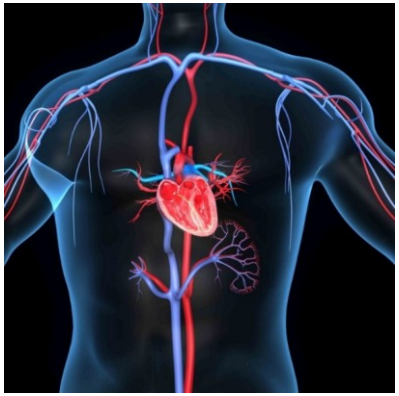
Pharmacotherapy of cardiovascular diseases



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Cardiovascular diseases

= diseases of heart and blood vessels!

- **Are closely connected to other disorders**

(atherosclerosis, dyslipidaemia, obesity, hypertension…)

CVS diseases remain a major health problem and leading cause of death around the world

Pharmacotherapy is usually complex and drugs from many classes are used in combinations

Risk factors

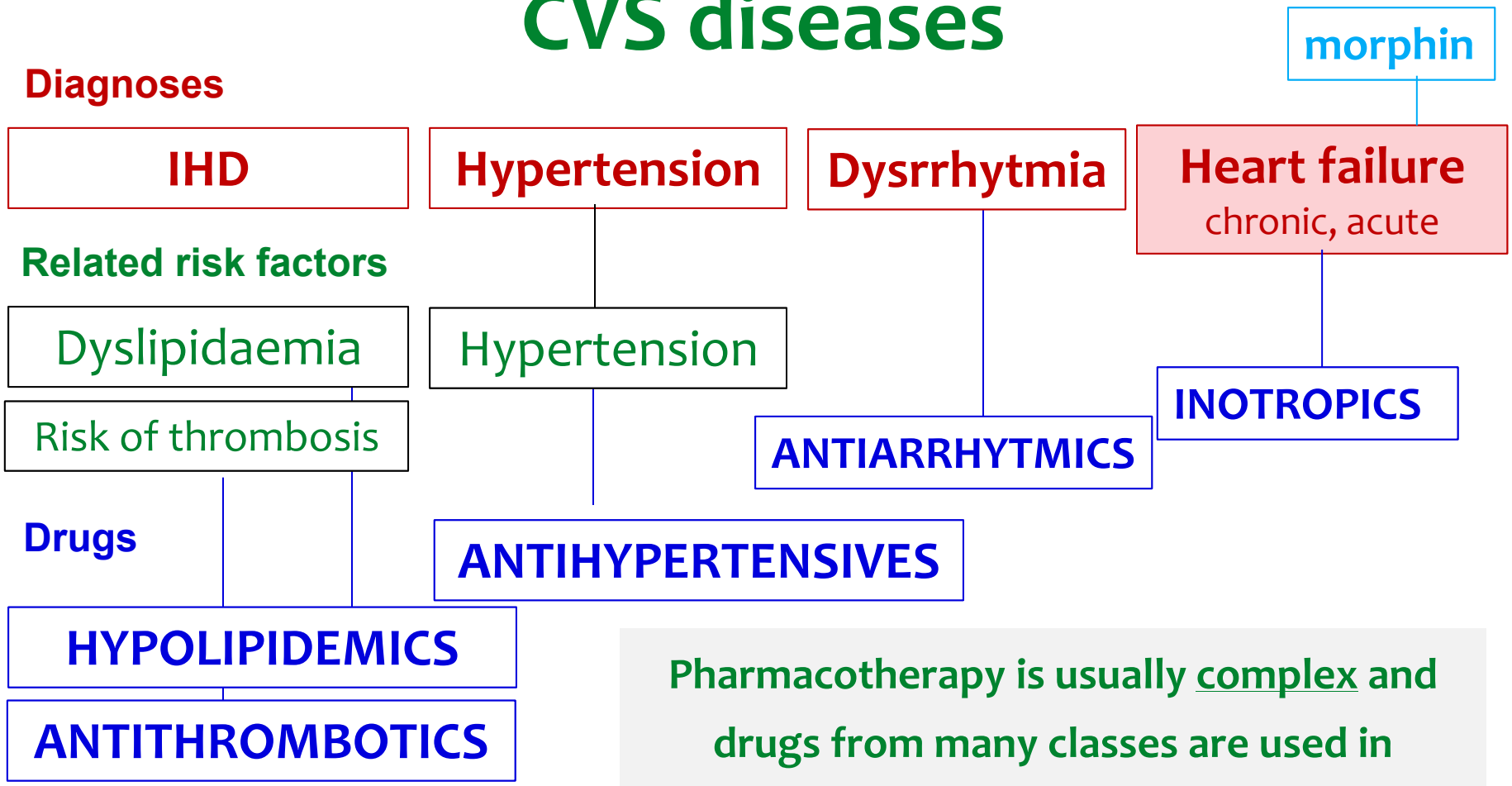
Given: age, gender, genetic disposition

Changeable: atherosclerosis, hypertension, dyslipidaemia/hyperlipoproteinaemia, smoking, diabetes mellitus, obesity, bad eating habits, stress…

Risky are ↑LDL-concentration, ↓ HDL- concentration

It is important do pay attention to those factors, which can be changed

COMPLEX THERAPY of CVS diseases



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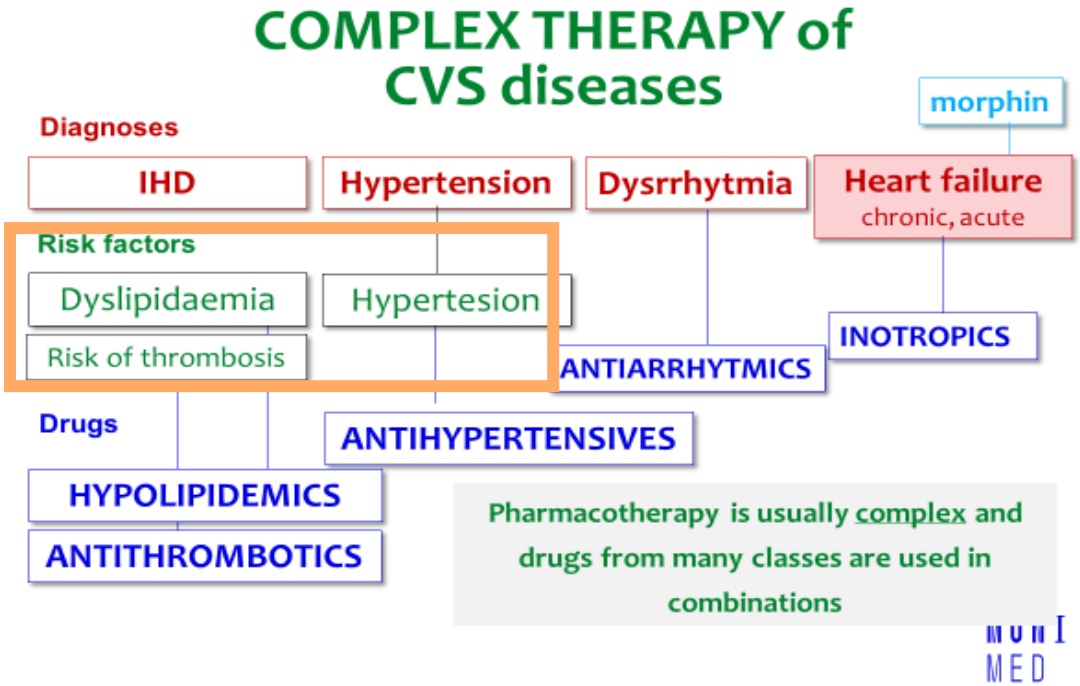

DYSLIPIDEMIA
together with
HYPERTENSION
are the main factors in development of
ATHEROSCLEROSIS

Atherosclerotic plaque obstructs the vessel ⇨ IHD
If ruptured, consequenting thrombus may occlude the vessel ⇨
AMI, stroke

RISK OF THROMBOSIS

ANTITHROMBOTICS

Anticoagulants

Thrombus prophylaxis
(usually in venous vessels)

heparin, nadroparin, dabigatran, apixaban
warfarin

Antiaggregants

Thrombus prophylaxis
(usually in arteries)

ASA, clopidogrel

Fibrinolytics

Dissolution of formed thrombus
(arteries and veins)

alteplase, reteplase

More in the lesson...

DYSLIPIDEMIAS

Some of the most often metabolic disorders

CHOLESTEROL → **Hypercholesterolemia**

TRIGLYCERIDES → **Hypertriglyceridemia**

Combined hyperlipoproteinemia
hyperlipidemia

NON-PHARMACOLOGICAL APPROACH

- Diet regimen with restriction of animal fat
- Healthy life-style (no smoking, regular exercise)

✓ **Primary**
Geneticaly determined

✓ **Secondary**
Result of another disease

HYPOLIPIDEMICS

1. Decreasing plasma CHol (LDL)

- Decrease of intestinal (re)absorption of bile acids/cholesterolu

  RESINS, EZETIMIB
- Inhibition of CH and VLDL synthesis

  STATINS
- Increase density of membrane LDL receptors

  PCSK9 inhibitors

2. Decrease of plasma TG

- Influence synthesis of VLDL and conversion of plasma lipoproteins

  FIBRATES, STATINS (INDIRECTLY)
- Gene therapy 3 x 1012 genome copies of human lipoprotein lipase in a viral vector to treat hyperlipoproteinemia I

  Glybera

1st choice drugs in all types of dyslipidaemia are STATINS!!

STATINS

1st choice drugs in atherosclerosis

MoA – competitive inhibitors of HMG-CoA reductase (*hydroxy methyl glutaryl CoA reductase*) + significant antiinflammatory effect

→ **↑ LDL clearence**

- **pleiotropic (extralipid) statin effects:**
  - antiinflammatory !!!
  - antiaggregant
  - positive effects in endothelial dysfunction

AE: liver disorders: ↑ activity of transaminases and kreatinkinase (monitoring is necessary!)

- **Myalgia, rhabdomyositis** (0,5% of pacients) can lead to rhabdomyolysis and kidney failure

(most often after combination with FIBRATES and CYP3A4 inhibitors)

- **interactions!!**

- ***simvastatin, atorvastatin***
- *lovastatin, fluvastatin, pravastatin, rosuvastatin (long acting)*

FIBRATES

MoA: *agonists of nuclear PPAR-α rec. (peroxisome proliferator-activated receptors)-*

inhibit liver production of VLDL and ↑ catabolism of VLDL

→ decrease export of TG to peripheral tissues

I: isolated hyper TG-emia (when resistant to statin)

AE: nausea, vomiting,
risk of bile stones (↑CH in bile),
myalgia (**dangerous is myositis or rhabdomyolysis)**

fenofibrate

ciprofibrate, bezafibrate

HYPERTENSION

- repeatedly increased blood pressure (BP) 140/90 mm Hg at least at 2 out of 3 measurements taken at least at two separated visits at the doctor

- prevalence in adult population 20-30 %

WHY TREAT HYPERTENSION AS IT IS NOT PAINFUL?

Vessels	Heart	Brain	Kidneys	Retinas
Endothelium dysfunction	AMI, HF	Stroke	Chronic KF	Loss of fuction

Classification of arterial hypertension according to etiology

- **primary (esencial)** – about 95 % of all patients with hypertension; multifactorial disease without identified cause

- **secondary** – disease with identified cause
  - nephrogenic – most often, kidney diseases
  - renovascular – narrowing of renal artery
  - endocrine – adrenal or thyroid glands disease
  - drug-associated hypertension – chronic therapy by corticoids, NSAID, hormonal contraception
  - hypertension in pregnancy

Therapy of arterial hypertension

Aim: BP under 140/90 mm Hg

in patients with ↑ CV risk DM under 130/85 mm Hg

Non-pharmacological approach:

- Lifestyle changes – smoking, alcohol, medications
- Aerobic exercise, no isometric load
- Increase amount of nonsaturated FA, Ca^{++}, K^{+}
- Body weight

Pathophysiological causes

- P=R.Q
- Change in peripheral resistence (R)
- Q – cardiac output
  - Increased circulating volume
  - Increased contractility
  - (Increased heart rate)

Farmacotherapy of hypertension

1. **ACE-inhibitors (ACE-I)**
2. **angiotensin II receptor blockers**
3. **Ca^{++} channel blockers**
4. **diuretics**
5. **betablockers**
6. **renin inhibitors**
7. **drugs acting centrally**
8. **alpha-blockers**
9. **drugs with direct vasodilatant mechanism**

Some of these drug classes are used also in therapy of

- IHD
- Arrytmias
- Chronic HF

ANTIHYPERTENSIVES

- act on three effector locations **(heart, vessels, kidney)**
- influence medium and long-term mechanisms of BP regulation

Drugs inhibiting RAAS

ACE-inhibitory (ACEi)

1st choice drugs

MoA: 1) reversible ACE inhibition
2) bradykinin degradation blockade (vasodilation)

captopril, perindopril

Angiotensin II receptor blockers (sartans)

MoA: Competitive antagonists on AT_1

1st choice drugs

valsartan, losartan

Renin inhibitors (kirens)

2nd choice!

MoA: bind to the active site of renin and inhibit the binding of renin to angiotensinogen, which is the rate-determining step of the RAAS cascade

aliskiren

Common pharmacodynamic effect of ACEi and sartans

- decrease in peripheral vessels resistance
  - (via low AT1 stimulation or ↑ bradykinin)

- decrease intravascular volume

- specific dilatation of vas efferens

- positive glycometabolic effects

- antiproliferative activity

ACEi

Kinetics: liver microsomal metabolisms (enalapril = prodrug)
VARIABILE HALF-LIFE (**captopril vs perindopril**)

AE:
- hypotension, hyperkalemia
- decrease degradation of several small neuropeptides (bradykinin)
  → **dry cough**
- angiooedema

CI:
- pregnancy, breast-feeding
- primary hyperaldosteronism

ACEi

Indications:

- hypertension
- heart insufficiency
- AMI

→ Significant decrease in mortality rate in AMI, CVD

1st choice in:
- state after AMI, CVA
- remodelation of heart and vessels – LV hypertrophy, heart failure
- DM

Sartans
Angiotensin II receptor blockers

Kinetics: variable

AE, indications, CI: the same as ACEi
BUT **NO cough!!**

Losartan, valsartan

Renin inhibitors - kirens

AE:
Hypotension
Diarrhoea
Angiooedema

2nd choice!

aliskiren

We do **not combine** drugs acting on RAAS!
(ACEi+sartans in patients with **diabetic nephropathy**)

Calcium channel blockers

Direct vasodilatants

MoA: specifically block L-channel in heart and vessel muscle cells

Smooth musscle cells
(vessels, bronchi, GIT, uterus)
⇨ **decrease in peripheral resistence**

Electrical conduction system of the heart
(SA, AV node) ⇨ **negative chronotropic and inotropic effect**

Dihydropyridines

affect mostly vessel smooth muscle (= are vasoselective) ⇨ **do not influence myocard, decrease blood pressure**

Antihypertensives
(monotherapy as well as in combinations)

Calcium channel blockers

Direct vasodilatants

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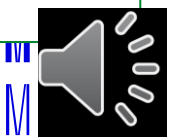
(vessels, bronchi, GIT, uterus)
⇨ **decrease in peripheral resistence**

Electrical conduction system of the heart
(SA, AV node) ⇨ **negative chronotropic and inotropic effect**

Non-dihydropyridines

strong effect also on **electric activity of heart incl coronary vessels**

Antiarrhytmics
Angina pectoris (IHD)



Calcium channel blockers

Dihydropyridines – affect mostly vessel smooth muscle

1.generation - lower vasoselectivity, shorter effect

nifedipin

2.generation - higher vasoselectivity, longer effect

nitrendipin (fast onset), felodipin, isradipin, nisoldipin, nilvadipin, nimodipin

3.generation - antiatherogenic effects, long effect

amlodipin

! **CAVE** – CCB have negative inotropic effect!

- not in decreased function of LV
- not to be combined with other negatively inotropic drugs (BB)

Non-dihydropyridines – strong effect also on electric activity of heart

diltiazem
verapamil

Calcium channel blockers

PK: variable bioavailability
variable half-life (e.g. nifedipin vs. amlodipin – 2 vs. 40 h)
CYP metabolisation

AE: gum hyperplasia
oedema, hypotension, headache
bradykardia (Non-DHP), reflexive tachycardia (DH pyridines)
negative inotropic effects
constipation

I: hypertension
angina pectoris
local vasodilation in interventions (i.a. application)
tachyarytmia (non-dihydropyridines)

CI: AV block, heart failure (verapamil, diltiazem)
tachykardia (DH pyridines)

Diuretics and aldosterone antagonists

- drugs increasing excresion of water and Na+
- act in **tubular system of kidneys**

Carboanhydrase inhibitors/proximal	acetazolamide
Thiazide diuretics/distal	hydrochlorothiazide, indapamid
Loop diuretics	furosemide
Potassium-sparing diuretics	amiloride
Aldosterone antagonists	spironolaktone, eplerenone
Osmotic diuretics	mannitol

Thiazides

Inhibit resorption of Na and Cl in distal tubulus.

⇨ Inhibition of water resorption ⇨ **increased diuresis,** (up to 12 h) + **vasodilation**

Hypotensive effects with delay 3-4 days, full clinical effect (in 3-4 w).

The most often prescribed diuretics (HT, HF).

Insufficient efficacy when impaired kidney function ⇨ **loop diuretics are indicated**

hydrochlorothiazide, indapamide

Loop diuretics

Inhibit co-transport of **Na/K/2Cl** in thick ascending loop of Henle

→ decrease interstitial osmolarity → decrease water reabsoption from lumen → **increased diuresis**

The strongest, short effect **+ vasodilatant efficacy**

Lots of AE: loss of ions (Na, Cl, K, Ca, Mg) , possibly hepato-, nephro-, ototoxic

I: HT, lung oedema, congestive heart failure, hypercalcemia, chronic renal failure

furosemide

ARE VERY EFFECTIVE (even in kidney insufficiency), BUT BIG LOSS OF IONS

Risk of activation of RAAS

Potassium-sparing diuretics
Aldosterone antagonists

Inhibit resorption of Na in collecting ducts

weaker effects, lower loss of K+, suitable for combinations
I: Rezistant hypertension and hyper-aldosteronismus

Increased diuresis
- Na^+ goes out
- K^+ stays in

amiloride
Potassium-sparing diuretic

Aldosterone antagonist
spironolakton

positive effects on remodelation → in heart failure also in monotherapy
AE: gynekomastia, menstruation problems

eplerenon (selective for mineralocorticoid rec)

Carboanhydrase inhibitors / proximal diuretics

Act in proximal tubule

MoA: Inhibit carboanhydrase

⇨ **Increase excretion of Na^+ and water**

⇨ **Urine is more alcalic**

⇨ **Metabolic acidosis**

INDICATIONS:

- glaucoma
- altitude sickness
- metabolic alkalosis
- epilepsy

acetazolamide

Osmotic diuretic

Act in the whole nephron

MoA: cannot be reabsorbed and cause leads to hyperosmolarity of filtrate

INDICATIONS:

- Forced diuresis
- Increased intraocular presuure,
- Acute renal failure

mannitol

Not used in therapy of HT

Diuretics

General characteristic:

Advantages:

usually possible combination with others AHT
potentiation of other AHT effects
no influence on CNS
cheap

Disadvantages:

metabolic effects
low tolerance (in elderly people)

Diuretics

General characteristic:

AE:
potassium depletion (except K^+ sparing)
hyperurikemia (thiazides, loop diuretics)
weakness, nausea
dysbalance in glycid and lipid metabolism (thiazides)
hypovolemia, hypotension (furosemid)
hyperkalemia, hypomagnezemia (amilorid, spironolakton)

CI:
gout (thiazides)
renal failure, hyperkalemia (K+ sparing)
Relative: pregnancy, metabolic syndrome

Diuretics

General characteristic:

AE:

potassium de
hyperurikemi
weakness, na
dysbalance ir
hypovolemia, hypotension (furosemid)
hyperkalemia, hypomagnezemia (amilorid, spironolakton)

All AE are strongly dose-dependent

⇨ If possible, the lowest effective doses are preffered

⇨ Usually combined with other AHT

CI:

gout (thiazides)
renal failure, hyperkalemia (K+ sparing)
Relative: pregnancy, metabolic syndrome

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Diuretics –INDICATIONS

1. HYPERTENSION

- combined therapy (**thiazides, potassium-sparing**)
- kidney failure **(loop diuretics)**
- in resistant hypertension **(Aldosterone antag.)**

2. HEART FAILURE

- Chronic HF **(thiazides, potassium sparing, loop d.)**

3. FORCED DIURESIS
   (loop, osmotic)
4. OEDEMAS (loop, osmotic)
5. HYPERKALCEMIA (loop)

Betablockers

MoA: block **adrenergic reactions** provided by activation of **β receptors** (CV effect mostly by β_1). Act as competitive antagonists of noradrenaline, dopamine and adrenaline.

Antihypertensive effects:

- targeting RAAS (inhibitit release of renin) ⇨ **decrease of volume**
- decrease of HR and cardiac output
- decrease of O2 consumption

} **antiischemic effects**

Final BP levels are reached in 14 days of therapy!!

They have most AE of all 1st choice drugs
(especially in young patients)

Betablockers

- **Lipofility /hydrofility**
- **Selectivity**
- **Parcial agonistic activity**
- **Other effects** (eg . α –rec blockade, direct vasodilatant eff…)

Bradines (ivabradine)
Alternative to betablockers
MoA: Inhibit Na/K chanell (I_f current) in SA node.
Negative chronotropic effect.

Classification by selectivity

NON-SELECTIVE $\beta_1 + \beta_2$ rec

W/O ISA	**sotalol** **timolol** *antiglaucomatic*
WITH ISA	**carteolol** *antiglaucomatic*

Not used in CV therapy

CARDIOSELECTIVE β_1 rec

W/O ISA	**metoprolol** **atenolol** **esmolol** $t_{1/2}$ = 2-10 min.
WITH ISA	**acebutolol**

nebivolol
$t_{1/2}$= 30-50 hod **+ mild vasodilatant**

celiprolol = β_1, α_1, α_2, vasodilatation (β_2 ISA)
labetalol, carvedilol = β_1, β_2, α_1

Beta blockers with combined effects

Apart from β1 and β2 act on

- **α_1- rec, Ca^{2+} channels**
- antioxidant eff.

carvedilol — **I:** hypertension, IHD, HF

labetalol — **I:** severe hypertension (i.v.)
in pregnancy (from the 2. trimester)

Beta-blockers

I: HT
AP
arytmia
chronic heart failure (cave!)
glaucoma, tremor

CI: asthma
AV block
CHOPD (relat.)
bradycardia
DM (relat.)
difficult erection

Abused by athletes!

AE:

Negative influence on lipid and glycid metabolism

- bronchospasm (non-selective)
- disrupted peripheral circulation (non-selective)
- bradyarrhytmia (BB without ISA)
- insomnia, sedation, depression (lipofilic BB)

rebound phenomenon

Beta-blockers

Individual choice of drug:

older	β_1 or with ISA
younger	NS
IHD, AMI	not with strong ISA
IHD, AP	BB generally suitable more than others
DM II.	low doses β_1, with ISA
pregnancy	β_1, alpha+beta
bradycardia under 50	withdraw BB (or with ISA)
heart failure	carve,bisopr,metopr
IDLE	β_1, with ISA, vasodil.
hyperliproteinemia	with ISA
HT during surgery	esmolol

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Farmacotherapy of hypertension

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2. angiotensin II receptor blockers
3. Ca^{++} channel blockers
4. diuretics
5. betablockers

6. **renin inhibitors**
7. **drugs acting centrally**
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Some of these drug classes are used also in therapy of

- IHD
- Arrytmias
- Chronic HF

ANTIHYPERTENSIVES

- act on three effector locations **(heart, vessels, kidney)**
- influence medium and long-term mechanisms of BP regulation

Centrally acting antihypertensives

Imidazoline receptor agonists

imidazoline I_1 receptor in medulla oblongata

I_1- in CNS and kidney
I_2- pain modulation, neuroprotection
I_3 - insulin secretion

Unlike central α_2-agonists
- **DO NOT CAUSE** sedation
- rebound fenomenon

↓ heart + vessels + kidney stimulation by sympathetic NS
↓ renin and vasopressin secretion
great positive effect on glycaemia and insulin resistance

moxonidine
rilmenidine

Centrally acting antihypertensives

Central α_2 agonists

α –metyldopa – false precursor of NA + α_2 stimulation
Indicated in **pregnancy**

clonidine - α2 stimulation, sedation, strong **rebound phenomenon**
Indicated in **hypertension crisis (ICU)**

Central α2 agonist + peripheral α1 antagonist

urapidil – very strong anti HT

Alpha blockers

- selective reversible α_1-lytics
- no effect on $\alpha_2$rcp. – do not increase NA
- advantageous effects in prostate hyperplasia

AE: postural hypotension especially after 1st dose (prazosin)
→ start with lower dose given in the evening before sleep

I: monotherapy in **BHP**
combination in **hypertension**

prazosin
doxazosin
terazosin

urapidil

Direct vasodilatators

Calcium channel blockers were discussed earlier

Nitrates

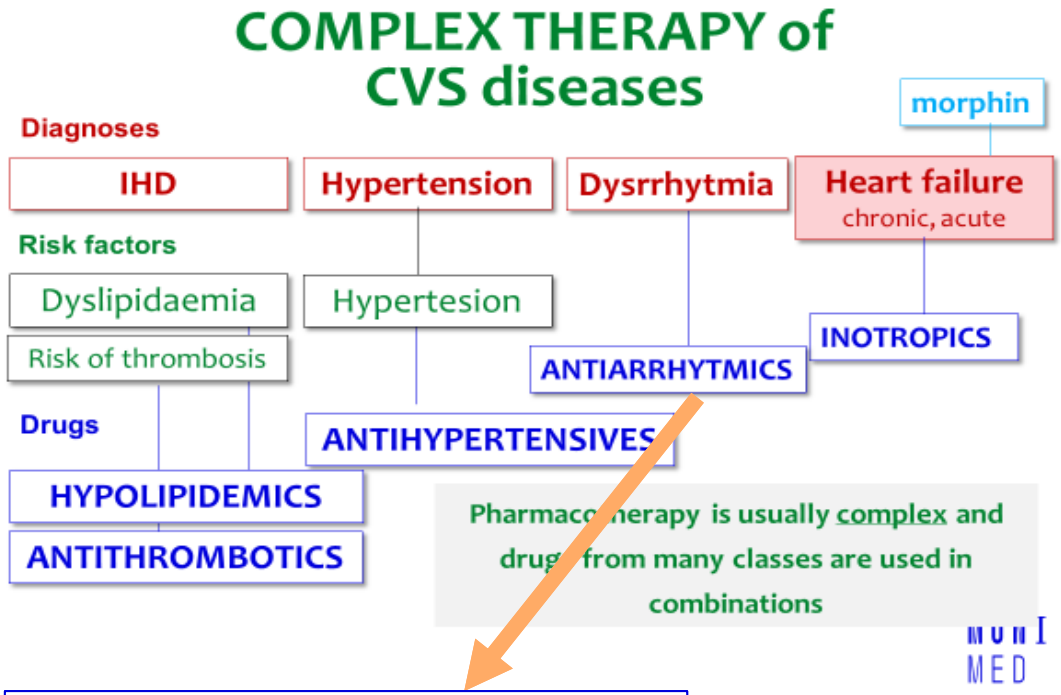
1st choice in angina pectoris, ↓ chronic efficacy

Using free SH- groups (from glutathion) they cause release of NO in endothelium (EDRF)
→ vasodilation
→ antithrombotic action

AE: Tachyphylaxis!, headaches, orthostatic hypotension

nitroglycerine – for acute attacks
natrium nitroprusside - for acute attacks
isosorbid dinitrate (ISDN) – infusion in HT crisis, prophylaxis
isosorbid 5-mononitrate (ISMN) – active metabolite, chronic AP

molsidomin – different structure, fibrinonolytic
minoxidil – vasodilatatory and prevention of hair loss



1. Classification by Vaughan-Williams

Classes I. (A,B,C) II, III, IV

2. Others AA

Catecholamines, digoxin, atropine,……

ANTIARRHYTMICS

Drugs, which DIRECTLY or UNDIRECTLY affect electrophysiological processes on membranes, thus influecing generation and lenght of action potential.

ANTIARRHYTHMIC DRUG CLASS	DRUG	PRIMARY MECHANISM OF ACTION*
Class IA	Quinidine, procainamide, disopyramide	Na^+ channel blocker, prolongs action potential duration (APD)
Class IB	Lidocaine, mexiletine	Na^+ channel blocker, rapid dissociation
Class IC	Flecainide, propafenone	Na^+ channel blocker, slow dissociation
Class II	Propranolol, sotalol, esmolol	β Adrenergic blocker
Class III	Amiodarone, sotalol, ibutilide, dofetilide, dronedarone	Prolongs APD (primarily by K^+ channel blockade)
Class IV	Verapamil, diltiazem	Ca^{2+} channel blocker (nondihydropyridine)
Miscellaneous	Adenosine	Adenosine receptor agonist
Miscellaneous	Digoxin	Na^+, K^+-ATPase inhibitor

Amiodarone -

MoA: K^+ ion channels block

ADVERSE EFFECTS

Dose-depentent frequency

1. MoA

- navození převodních poruch
- negative inotropic eff.

2. Specific AE

- fotosenzitisation (10%)
- irreversible lung fibrosis

3. Effects on thyroid

- **HYPOTHYREOSIS** (10%)
- **THYREOTOXIKOSIS** (rare)

INDICATION

- Prophylaxis of fibrilation or flutter of atrium (in CHF)
- Pharmacological cardioversion of fibrilation or flutter of atrium

Highly lipofilic ⇨ **accumulates in liver and body fat**

Very long half-life

Lots of interactions *(P-glp., CYP)*

Digoxin – Heart glycoside
kardiotonic + antiarrhytmic drug

INDICATION:

- CHF (positive inotropic eff)
- Arrhytmia (atrial fibrillation with fast response)

- **Activates parasympaticus via nervus vagus** ⇨ antiarrhytmic effects ⇨ **negative chronotropic eff**
- **Inotropic effect** is caused by inhibition of **Na/K ATP-ase pump** ⇨ **positive inotropic eff**

Narrow therapeutic window (TDM)

Large volume of distribution

Renal elimination

Lots of interactions *(P-glp.)*

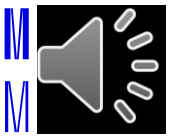
AE: inhibiction of Na/K pump in **myocardium, CNS and GIT**

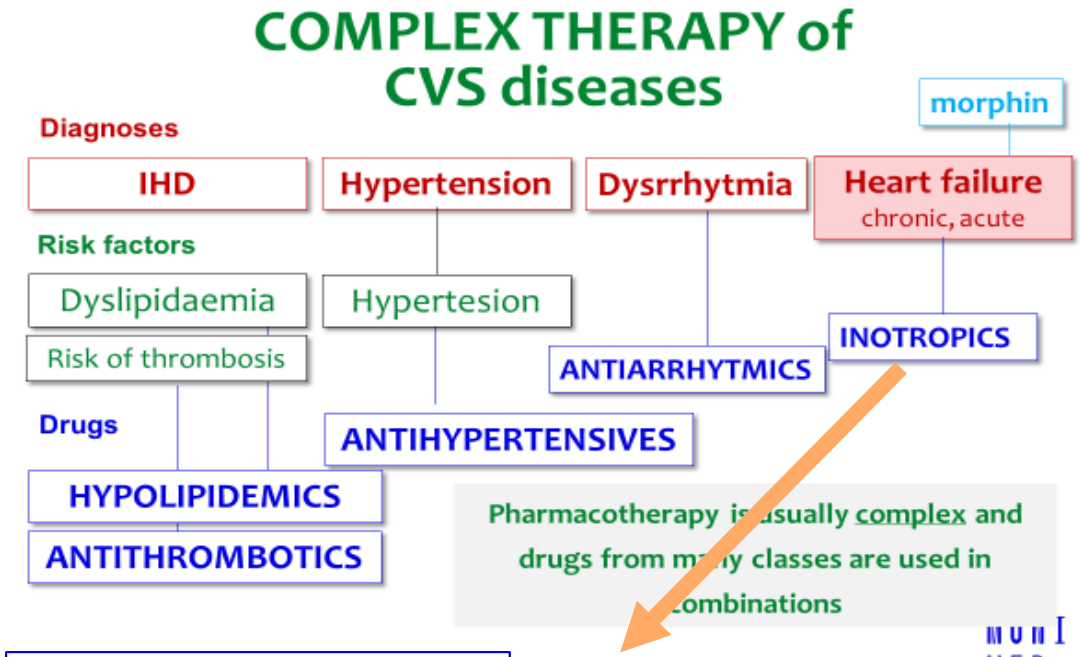
AV blockades, sinus bradycardia, excitability

Digitalis intoxication

Weakness, depression, halucinations, yellow color perception

Nauzea, vomiting, diaorrhea, sweating





INOTROPICS

DRUGS WITH POSITIVE INOTROPIC EFFECT

Heart glycosides (cardiotonics)

DO NOT INCREASE FREQUENCY

Chronic HF

Catecholamines

Inhibitors of PDE-3

Calcium sensitisers

INCREASE FREQUENCY, EXCITABILITY AND CONDUCTION

Acute HF

INOTROPICS

DRUGS WITH POSITIVE INOTROPIC EFFECT

Heart glycosides (cardiotonics)

digoxin

MoA: inhibition of **Na/K ATP-ase pump** ⇨ influx of Ca^{2+} into sarcoplasma

Catecholamines

adrenaline, dobutamine, noradrenaline, dopamine

MoA: stimulation of β rcp. ⇨ indirect effect on Ca^{2+} influx

Inhibitors of PDE-3

milrinone

MoA: specific blockade of phosphodiesterase -3 in myocardium ⇨ bloc degradation of cAMP ⇨ **cardiostimulation**

Calcium sensitisers

levosimendan

MoA: strogner binding of myofilaments to troponin C ⇨ **increased contractility**

Conclusions

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Pharmacotherapy of hypertension

1. **Non-pharmacological approach**

2. **Hypertension is often accompanied by other CV diagnoses** (combined therapy)

3. **Antihypertensives of the 1st choice, alone, or in combinations**
   - ⇨ RAAS Inhibitors
   - ⇨ Ca channels blockers
   - ⇨ Diuretics, betablockers….

Pharmacotherapy of IHD

(dyslipidemia, hypertension, obesity, DM2, thrombosis prevention)

⇨ **NITRATES and NO donors**
⇨ **Dihydropyridines** (in case of present hypertension)

Decreasing metabolic demands of the heart

- **decrease of workload** (negative chronotropic, dromotropic ef)
- **prolong oxygen delivery to myocardium** (longer diastole)

→ **slower frequency and conduction**

⇨ **BETABLOCKERS**
⇨ **Non-dihydropyridines**

Pharmacotherapy of chronic HF

1. **Decrease water retention** → **DIURETICS**
   Inhibition of RAAS

2. **Decrease myocardium remodelation** → **ACEi, sartans**, **Aldosterone antag.**

3. **Increase myocadrium contractility ⇨** **digoxin**

4. **Decrease peripheral resistence ⇨** **Vasodilatants**

5. **Optimalisation of frequency and sympathetic activity ⇨** → **Beta blockers**

6. **Therapy of arrhytmias** → **digoxin, amiodarone**

Pharmacotherapy of acute HF

1. Acute oedemas⇨ **DIURETICS – furosemide i.v.**

2. Hypertension crisis ⇨ **Vasodilatants – nitroglycerin i.v., ISDN**

3. Severe systemic HYPOTENSION ⇨ **noradrenaline i.v.**

4. Increasing CONTRACTILITY of MYOCARDIUM ⇨ **Positively inotropic drugs levosimendan, dopamine, dobutamine**

5. ARRHYTMIAS ⇨ **Choose of AA according to the type of dysrrhytmia**

Often are surgical solutions of acute dysrrhytmias.
Important is prevention.

Thank you for your attention