Hypertension

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I KATEDRA i KLINIKA KARDIOLOGII
WARSZAWSKIEGO UNIWERSYTETU MEDYCZNEGO

Hypertension

- It is an arbitrarily defined disorder to which both environmental and genetic factors contribute

- Major **risk factor** for:
  - cerebrovascular disease
  - myocardial infarction
  - peripheral vascular disease
  - heart failure
  - renal failure

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

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

- Blood pressure is a continuous variable which fluctuates widely during the day
  - physical stress
  - mental stress

- The definition of hypertension has been arbitrarily set as:

  That blood pressure above which the benefits of treatment outweigh the risks in term of morbidity and mortality

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

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

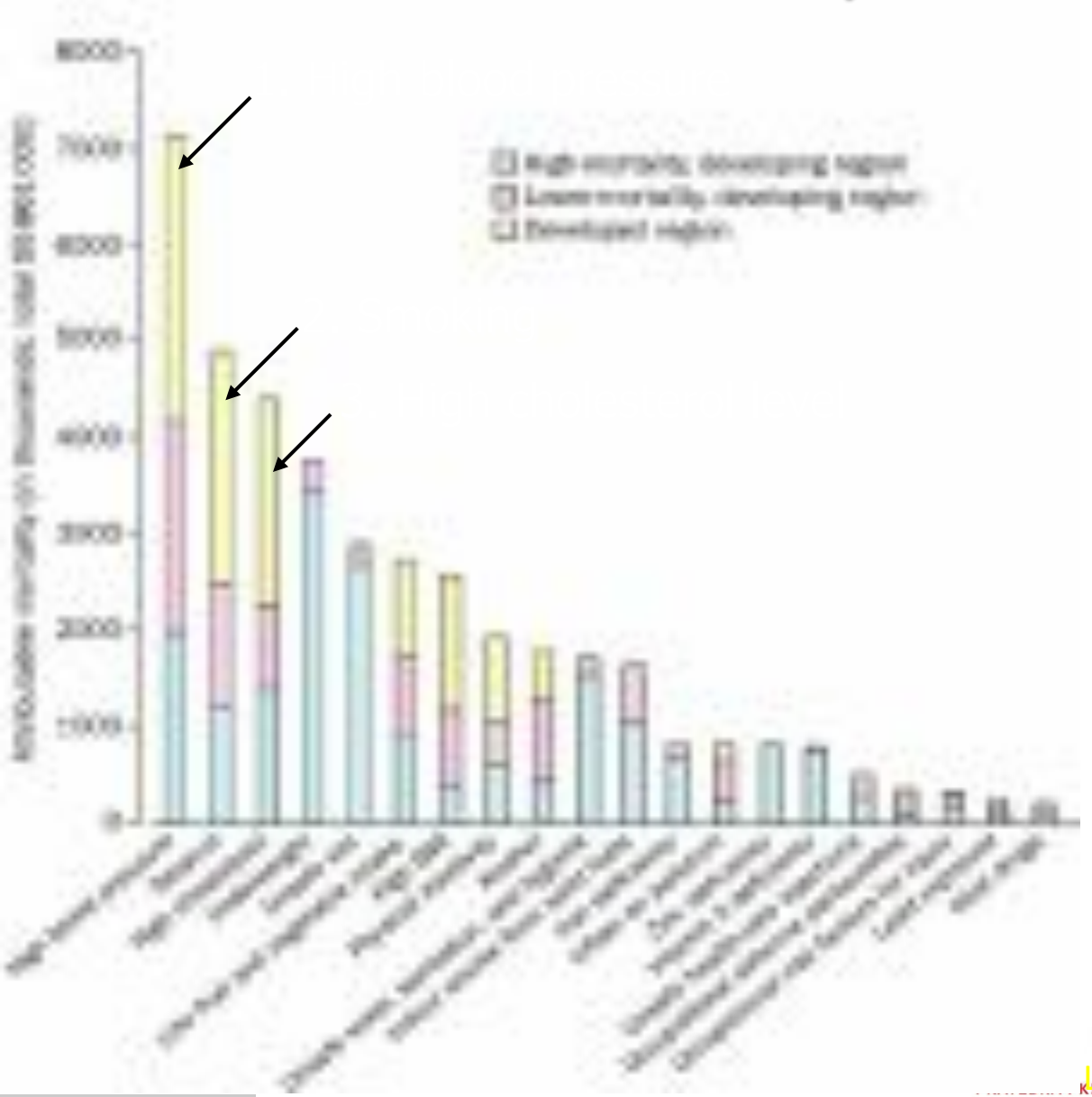
Blood Pressure

- Exhibits a normal distribution within the population
- Increasing blood pressure is associated with a progressive increase in the risk of stroke and cardiovascular disease
- Risk however rises exponentially and not linearly with pressure

Epidemiology

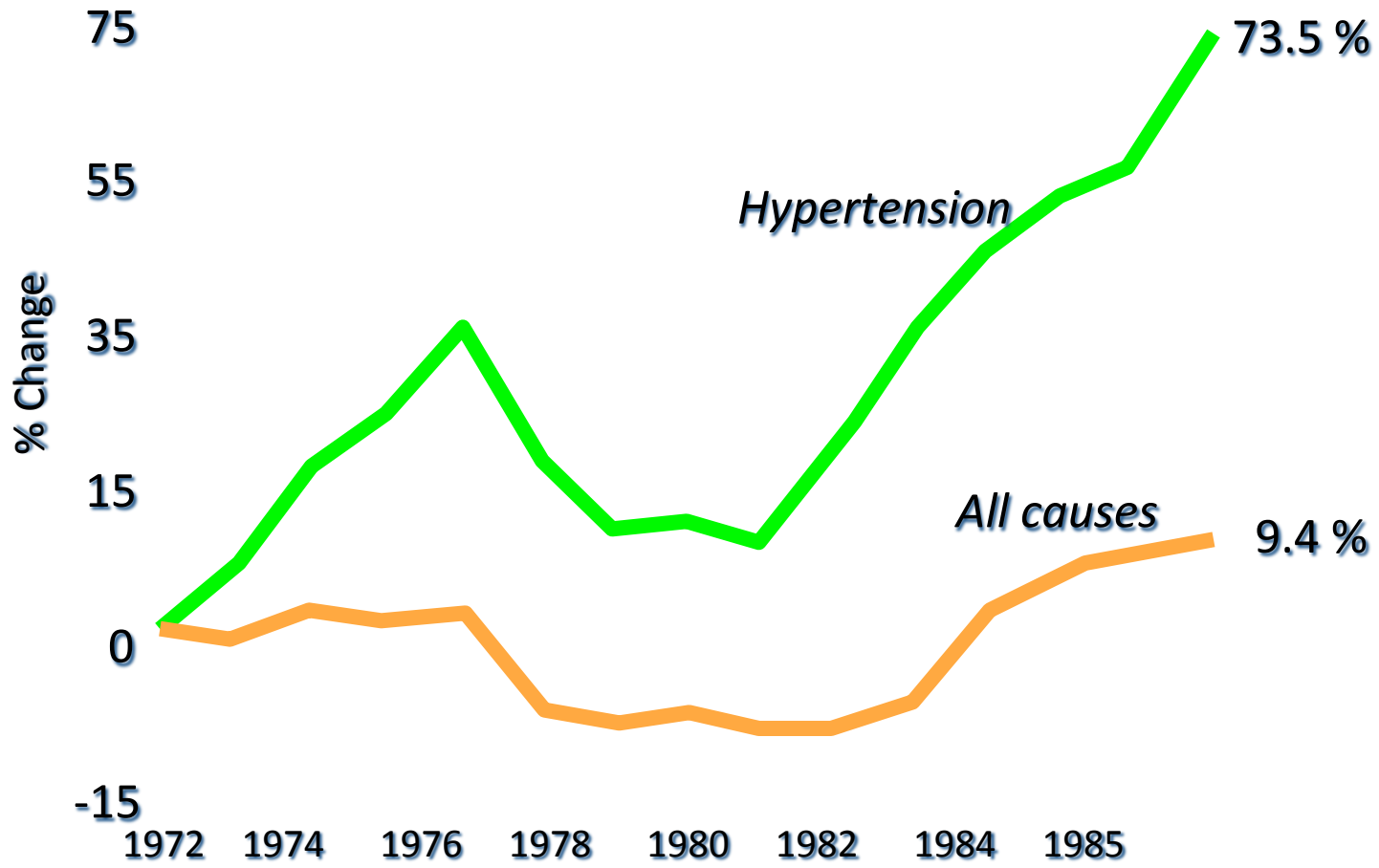
Most important factors on mortality - world

World Health Organization



Lancet 2002

Percentage of change in numbers of visits in the USA for all causes and for hypertension



Global burden of hypertension: analysis of worldwide data

Patricia M Kearney, Megan Whelton, Kristi Reynolds, Paul Muntner, Paul K Whelton, Jiang He

2000

26,4 %

2025

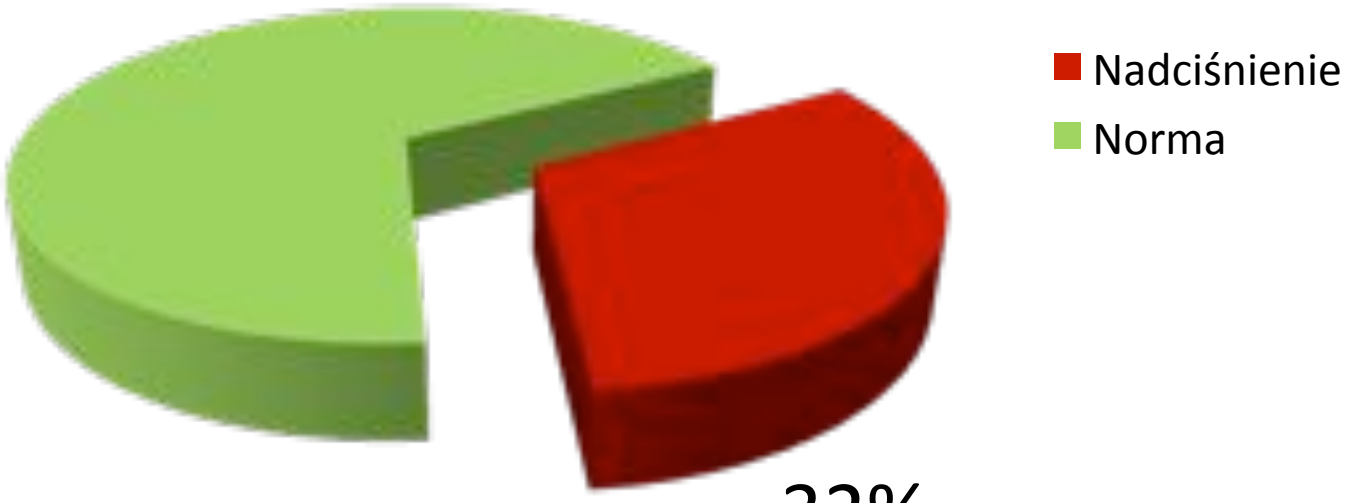
29,0 %

972 mln

1560 mln

Lancet 2005; 365: 217-223

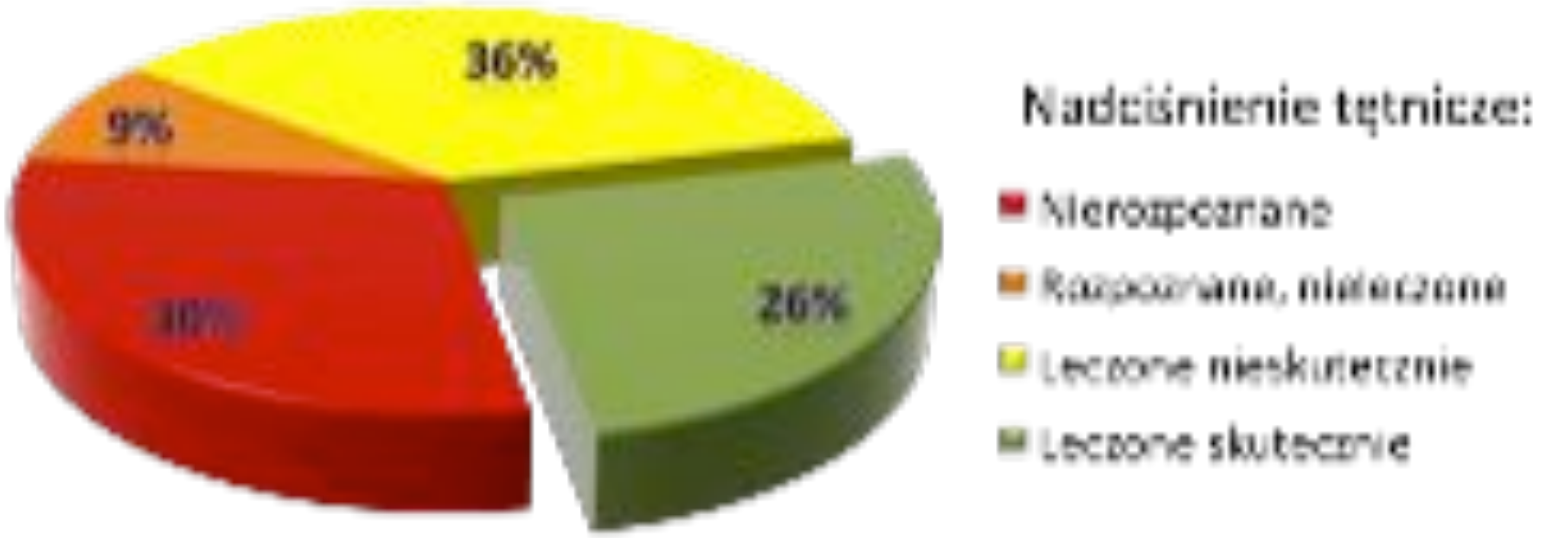
Hypertension (≥140/90 mmHg)



32%

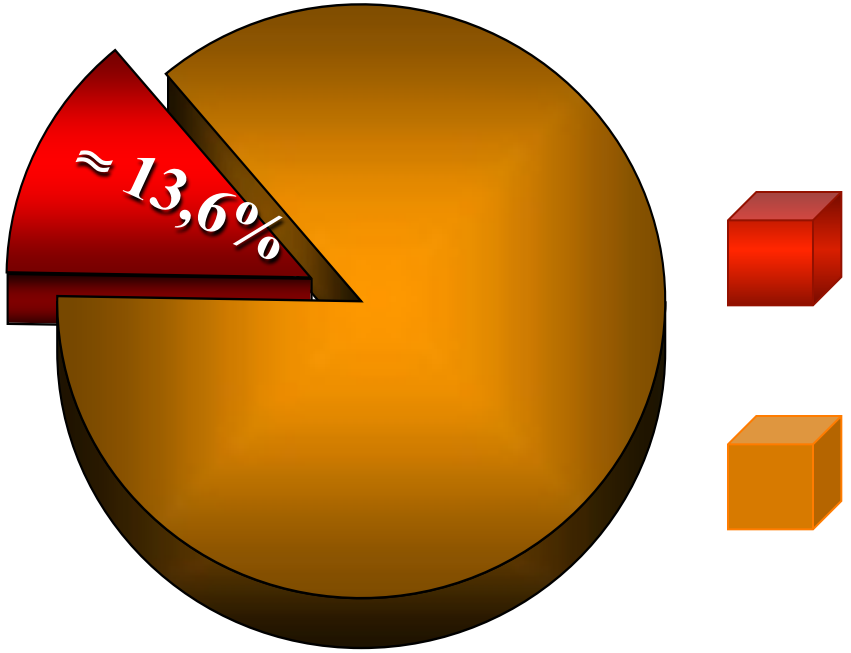
=9,5 mln osób

Control of HT in Poland



Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data

Alan D Lopez, Colin D Mathers, Majid Ezzati, Dean T Jamison, Christopher J L Murray

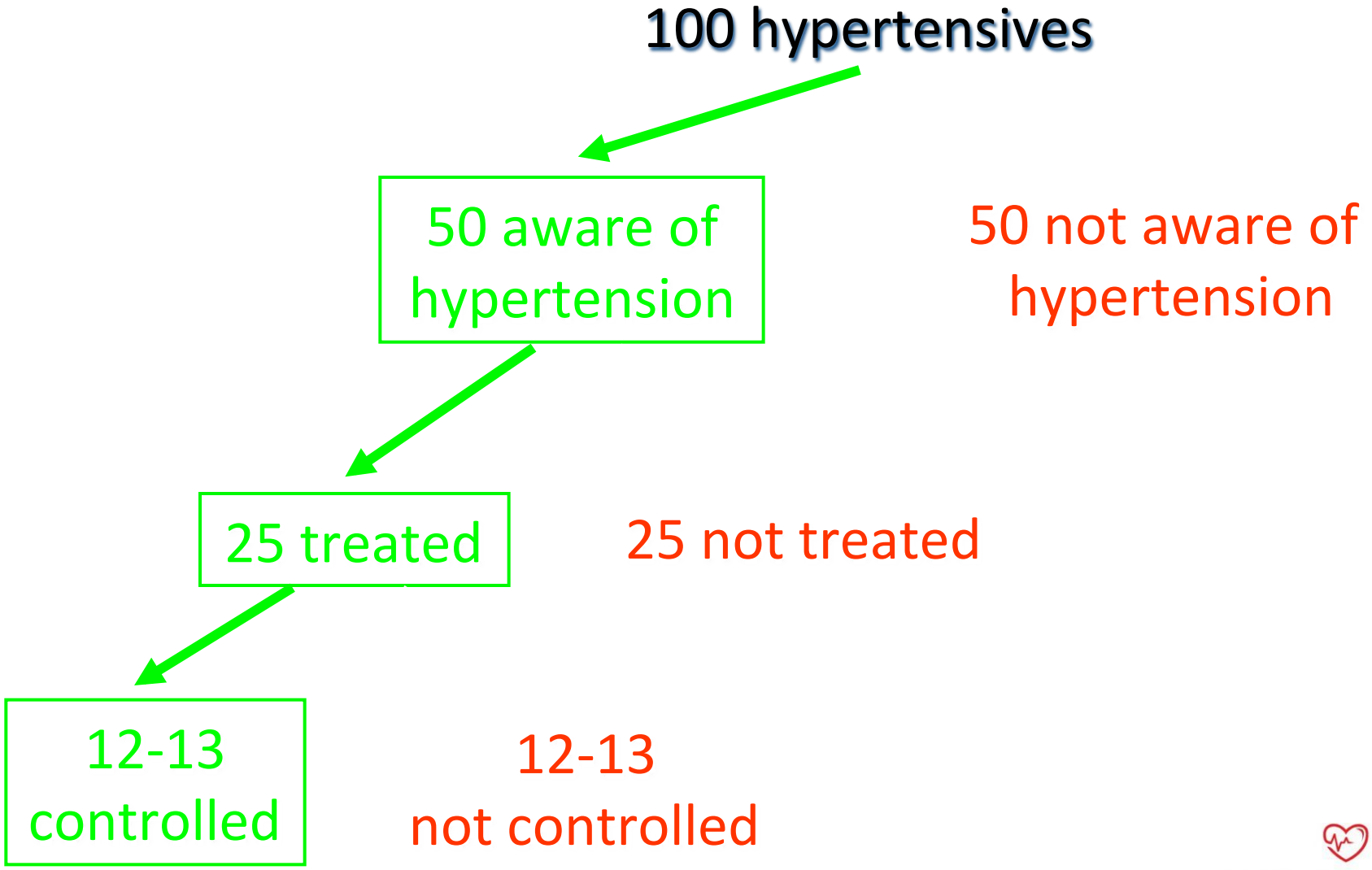


Deaths due to HT

Deaths other

≈ 56 mln die/year – 14% die due to HT

Rule of halves – probably truth everywhere



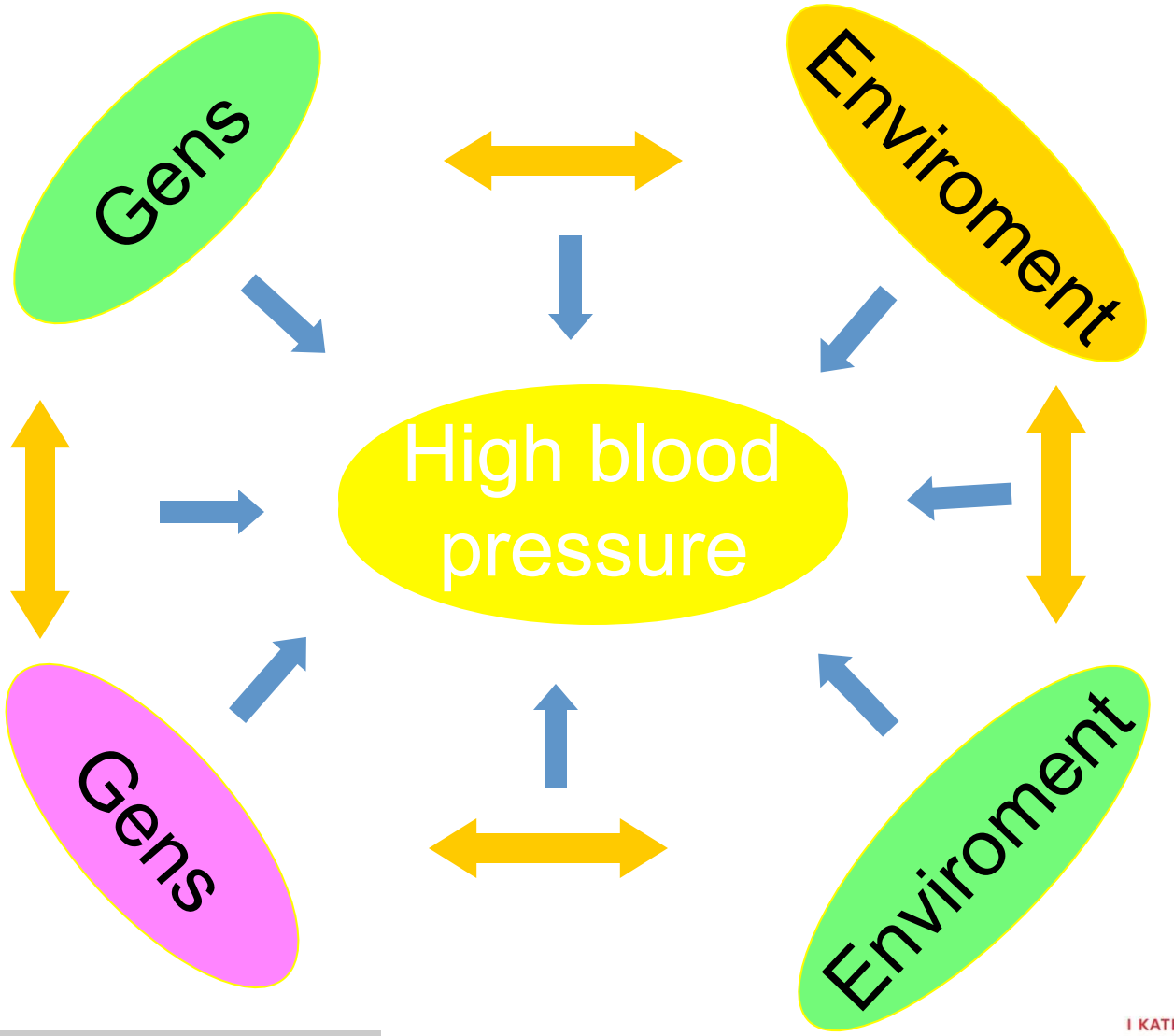
Aetiology

- In 95% of cases no cause can be found

- In 5-10% a cause can be found
  - Chronic renal disease
  - Renal artery stenosis
  - Endocrine disease, Cushings, Conn's Syndrome, Phaeochromocytoma

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

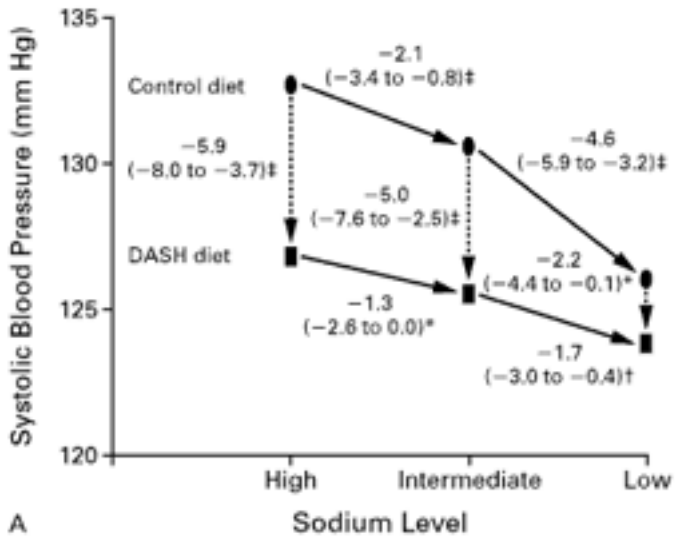
Pathogenesis of essential hypertension

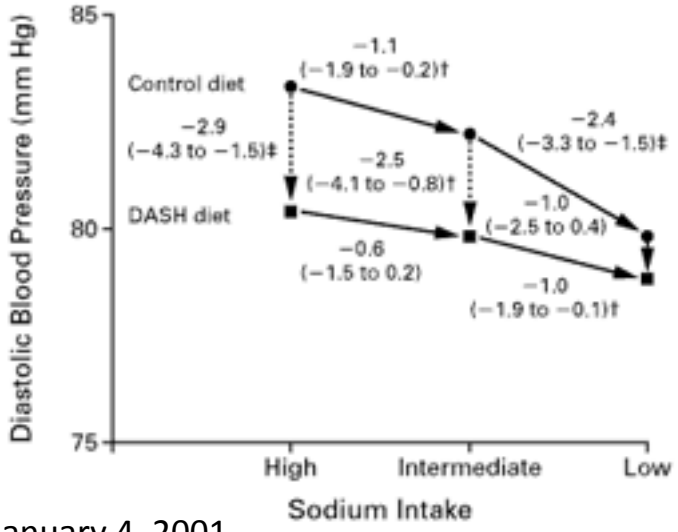


Enviromental factors influencing BP

- NaCl
- Alcohol
- Obesity
- Low physical activity
- Stress
- Low birth weight (?)
- Low ingestion of Ca and K (?)

Diet and sodium intake vs BP
(*Dietary Approaches to Stop Hypertension*)





- Weight
  - Obese patients have a higher BP
  - Up to 30% of hypertension is attributable in part or wholly to obesity
  - If a patient loses weight BP will fall
  - In untreated patients a weight loss of 9 Kg has been reported to produce a fall in BP of 19/18 mmHg
  - In treated patients a fall in BP of 30/21 mmHg has been reported
  - Weight reduction is the most important non-pharmacological measure available

- ALCOHOL
  - Affects 1% of the population
  - Small amounts of alcohol tend to decrease BP
  - Large amounts of alcohol tend to increase BP
  - If alcohol consumption is reduced BP will fall over several days to weeks.
  - Average fall is small 5/3 mmHg

Sympathetic Nervous System

- Sympathetic system activation produces
  - vasoconstriction
  - reflex tachycardia
  - increased cardiac output
- In this way blood pressure is increased
- The actions of the sympathetic system are rapid and account for second to second blood pressure control

The renin-angiotensin-aldosterone system

- The RAAS is pivotal in long-term BP control
- The RAAS is responsible for:
  - maintenance of sodium balance
  - control of blood volume
  - control of blood pressure

- The RAAS is stimulated by:
  - fall in BP
  - fall in circulating volume
  - sodium depletion
- Any of the above stimulates renin release from the juxtaglomerular apparatus
- Renin converts angiotensinogen to angiotensin I
- Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE)

- Angiotensin II is a potent
  - vasoconstrictor
  - anti-natriuretic peptide
  - stimulator of aldosterone release from the adrenal glands
- Aldosterone is also a potent antinatriuretic and antidiuretic peptide
- Angiotensin II is also a potent hypertrophic agent which stimulates myocyte and smooth muscle hypertrophy in the arterioles

- Cardiomyocyte and smooth muscle hypertrophy:
  - are both poor prognostic indicators in patients with hypertension
  - partially explain why hypertension and the risks of hypertension persist in some patients despite treatment

- Both the sympathetic and RAAS are key targets in the treatment of hypertension

Genes

- Familial history of hypertension
- Different genes are involved
- Monogenic hypertension is rare

- GENETICS
  - A history of hypertension tends to run in families
  - The closest correlation exists between sibs rather parent and child
  - It is also possible that environmental factors common to members of the family also have a role in the development of hypertension

Therapy of hypertension

KEY QUESTIONS

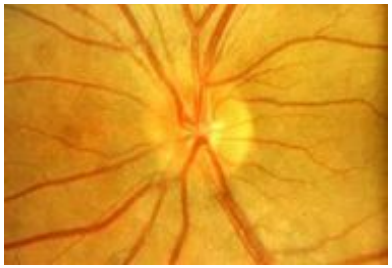
1. **Is my patient hypertensive ?**
2. When do I start pharmacotherapy ?
3. Hospital or ambulatory treatment ?
4. Which drug ?
5. What may influence a drug choice ?
6. How to improve patient's compliance ?

1. Is my patient hypertensive ?

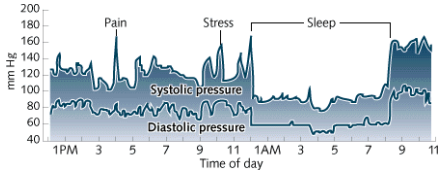
1. BP measurements

(home BP)

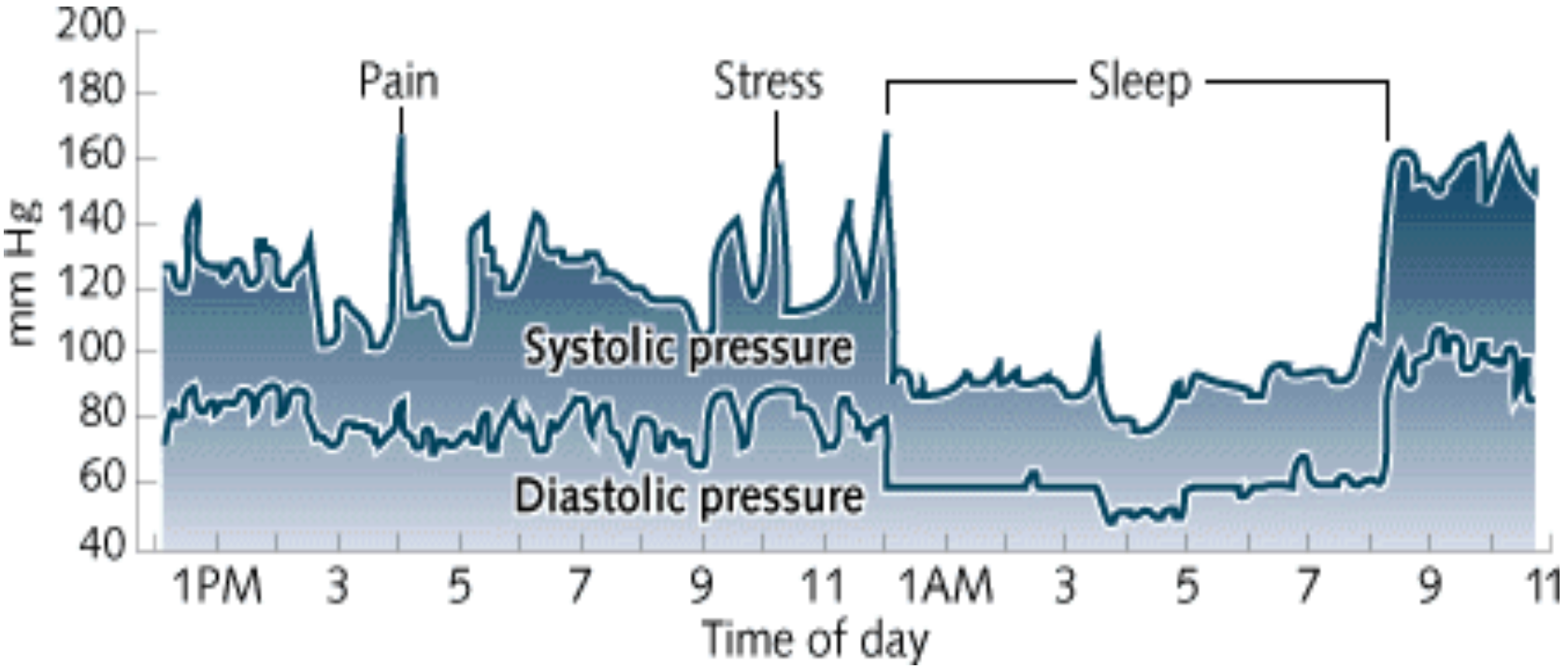
2. Optic fundus or other end – organ damage



3. ABPM



ABPM


200
180
160
140
120
100
80
60
40
mm Hg
Pain
Stress
Sleep
Systolic pressure
Diastolic pressure
1PM
3
5
7
9
11
1AM
3
5
7
9
11
Time of day

KEY QUESTIONS

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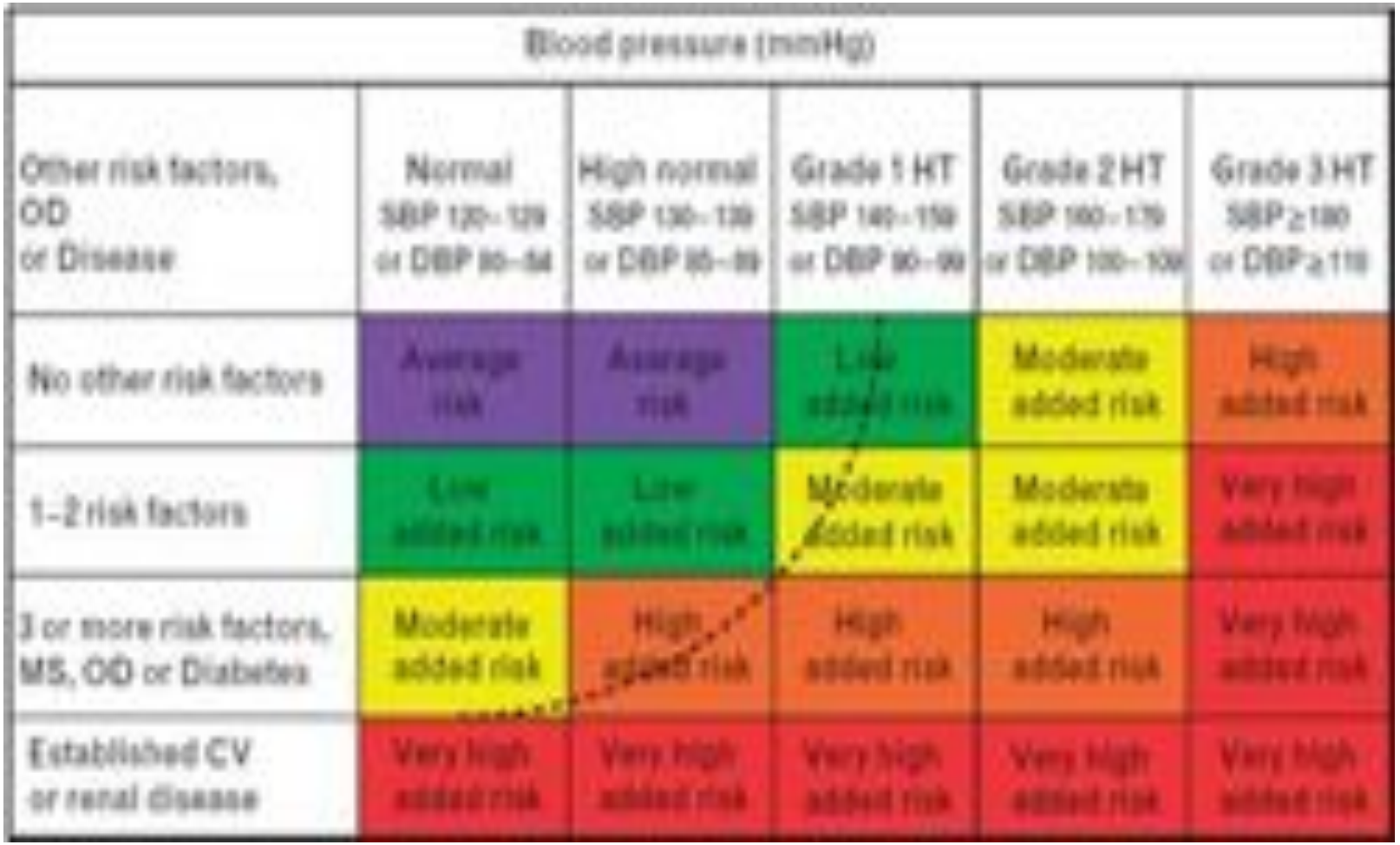
Risk stratification ESH 2013



In conclusion, it might be appropriate to use a classification of blood pressure without the term ‘‘hypertension’’. .....the real threshold for hypertension must be considered as flexible.

Journal of Hypertension 2007, 25:1105–1187

Risk stratification ESH 2013

Risk factors
Male sex
Age (men ≥55 years; women ≥65 years)
Smoking
Dyslipidaemia
Total cholesterol >4.9 mmol/L (190 mg/dL), and/or
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or
Triglycerides >1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity [BMI ≥30 kg/m^2 (height^2)]
Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)
Family history of premature CVD (men aged <55 years; women aged <65 years)

Asymptomatic organ damage
Pulse pressure (in the elderly) ≥60 mmHg
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or
Echocardiographic LVH [LVM index: men >115 g/m^2; women >95 g/m^2 (BSA)][a]
Carotid wall thickening (IMT >0.9 mm) or plaque
Carotid–femoral PWV >10 m/s
Ankle-brachial index <0.9
CKD with eGFR 30–60 mL/min/1.73 m^2 (BSA)
Microalbuminuria (30–300 mg/24 h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)

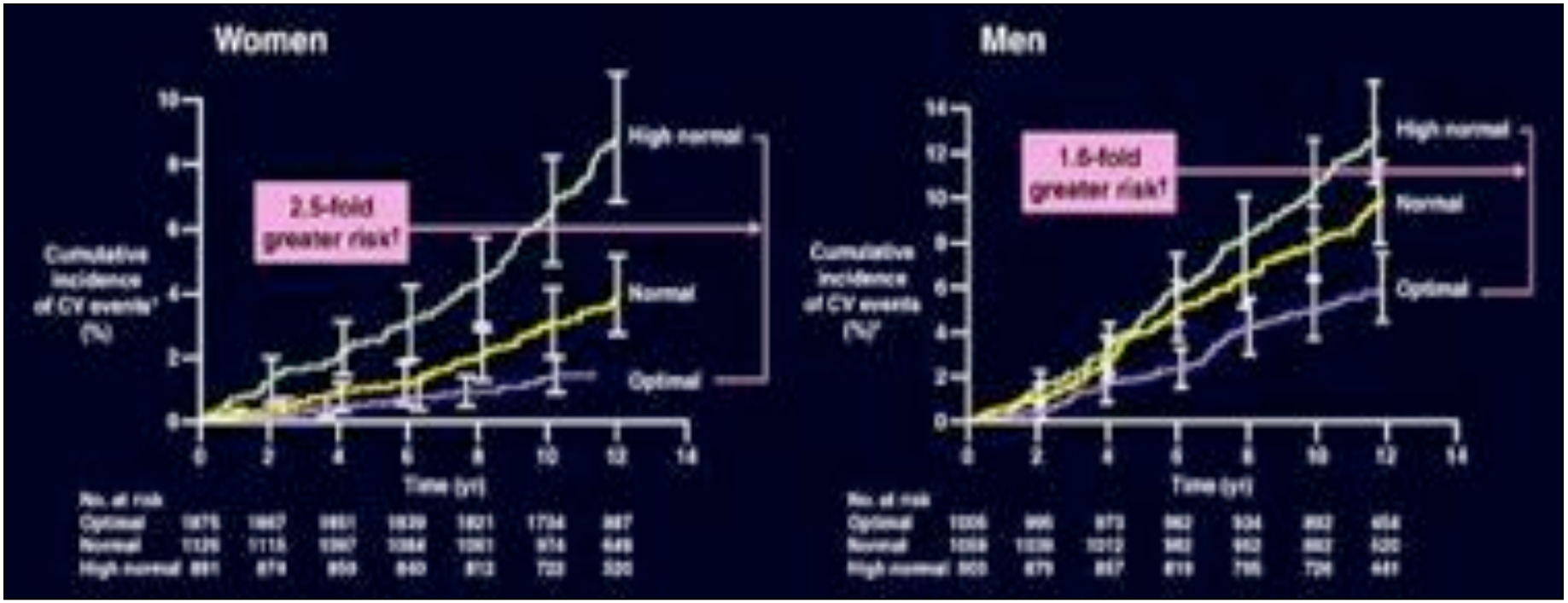
Risk stratification ESH 2013

Diabetes mellitus
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or
HbA_{1c} >7% (53 mmol/mol), and/or
Post-load plasma glucose >11.0 mmol/L (198 mg/dL)
Established CV or renal disease
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral artery disease
CKD with eGFR <30 mL/min/1.73m^2 (BSA); proteinuria (>300 mg/24 h).
Advanced retinopathy: haemorrhages or exudates, papilloedema

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

Framingham Heart Study

"High-normal" BP Is Not Benign



*CV death, MI, stroke, CHF
†Adjusted for concomitant CV risk factors
Optimal = <120/<80 mmHg
Normal = 120–129/80–84 mmHg
High normal = 130–139/84–89 mmHg

Vasan RS et al. *N Engl J Med.* 2001;345:1291–1297.

3. Hospital or ambulatory treatment ?

- BP values
- Concomitant complications
- Hypertensive emergencies or urgencies
- Patient's will

Hypertensive Emergencies and Urgencies

- **Emergencies** require immediate blood pressure reduction to prevent or limit target organ damage.
- **Urgencies** benefit from reducing blood pressure within a few hours.
- Elevated blood pressure alone rarely requires emergency therapy.
- Fast-acting drugs are available.

Hypertensive Emergencies

- Hypertensive encephalopathy
- Hypertensive left ventricular failure
- Hypertension with myocardial infarction
- Hypertension with unstable angina
- Hypertension and dissection of the aorta
- Severe hypertension associated with subarachnoid haemorrhage or cerebrovascular accident
- Crisis associated with phaeochromocytoma
- Use of recreational drugs such as amphetamines, LSD, cocaine or ecstasy
- Hypertension perioperatively
- Severe pre-eclampsia or eclampsia

Drugs Available for Hypertensive Emergencies

- **Vasodilators iv**
- Nitroprusside
- Nicardipine
- Fenoldopam
- Nitroglycerin
- Enalaprilat
- Hydralazine

- **Adrenergic Inhibitors**
- Labetalol
- Esmolol
- Phentolamine

- **i ACE**
- Captopril sl

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Therapy - goals

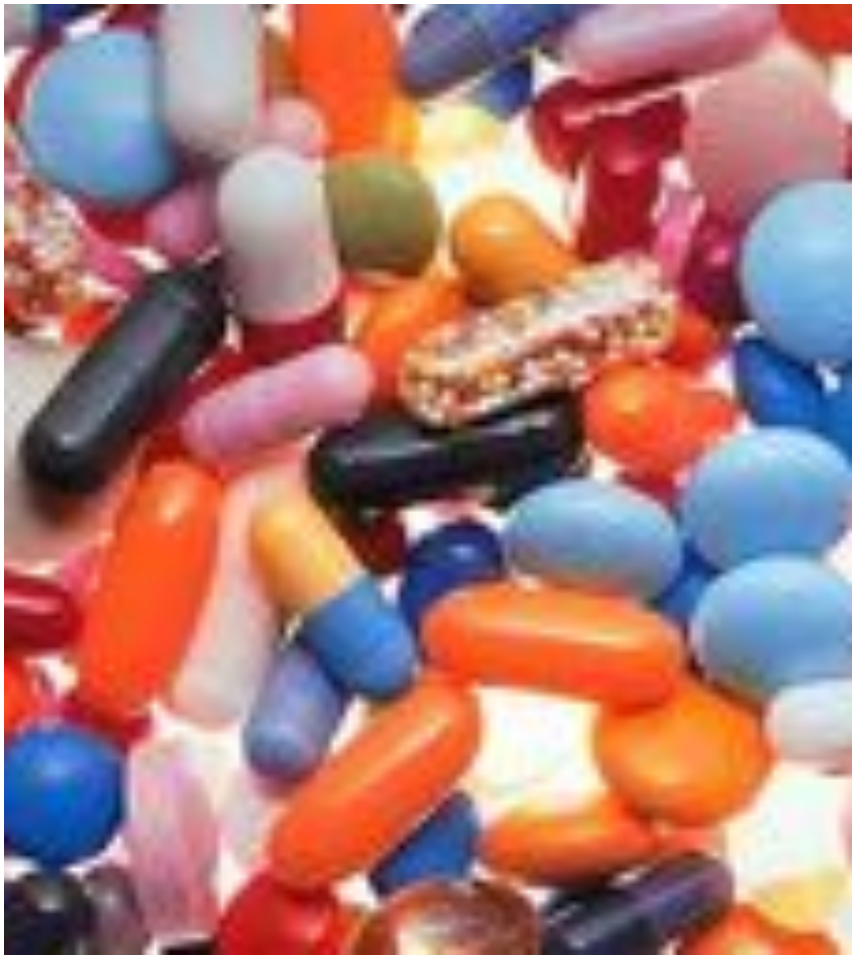
Reduce CV morbidity and mortality

BP reduction < 140/90 mm Hg

Lifestyle changes

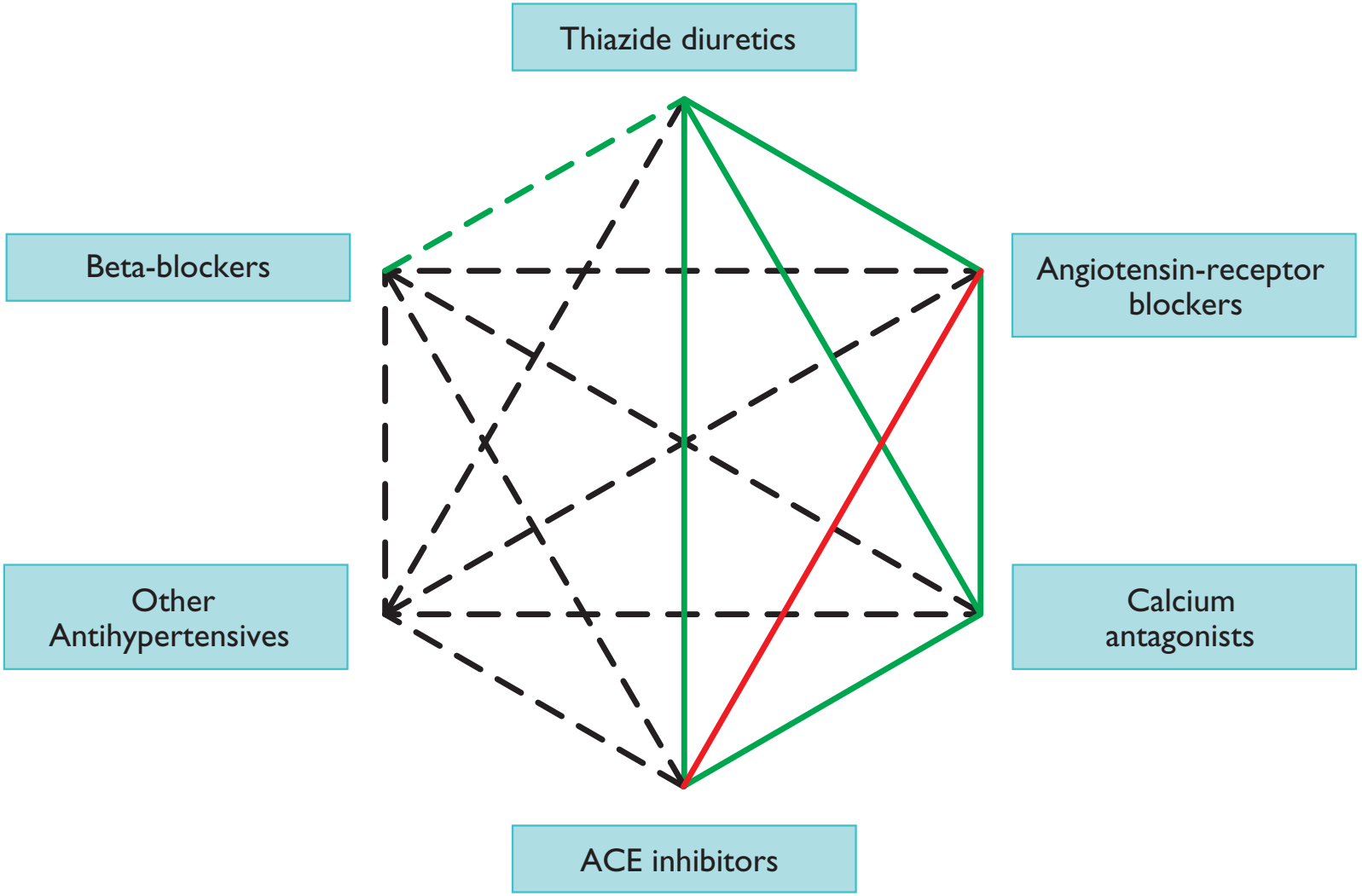
- Lose weight if overweight.
- Limit alcohol intake to no more than 30 ml ethanol (720 ml beer, 300 ml wine) per day or 15 ml ethanol per day for women.
- Increase aerobic physical activity (30 to 45 minutes most days of the week)
- Reduce sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).
- Maintain adequate intake of dietary potassium (approximately 90 mmol per day).
- Maintain adequate intake of dietary calcium and magnesium for general health.
- Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health.

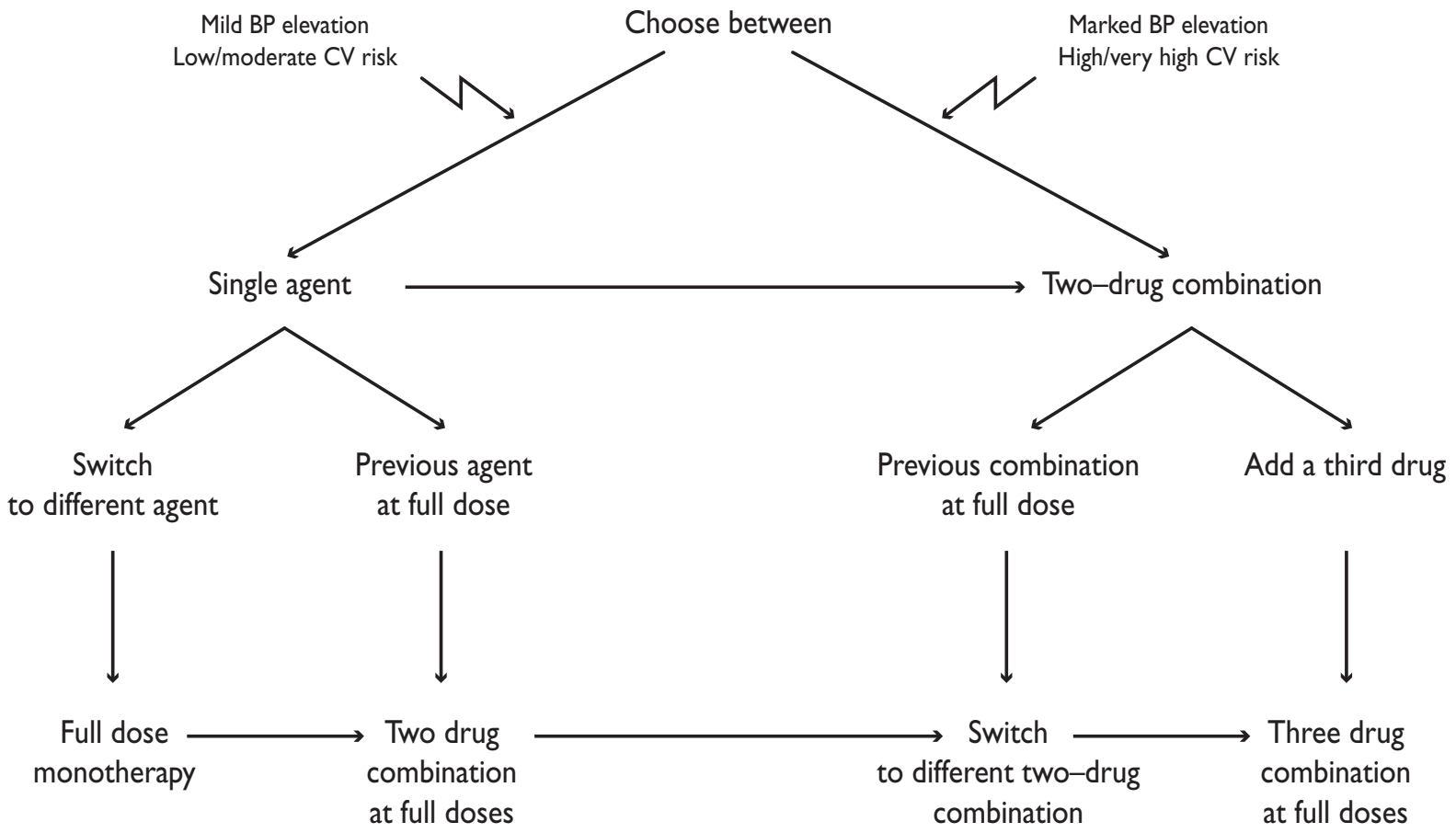
4. Which drug ?



Drug Therapy - Principles

- **A low dose of initial drug should be used, slowly titrating upward.**
- **Optimal formulation should provide 24-hour efficacy with once-daily dose with at least 50% of peak effect remaining at end of 24 hours.**
- **Combination therapies may provide additional efficacy with fewer adverse effects.**


Thiazide diuretics
Beta-blockers
Angiotensin-receptor blockers
Other Antihypertensives
Calcium antagonists
ACE inhibitors



BP = blood pressure; CV = cardiovascular.

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

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

Drug	Compelling	Possible
Diuretics (thiazides)	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 (dihydropyridines)		Tachyarrhythmia Heart failure
Calcium antagonists (verapamil, diltiazem)	A–V block (grade 2 or 3, trifascicular block) Severe LV dysfunction Heart failure	
ACE inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Mineralocorticoid receptor antagonists	Acute or severe renal failure (eGFR <30 mL/min) Hyperkalaemia	