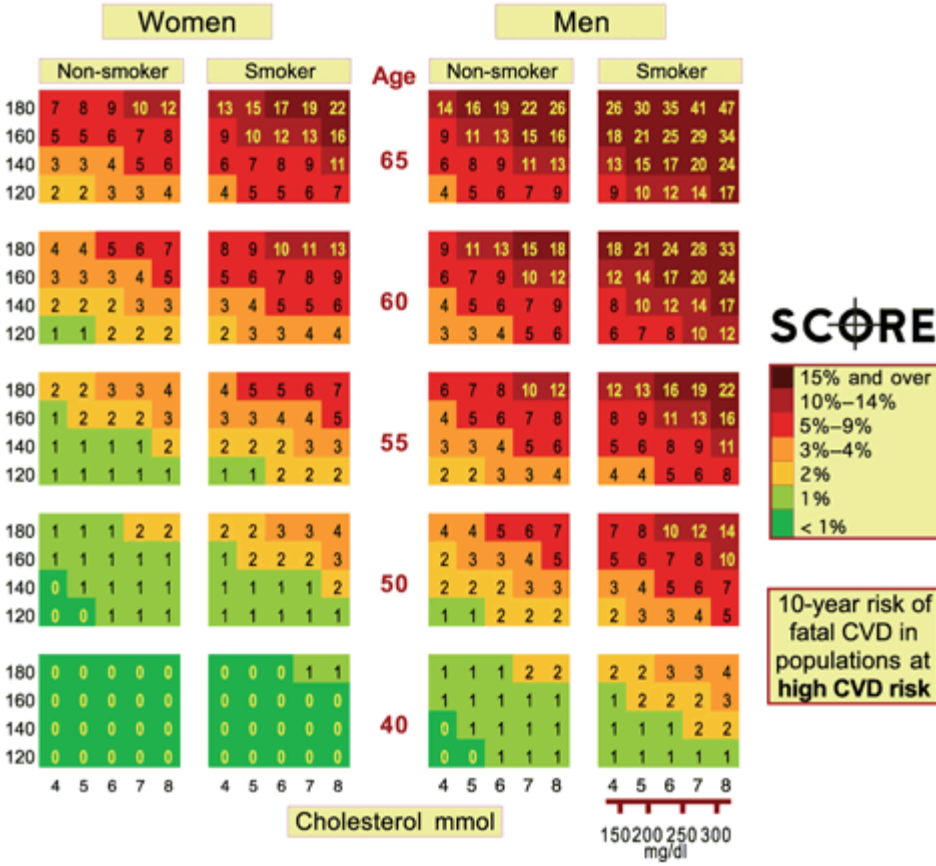
SCORE chart: 10-year risk of fatal cardiovascular disease (CVD)





Low CVD countries are Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom.

High CVD risk countries are Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia FYR, Moldova, Russia, Ukraine, and Uzbekistan.

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The stratification of total cardiovascular risk in different categories in hypertension is based on:

- blood pressure category,
- other cardiovascular risk factors,
- asymptomatic organ damage,
- presence of diabetes mellitus,
- symptomatic cardiovascular disease or chronic kidney disease.

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Total cardiovascular risk stratification

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

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Total cardiovascular risk stratification
Risk factors

- Male sex.
- Age (≥ 55 yrs in men; ≥ 65 yrs in women).
- Smoking.
- Dyslipidaemia:
  - TC >4.9 mmol/L (190 mg/dL), and/or
  - LDL-C >3.0 mmol/L (115 mg/dL), and/or
  - HDL-C <1.0 mmol/L (40 mg/dL) in men; <1.2 mmol/L (46 mg/dL) in women, and/or
  - TG >1.7 mmol/L (150 mg/dL)
- Fasting plasma glucose 5.6-6.9 mmol/L (102-125 mg/dL).
- Abnormal glucose tolerance test.
- Obesity (BMI ≥30 kg/m^2).
- Abdominal obesity: waist circumference ≥102 cm in men; ≥88 cm in women (in Caucasians).
- Family history of premature CV disease (<55 yrs in men; <65 yrs in women).

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Total cardiovascular risk stratification
Asymptomatic organ damage

- Pulse pressure ≥60 mmHg (in the elderly).
- Electrocardiographic LVH (Sokolow-Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mm*ms), or
- Echocardiographic LVH (LVM index >115 g/m² in men; >95 g/m² in women).
- Carotid wall thickening (IMT >0.9 mm) or plaque.
- Carotid-femoral pulse wave velocity >10 m/s.
- Ankle-brachial index <0.9.
- Chronic kidney disease stage 3 (eGFR: 30-60 mL/min/1.73 m²).
- Microalbuminuria (30-300 mg/24 h), or albumin-creatinine ratio (30-300 mg/g or 3.4-34 mg/mmol) (preferentially on morning spot urine).

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Total cardiovascular risk stratification
Diabetes mellitus

- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or
- HbA_{1c} >7% (53 mmol/mol), and/or
- Post-load plasma glucose >11.0 mmol/L (198 mg/dL).

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Total cardiovascular risk stratification
Established CV or renal disease

- Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack.
- Coronary heart disease: angina; myocardial infarction; revascularization with PCI or CABG.
- Heart failure, including heart failure with preserved ejection fraction.
- Symptomatic lower extremities peripheral artery disease.
- Chronic kidney disease stage 4 (eGFR <30 mL/min/1.73 m^2).
- Proteinuria >300 mg/24 h.
- Advanced retinopathy: haemorrhages or exudates, papiloedema.

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Recommendations on diagnostic evaluation of heart, arteries, kidney, retina and brain

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Diagnostic evaluation - Recommendations Heart

Recommendations
An ECG is recommended in all hypertensive patients to detect left ventricular hypertrophy, left atrial dilatation, arrhythmias, or concomitant heart disease.
In all patients with a history or physical examination suggestive of major arrhythmias, long-term ECG monitoring, and, in case of suspected exercise-induced arrhythmias, a stress ECG test should be considered.
An echocardiogram should be considered to refine CV risk, and confirm ECG diagnosis of left ventricular hypertrophy, left atrial dilatation or suspected concomitant heart disease.
Whenever history suggests myocardial ischaemia, a stress ECG test is recommended, and, if positive or ambiguous, an imaging stress test (stress echocardiography, stress cardiac MRI or nuclear scintigraphy) is recommended.

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Diagnostic evaluation - Recommendations
Arteries

Recommendations
Ultrasound scanning of carotid arteries should be considered to detect vascular hypertrophy or asymptomatic atherosclerosis, particularly in the elderly.
Carotid-femoral pulse wave velocity should be considered to detect large artery stiffening.
Ankle-brachial index should be considered to detect peripheral artery disease.

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Diagnostic evaluation - Recommendations Kidney

Recommendations
Measurement of serum creatinine and estimation of GFR is recommended in all hypertensive patients.
Assessment of urinary protein is recommended in all hypertensive patients by dipstick.
Assessment of microalbuminuria is recommended in spot urine and related to urinary creatinine excretion.

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Diagnostic evaluation - Recommendations
Retina and Brain

Recommendations
Retina
Examination of the retina should be considered in difficult to control or resistant hypertensive patients to detect haemorrhages, exudates, and papiloedema, which are associated with increased CV risk.
Examination of the retina is not recommended in mild-to-moderate hypertensive patients without diabetes, except in young patients.
Brain
In hypertensive patients with cognitive decline, brain magnetic resonance imaging or computed tomography may be considered for detecting silent brain infarctions, lacunar infarctions, microbleeds, and white matter lesions.

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Signs suggesting secondary hypertension
• Features of Cushing syndrome.
• Skin stigmata of neurofibromatosis (pheochromocytoma).
• Palpation of enlarged kidneys (polycystic kidney).
• Auscultation of abdominal murmurs (renovascular hypertension).
• Auscultation of precordial or chest murmurs (aortic coarctation; aortic disease; upper extremity artery disease).
• Diminished and delayed femoral pulses and reduced femoral blood pressure compared to simultaneous arm BP (aortic coarctation; aortic disease; lower extremity artery disease).
• Left–right arm BP difference (aortic coarctation; subclavian artery stenosis).

Laboratory Investigations
Routine tests

- Haemoglobin and haematocrit.
- Fasting plasma glucose.
- Serum total, LDL and HDL cholesterol.
- Fasting serum triglycerides.
- Serum potassium and sodium.
- Serum uric acid.
- Serum creatinine with estimation of GFR.
- Urine analysis: microscopic examination; urinary protein by dipstick test; test for microalbuminuria.
- 12-lead electrocardiogram.

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Laboratory Investigations
Additional tests, based on history, physical examination, and findings from routine tests

- Haemoglobin A_{1c} (if fasting glucose >5.6 mmol/L (102 mg/dL) or previous diagnosis of diabetes).
- Quantitative proteinuria (if dipstick test positive); urinary potassium and sodium concentration and their ratio.
- Home and 24-h ambulatory BP monitoring.
- Echocardiogram.
- Holter monitoring in case of arrhythmias.
- Exercise testing.
- Carotid ultrasound.
- Peripheral artery/abdominal ultrasound.
- Pulse wave velocity.
- Ankle-brachial index.
- Fundoscopy.

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Laboratory Investigations
Extended evaluation (mostly domain of the specialist)

- Further search for cerebral, cardiac, renal, and vascular damage, mandatory in resistant and complicated hypertension.
- Search for secondary hypertension when suggested by history, physical examination, or routine and additional tests.

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Treatment strategies

Lifestyle changes

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Treatment strategies
Lifestyle changes

- Appropriate lifestyle changes are the cornerstone for the prevention of hypertension and are also important for its treatment.

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Recommendations on lifestyle changes

Are recommended
Salt restriction to 5-6 g per day.
Moderation of alcohol consumption to no more than 20-30 g of ethanol per day in men and 10-20 g of ethanol per day in women.
Increased consumption of vegetables, fruits, and low-fat dairy products.
Reduction of weight to BMI of 25 kg/m^2 and of waist circumference to <102 cm in men and <88 cm in women, unless contraindicated.
Regular exercise, i.e. at least 30 min of moderate dynamic exercise on 5 to 7 days per week.
Advice to quit smoking and to offer assistance to all smokers.

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Treatment strategies

Initiation of antihypertensive drug treatment

'The initiation of antihypertensive drug treatment is based on the initial level of total cardiovascular risk'

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Initiation of lifestyle changes and antihypertensive drug treatment based on total CV risk

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

(In patients with diabetes, the optimal diastolic BP target is 80-85 mmHg)

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Treatment strategies

- Choice of drugs
- Monotherapy vs combination therapy

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Drugs to be preferred in specific conditions (a)

Asymptomatic organ damage	
Left ventricular hypertrophy	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB

Clinical event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonist
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB
Atrial fibrillation, rate control	BB, non-dihydropiridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist

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Drugs to be preferred in specific conditions (b)

Condition	
Isolated systolic hypertension (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

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

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

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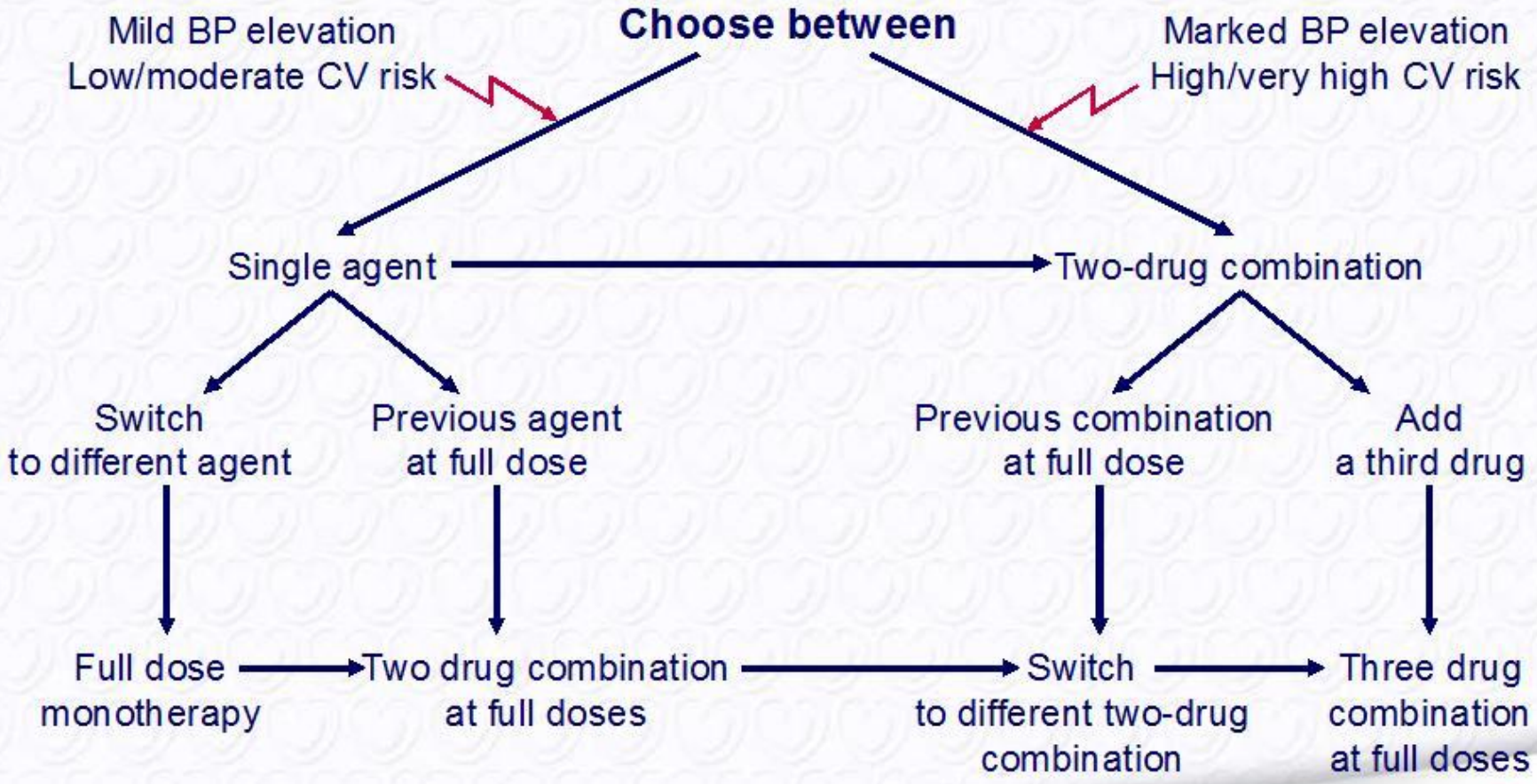
Monotherapy vs drug combination therapy
Moving from a less intense to a more intense therapeutic strategy to achieve target blood pressure



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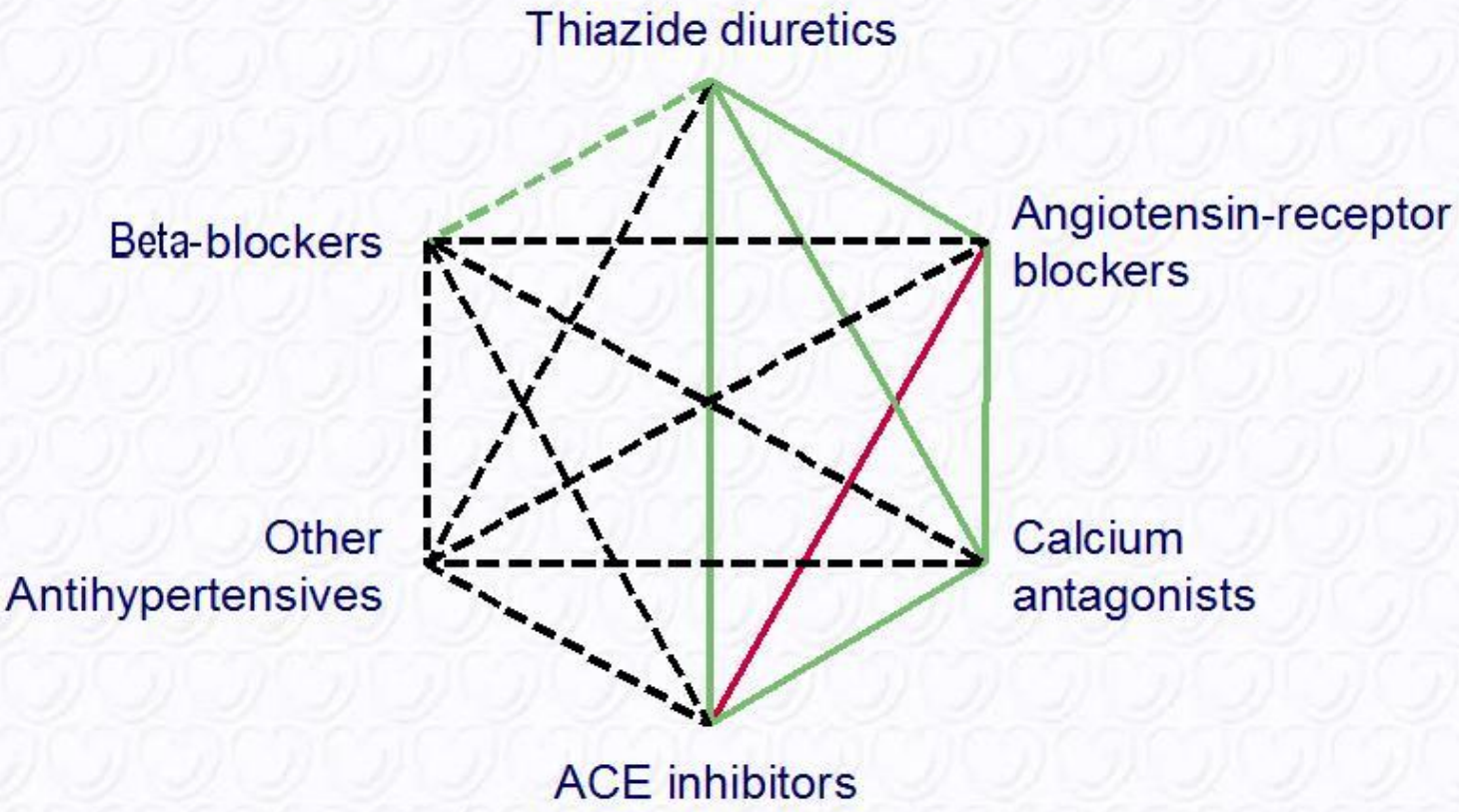
Possible combinations of classes of antihypertensive drugs



Green continuous lines: preferred. **Green dashed lines**: useful combinations with some limitations

Black dashed line: possible combinations (only DHP calcium antagonists should normally be combined with beta-blockers)

Red continuous line: not recommended combination

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Treatment strategies in special conditions/populations

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Treatment strategies in special conditions

- White-coat and masked hypertension
- Young adults
- Elderly
- Women
- Metabolic syndrome
- Diabetes mellitus
- Heart disease
- Cerebrovascular disease
- Atherosclerosis, arteriosclerosis and peripheral artery disease
- Nephropathy
- Resistant hypertension
- Renovascular hypertension
- Obstructive sleep apnoea
- Malignant hypertension

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White-coat and masked hypertension

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

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Young adults

Recommendations
Despite absence of evidence from randomized controlled trials, antihypertensive drug treatment may be considered prudent in young hypertensives and, especially when other risk factors are present.
Young individuals with white-coat hypertension can be followed with lifestyle measures only.
Lack of evidence does also not allow recommending to initiate antihypertensive drug therapy in young individuals with isolated elevation of brachial SBP, but these individuals should be followed closely with lifestyle recommendations.

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Elderly

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

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Women

Recommendations
Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended.
Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms.
In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal haemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered.
Hormone therapy and selective oestrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks.
In women with child-bearing potential renin-angiotensin system blockers are not recommended and should be avoided.
Methyldopa, labetalol and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia).

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Metabolic syndrome

Recommendations
Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but also the metabolic components of the syndrome, and delay diabetes onset.
As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as blockers of the renin-angiotensin system and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating beta-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent.
It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg.
BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP.

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Diabetes mellitus

Recommendations
While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg.
A SBP goal <140 mmHg is recommended in patients with diabetes.
The DBP target in patients with diabetes is recommended to be <85 mmHg.
All classes of antihypertensive agents are recommended and can be used in patients with diabetes; blockers of the renin-angiotensin system may be preferred, especially in the presence of proteinuria or microalbuminuria.
It is recommended that individual drug choice takes comorbidities into account.
Simultaneous administration of two blockers of the renin-angiotensin system is not recommended and should be avoided in patients with diabetes.

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Heart disease

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

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Cerebrovascular disease

Recommendations
It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values.
Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or TIA, even when initial SBP is in the 140-159 mmHg range.
In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered.
In elderly hypertensives with stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher.
All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced.

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Atherosclerosis, arteriosclerosis and peripheral artery disease

Recommendations
In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and beta-blockers.
In hypertensive patients with a pulse wave velocity above 10 m/s all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved.
Antihypertensive therapy is recommended in hypertensive patients with peripheral artery disease to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death.
Though a careful follow-up is necessary, beta-blockers may be considered for the treatment of arterial hypertension in patients with peripheral artery disease, since their use does not appear to be associated with exacerbation of symptoms.

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Nephropathy

Recommendations
Lowering SBP to <140 mmHg should be considered.
When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored.
Blockers of the renin-angiotensin system are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria.
Reaching BP goals usually requires combination therapy, and it is recommended to combine blockers of the renin-angiotensin system with other antihypertensive agents.
Combination of two blockers of the renin-angiotensin system, though potentially more effective in reducing proteinuria, is not recommended.
Aldosterone antagonists cannot be recommended in CKD, especially in combination with a blocker of the renin-angiotensin system, because of the risk of excessive reduction in renal function and of hyperkalaemia.

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Resistant hypertension

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

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Renovascular hypertension

- Renovascular artery stenosis secondary to atherosclerosis is relatively frequent, especially in the elderly population.
- It is still debated whether these patients benefit from intervention, mostly percutaneous renal artery stenting.
- Intervention is not recommended if renal function has remained stable over the past 6-12 months and if hypertension is controlled by an acceptable medical regimen (Class III, LoE B).
- Fibromuscular dysplasia is more common in younger mostly female patients with uncontrolled hypertension, in whom there is convincing though uncontrolled information favouring the intervention (Class IIa, LoE B).

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Obstructive sleep apnoea

- The association between obstructive sleep apnoea (OSA) and hypertension is well documented, particularly when nocturnal hypertension is concerned.
- Because of the relationship between obesity and OSA, weight loss and exercise are commonly recommended.
- Continuous positive airway pressure therapy is a successful procedure for reducing OSA, but the effect on BP appears to be very small.

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Malignant hypertension

- Malignant hypertension is a hypertensive emergency, clinically defined as the presence of very high BP associated with ischaemic organ damage (retina, kidney, heart or brain).
- Treatment is founded on agents that can be administered by intravenous infusion and titrated.

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Treatment strategies

Treatment of risk factors associated with hypertension

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Recommendations of treatment of risk factors associated with hypertension

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

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Hypertension Emergencies

- Hypertension Emergencies are situation in which severe hypertention (usually grade 3) is associated with acute organ damage, which requires immediate but careful intervention to lower BP, in hospital, usually with intravenous therapy.
- **Clinical presentation**:
- Malignant hypertation with or without acute renal failure -reduce MAP by 20-25%- Labetalol, Nicardipin; Nitroprusside, Urapidil
- Hypertensive encephalopathy- Imediately reduce MAP by 20-25%- Labetalol, Nicardipin; Nitroprusside

- Acute coronary event- Immediate reduce SBP to <140 mmHg- Nitroglycerine, Labetalol; Urapidil
- Acute cardiogenic pulmonary oedema- Immediate reduce SBP to <140 mmHg- Nitroprusside OR Nitroglycerine + loop diuretic; Urapidil + loop diuretic
- Acute aortic diseection - Immediate reduce SBP to <120 mmHg and HR to <60 bpm- Esmolol and Nitroprusside OR Nitroglycerine Or nicardipine; Labetalol or metoprolol
- Eclampsia and severe pre-eclampsia/HELLP- Immediately reduce SBP <160 mmHg and DBP <105 mmHg- Labetalol ornicardipine and magnesium sulphate

Hypertension urgency

- Severe hypertension in patients in whom there is no clinical evidence of acute HMOD. Whilst these patients recuire BP reduction, they rarely require admission to hospital, and BP reduction is best achived with oral medication.
- With few exceptions, it is recommended to reduce blood pressure by <25% in the first hours with careful follow-up