

Antihypertensive therapy

Notes for Pharmacology lectures

This study material is exclusively for students of general medicine in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for tests in practicals and the final exam.

Treatment goals in hypertensive patients

2013 ESH/ESC Guidelines for the management of arterial HT

SBP < 140 mm Hg

low- moderate CV risk

diabetes

previous stroke or TIA

CHD

CKD

SBD between 150 and 140 mm Hg

elderly < 80 years

elderly > 80 years provided good condition

DBP < 90 mmHg

always recommended, except DM (< 85 mm Hg)

CV=cardiovascular, CHD=coronary heart disease, TIA = transient ischemic attack, CKD=chronic kidney disease, SBD= systolic blood pressure, DBP = diastolic blood pressure

Reducing SBP by 10 mmHg & DBP by 5 mmHg:

reduces stroke risk	by 45%
reduces heart attack risk	by 20%
reduces CV event risk	by 33%

Treatment goals

- Primary prevention
HbA1c < 45 mmol/mol
- Secondary prevention
HbA1c < 60 mmol/mol

HbA1c = glycosylated hemoglobin standard =20–37 mmol/mol (by SZÚ = NIPH = National Institute of Public Health)

Arterial hypertension - DEFINITION

- repeated increase of BP (systolic-diastolic) 140/90 mmHg or higher in patients older than 18 years in at least 2-3 measurements in two different checks
- the most frequent disease of CV system
- AH + hyperlipidemia +DM + nicotine addiction
- increases the risk of premature atherosclerosis & ischemic heart disease
- usually it is a stable; sustained HT, paroxysmal HT may occur

AH= arterial hypertension, DM = diabetes mellitus

Current situation in Czech Republic

Prevalence	35%
Patients over 60 years	> 50%

60 -70 % of the hypertensive patients are treated

45 % patients treated **achieve** BP target values

55 % patients treated **don't achieve** BP target values

Treatment goals in HT

Medium Risk (1-4 % SCORE)	High Risk (5-9 % SCORE)	Very High Risk (≥ 10 % SCORE)
LDL < 3,0 mmol/l	LDL < 2,5 mmol/l ApoB < 1,0 mmol/l	LDL < 1,8 mmol/l ApoB < 0,8 mmol/l

Non-pharmacological approaches

- reduction of BW, BMI < 27, BMI = m(kg)/v(m)²
- reduction of salt intake up to 5 - 6 g/day
- balanced intake of potassium, magnesium, calcium, vitamins and unsaturated FA
- fruits and vegetables
- low alcohol intake up to 40 g/day (2 beers, 3dcl wine, 2 shots/day) in males, ½ in females
- absence of nicotine
- physical aerobic activity (without isometric)
- yoga, psychotherapy

Ideal fixed combination?

- combination of 2 or 3 drugs with long acting efficacy
- dosing of all components once daily
- additive antihypertensive effect, influencing other pathogenic mechanisms (atherosclerosis, kidney, metabolism, increased heart rate,..)
- preferred drug combinations

ACE-I or sartan
+
dihydropyridine Ca blocker
+
diuretic (not loop)

Combination therapy of hypertension

- to reach target blood pressure below 140/90 mmHg
- combination is necessary in **70-80%** hypertensive pts
- if the patient treated with adequate triple combination in adequate doses is taking prescribed medication,
- we reach the target in 90%!

Causes of poor control of HT and high cardiovascular risk

- insufficient use of drug combinations
- insufficient use of fixed combinations
- complicated treatment schedule
- poor compliance

Antihypertensive drugs

I. Drugs affecting RAAS (renin – angiotensin aldosterone system)

Angiotensin converting enzyme inhibitors (ACEI)

Angiotensin receptor blockers (ARBs)

Renin inhibitors

II. Diuretics

Thiazide diuretics

Loop diuretics

Potassium sparing diuretics

III. Vasodilators

Calcium-channel blockers

Direct acting arterial dilators

IV. Drugs affecting sympathetic nervous system

Beta-blockers

Alfa-blockers

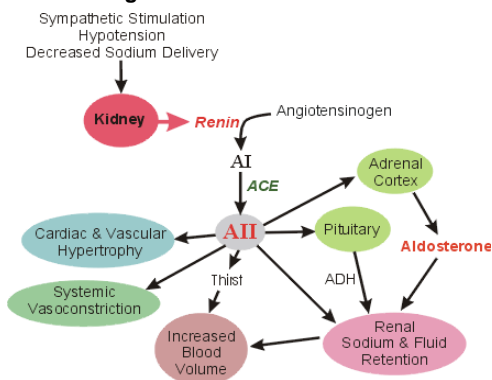
Alfa/ beta blockers

Centrally acting sympatholytics

Adrenergic neurons blockers

Ganglionic blockers

RAAS – target of ACEI



ACEI - CLASSIFICATION

- **sulphydryl group** – captopril, zofenopril
- **carboxyl group** – enalapril, ramipril, perindopril, lisinopril, quinapril, trandolapril, spirapril
- **phosphoryl group** - fosinopril

Therapeutic Use of ACE Inhibitors:

Hypertension, Heart failure, Post-myocardial infarction, DM-I with nephropathy with microalbuminuria

CI: pregnancy

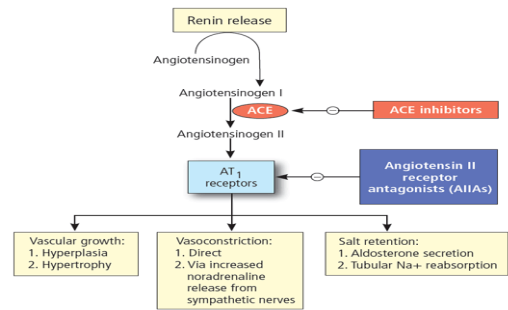
Make regular checks of potassium and creatinine!

1. Effects of ACE Inhibitors (cardio-renal)

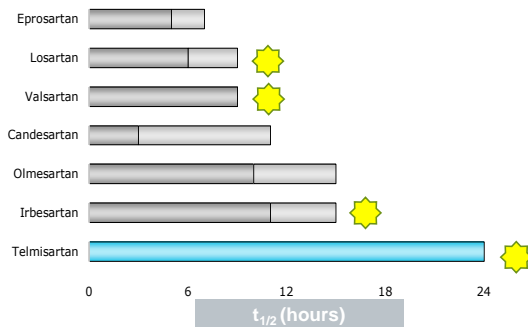
- vasodilation
- reduce arterial + venous pressure
(by blocking AT II, inhibiting bradykinin metabolism)
- decrease blood volume
- natriuretic and diuretic effect (by blocking aldosteron secretion)
- **inhibition of cardiac and vascular hypertrophy**
associated with chronic hypertension
- **down regulation of sympathetic adrenergic activity**
(by blocking AT II effect on sympathetic nerve release/ reuptake NE)

ATII = angiotensin, NE = norepinephrine = noradrenaline

2. Angiotensin receptor blockers (ARB)



2. Angiotensin receptor blockers (ARB)



3. Renin inhibitors

aliskiren

PK : effect is not influenced by food
long T_{1/2} (about 24 hrs)

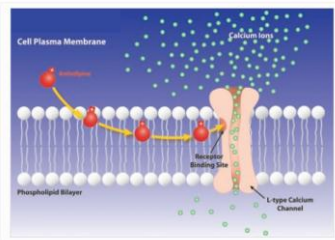
D: once daily
maximal antihypertensive effect up to 2 weeks

effective in monotherapy
in patients with DM and kidney failure DO NOT combine
with ACEi and ARB common combination with diuretics

AE: well tolerated, diarrhea (3%) , angioedema (< 1%)

CI: pregnancy

4. Calcium channel blockers (CCBs)



MOA:
block the inward movement of calcium by binding to the **L-type calcium channels** in the cardiac myocytes, vascular smooth muscle and cardiac nodal tissue (SA and AV nodes)

4. Calcium channel blockers (CCBs) – specific drugs

A/ Dihydropyridines – most selective to smooth muscle

1.generation – **nifedipine** – lower vascular selectivity, shorter t_{1/2}

2.generation - **felodipine, isradipine, nicardipine, nitrendipin**

– high vascular selectivity, longer t_{1/2}

3.generation - **amlodipine, lacidipine, lercanidipine**

– antiatherogenic affect,

– slow onset, long duration action

4. Calcium channel blockers (CaCBs) – specific drugs

B/ Non-dihydropyridines

diltiazem (benzothiazepin), **intermediate selectivity** between verapamil and dihydropyridines

verapamil (phenylalkylamin) **selective for myocardium**

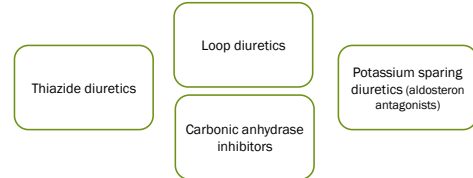
5. Diuretics

Mechanism of antihypertensive action:

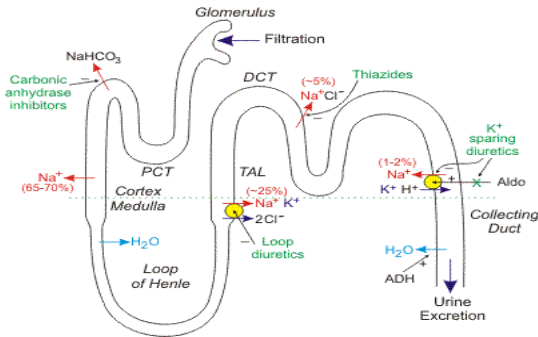
inhibiting the reabsorption of sodium - at different segments of the renal tubular system → increase urine output by the kidney (promote diuresis)

→ fall in systemic vascular resistance (unknown mechanism)

→ vasodilation



5. Diuretics



PCT = Proximal convoluted tubule, TAL = Thick ascending limb, DCT = Distal convoluting tubules

5a. Thiazide diuretics

- most commonly used diuretics in HT
- inhibit Na^+ a Cl^- transporter **in the distal tubule** (about 5% of Na^+ reabsorption capacity)
- **long** term effect (up to 12 hrs)
- full effect with **latention 3-4 days**
- less efficacious diuresis

hydrochlorothiazide
chlorthalidon
indapamide
(metipamide)

5b. Loop diuretics

- inhibit the Na-Cl-K co-transporter in the TAL
- (25% of Na^+ reabsorption capacity)
- powerful diuretics, short T1/2
- vasodilation
- loss of Na, Cl, K, Ca, Mg – risk of hypokalemia

Therapeutic Use

Hypertension
Pulmonary oedema
Congestive Heart Failure
Hypercalcemia

FUROSEMIDE
ethacrynic acid
torasemide

SE: hypotension, hypovolemia, hyperuricemia, hypokalemia

5c. Potassium sparing diuretics

- weak diuretic effect
- MoA: inhibit aldosterone-sensitive Na^+ reabsorption →
- limit loss of K^+ by urine → **DO NOT** produce hypokalemia
- used in combination with thiazides and loop diuretics

AMILORIDE – prevention of hypokalemia
TRIAMTEREN – similar to amiloride
SPIRONOLACTONE – primary hyperaldosteronism, ascites, liver cirrhosis

6. Beta-Adrenoceptor Antagonists (Beta – Blockers)

Classification

I. **non-selective** - block both $\beta_1 + \beta_2$ adrenoceptors
metipranolol, propranolol, timolol, nadolol, sotalolol

II. **cardioselective** relatively selective to β_1
metoprolol, atenolol, bisoprolol, betaxolol, esmolol,
nebivolol

III. **non-selective with ISA** - pindolol, bopindolol,

IV. **cardioselective with ISA** - acebutolol, celiprolol

V. **other** – $\beta_1, \alpha_1, \alpha_2$, vasodilatation (β_2 ISA) - celiprolol
 $\beta_1, \beta_2, \alpha_1$ - labetalol, carvedilol

7. Central-acting antihypertensive agents

7b: Central-acting α_2 agonists (α_2 sympathomimetics)

α –metyldopa

false NRA precursor/ prodrug
 α –metyldopa \rightarrow α –**methylnorepinephrine** \rightarrow activation of
 α_2 adrenergic receptors
DO Not compromise the renal perfusion (GFR) \rightarrow
use in renal insufficiency, pregnancy

SE: depression, fatigue, anxiety, apathy, orthostatic hypotension

clonidine

α_2 receptors agonist, direct effect on α_2 receptors
- rebound fenomen

8. Alpha Blockers (Alpha-Adrenoceptor Antagonists)

8b. non - selective α_1 and α_2 sympatholytics

antagonistic effect on both α_1 and α_2 receptors

fentolamine - *reversible effect*
fenoxybenzamine – *irreversible effect*

7. Central-acting antihypertensive agents

7a: Imidazoline receptor agonists

imidazoline receptor - different from α rcp. in medulla
 I_1 in CNS and kidneys, I_2 many other tissues

moxonidin
rilmidenin

\downarrow sympathetic stimulation of cardiovascular system
 \downarrow renin secretion
 \downarrow sympathetic stimulation
 \downarrow vasopressin secretion
CI: pregnancy

8. Alpha Blockers (Alpha-Adrenoceptor Antagonists)

8a. selective reversible α_1 sympatholytics

α_1 antagonists = vasodilation (both arteries and veins)
 \rightarrow periferal vascular resistance
Risk of postural hypotension (1st dose - prazosin)
Initial doselower dose at bedtime

(prazosin)
doxazosin
terazosin

9. Direct vasodilators (potassium channel openers)

MoA: interference with Ca^{++} (decrease of intracellular Ca)
vascular smooth muscle relaxation \rightarrow vasodilation

chronic use – many adverse events (through \uparrow sympathetic stimulation – increase of BP, fluid retention)
NOT monotherapy, only combination with Beta Blockers and diuretics

hydralazine (reflex tachykardia, headache)
minoxidil (T wave changes, hypertrichosis)
diazoxide
nitropruside

10. Ganglionic Blockers

MoA: interfere with neurotransmission within both sympathetic and parasympathetic ganglia
↓ sympathetic vascular tone = vasodilation - ↓ BP

large number of SE
NOT used for chronic hypertension treatment
only for hypert. emergency

(trimetaphan)

SE: excessive hypotension, constipation, urinary retention, dry mouth, histamin release

Special situations in therapy of HT

DM	Acute IHD
Hyperlipidemia	Chronic IHD
Metabolic syndrom	Acute heart failure
Renal disease	Chronic heart insufficiency
Pregnancy	Systolic
Elderly	Diastolic
HT crisis	Acute CVD
emergent, urgent	Prevention of CVD
Perioperative HT	ICHDKK
	Cocaine intoxication

Special situations in therapy of HT

Renal disease

AIM: decrease of proteinuria
RAAS blockade = prevention of nephrosclerosis
(bigger effect than lowering the BP itself)

AIM: BP ~ 130/80 mmHg
usually combination therapy with a diuretic
(creatinine >180 use loop diuretic) or CaB

1st choice:

ACE inhibitors + sartans
drugs of all classes in combination to reach the aim

Antihypertensive therapy the most common combinations

IDEAL FIXED antihypertensive combination

- combination of 2 - 3 drugs with long effect
- once daily
- additional antihypertensive effect via different pathogenetic mechanisms

ACE – inhibitor (AT 1 – blocker) + diuretic

ACE – inhibitor (AT1 – blocker) + CaB

Beta – blocker + diuretic

Beta – blocker + CaB

ACE – inhibitor + CaB + diuretic

Special situations in therapy of HT

Diabetes Mellitus

aim: BP ~ 135/85 mmHg

usually combination therapy

Renoprotective antihypertensives – 1st choice:

ACE inhibitors (sartans)

combination to reach the aim:

CaCB, diuretics in low doses, rilmenidin, betablockers

Special situations in therapy of HT

Pregnancy

BP ≥ 170/110 mmHg (immediate therapy, hospitalization)

Pharmacotherapy BP ≥ 140/90 mmHg

Gestation HT (after 28th week)

Preexisting HT with organic dysfunction

Preexisting HT with gestation HT

other cases with BP ≥ 150/95 mmHg

Pregnancy

Absolute drug CI:

ACEi, sartans (fetus malformation)
Diuretics (in gestational HT, ↓ perfusion of placenta)

Preexisting HT

Therapy as before (according to BP, dose reduction)
Diuretics in the lowest dose, no ACEi, no sartans !!!

Gestational HT

α methyl dopa
Betablockers cardioselective (1. trimester relative CI)
Dihydropyridins, verapamil (cave Mg, hypotension !)
Urapidil
Metoprolol
Nitrates
Labetalol

Special situations in therapy of HT Elderly

AIM: systolic BP ~ 140 mmHg - combination of 2 – 3 drugs
Antihypertensive therapy at the age over 80 yrs =
lowering CV and total mortality (AIM BP ~ 150/90 mmHg)

Special situations in therapy of HT HT crisis

Definition: patient in danger of death, life organs failure

AIM: within 1 hr lowering BP at least 20%
or diastolic BP cca 100-110 mmHg

captopril
isosorbid dinitrate
hospitalization monitoring
parenteral therapy to prevent the organ failure

Emergency therapy according to a situation to prevent life organs failures

metoprolol
nitrates
nitropruside
urapidil
enalapril
furosemide
nimodipine
phenolamine (feochromocytoma)
labetalol

Special situations in therapy of HT Perioperative HT

High risk of complication: BP ≥ 180/110 mmHg

Before the surgery

use antihypertensives individually according BP
in patients with ICHD add betablocker (14 days ahead)

On the day of surgery give morning medication BUT:

withdraw sartans and diuretics (risk of hypotension)
use ½ of the dose of ACE inhibitors

During surgery and after:

Nitrates
Metoprolol
Urapidil
Furosemide

Special situations in therapy of HT Acute IM

AIM: lowering BP ~ 130/80 mmHg analgesic

Drugs:

phentanyl
nitrates (Ntg sublingually)
metoprolol
furosemide
ASA

AIM: lowering BP ~ 130/80 mmHg in chronic IHD

Drugs:

ACEi(sartans)
Betablockers (cardioselective, with mild ISA)
CaCBs with long effect
Diuretics (combination)
Antiaggregants, statins

Special situations in therapy of HT
Acute heart failure

Drugs:

Captopril
Furosemide
Nitrates
Enalapril
Oxygen, elevated position of the chest
Morphine

Special situations in therapy of HT
Chronic heart insufficiency
Systolic
Diastolic

Systolic dysfunction of left ventricle (EF below 40%)

ACEI/S
Diuretics (usually loop..)
Betablockers (metoprolol ret.,
carvedilol, bisoprolol)
Spironolakton, Digoxin
CaCBs not used

Special situations in therapy of HT

Chronic heart insufficiency
Systolic
Diastolic

Diastolic dysfunction of left ventricle (EF normal)

ACEI (sartans)
CaCBs
Betablockers
Diuretics (low doses, thiazides)
Digoxin not used

Drugs causing hypertension

- sympathomimetics
- corticoids
- NSAIDs
- contraceptives
- ..