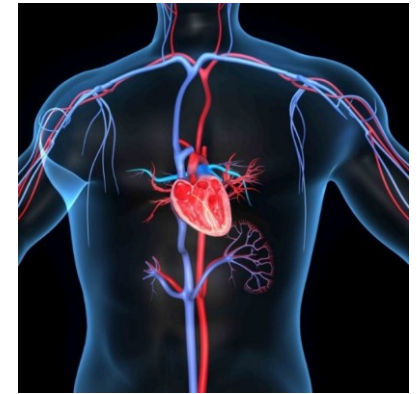


Pharmacotherapy of cardiovascular diseases



□ MUDr. Alena Máchalová, Ph.D., Department of Pharmacology

Tato prezentace je autorským dílem vytvořeným zaměstnanci Masarykovy univerzity.
Studenti předmětu ZLFA0722p mají právo pořídit si kopii prezentace pro potřeby vlastního studia



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

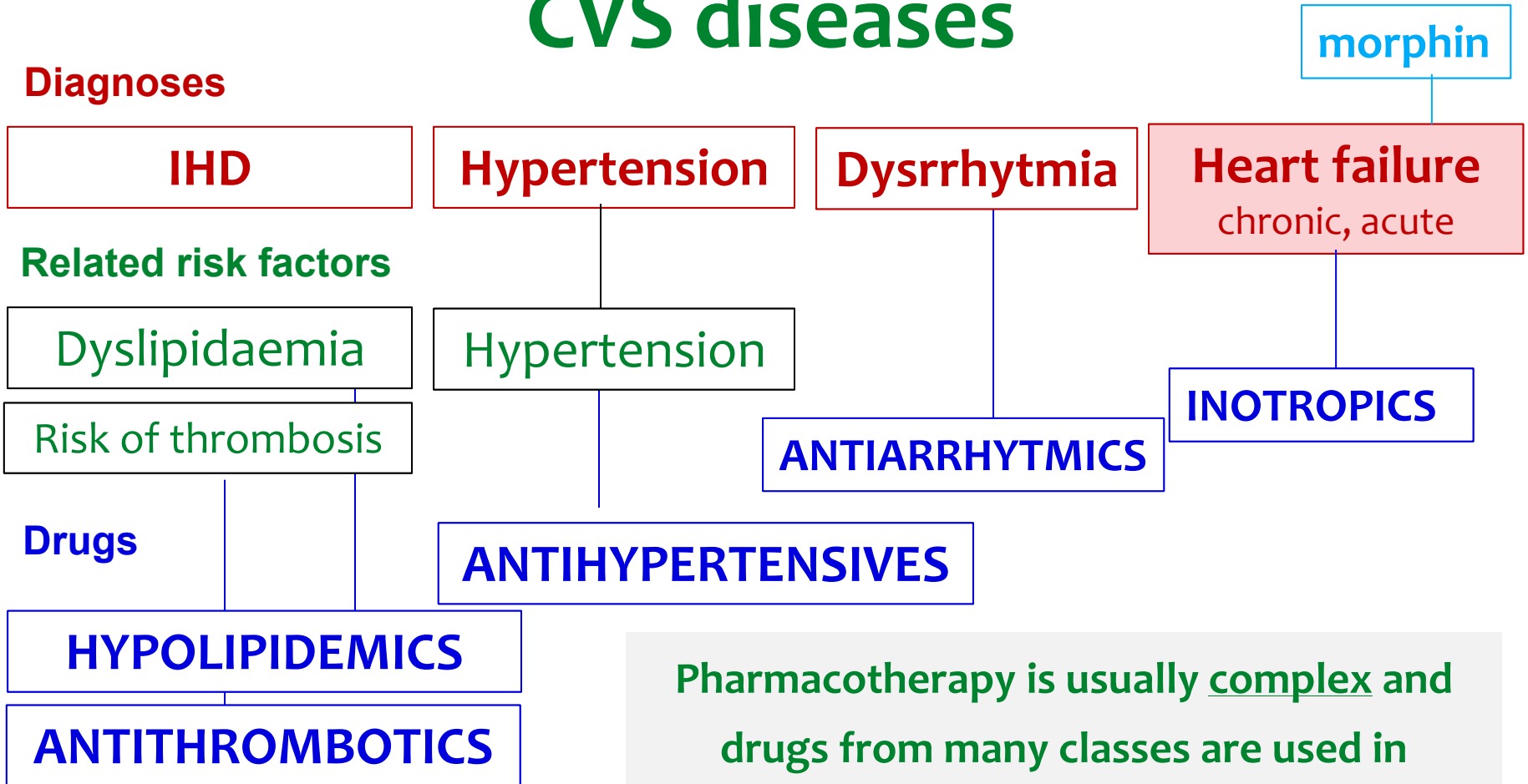
Changeable: atherosclerosis, hypertension, dyslipidaemia/hyperlipoproteinaemia, smoking, diabetes mellitus, obesity, bad eating habits, stress...

Risky are \uparrow LDL-concentration, \downarrow HDL- concentration

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



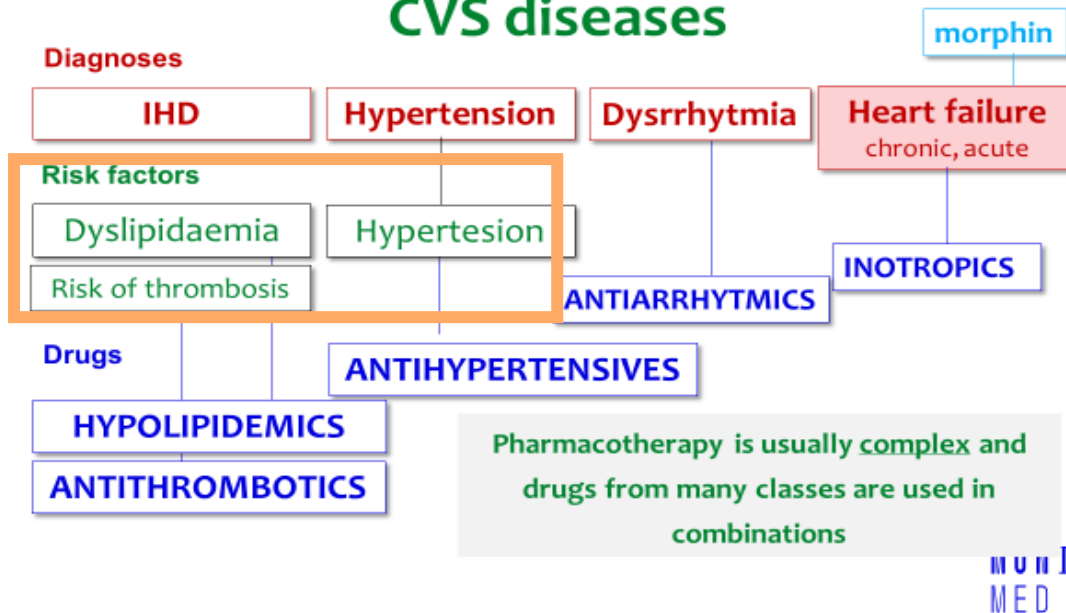
COMPLEX THERAPY of CVS diseases



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



COMPLEX THERAPY of CVS diseases



DYSLIPIDEMIA

together with

HYPERTENSION

are the main factors
in development of

ATHEROSCLEROSIS



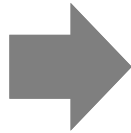
Atherosclerotic plaque obstructs the vessel ⇒ **IHD**

If ruptured, consequent 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)

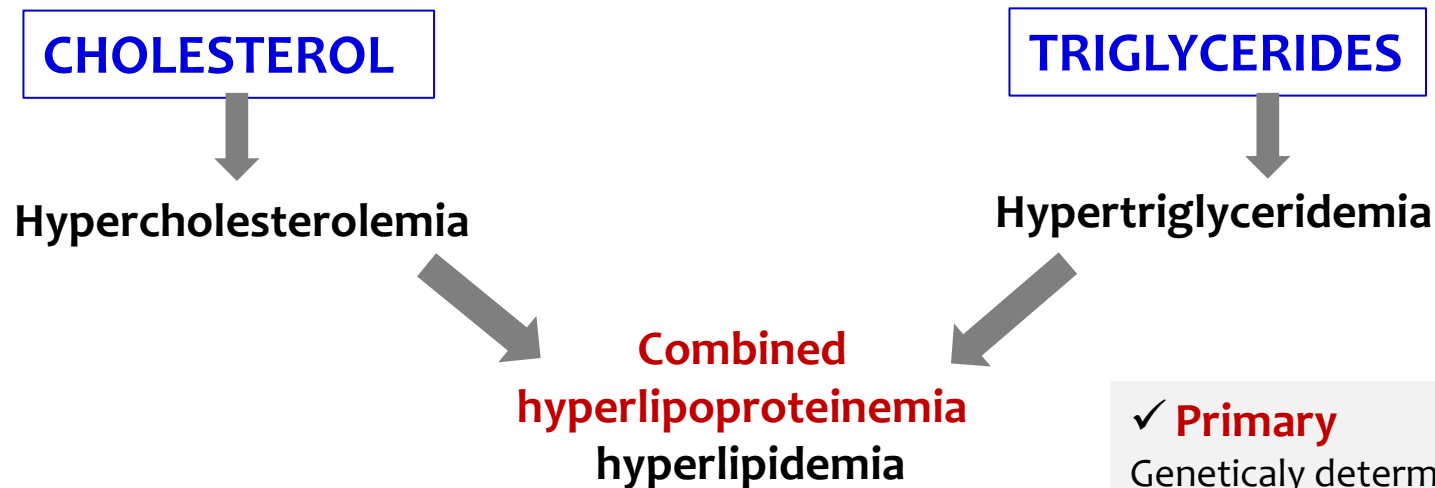
alteplase, reteplase

More in the lesson...



DYSLIPIDEMIAS

Some of the most often metabolic disorders



NON-PHARMACOLOGICAL APPROACH

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

- ✓ **Primary**
Genetically determined
- ✓ **Secondary**
Result of another disease



HYPOLIPIDEMICS

1. Decreasing plasma CHol (LDL)

- Decrease of intestinal (re)absorption of bile acids/cholesterol
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 drug in all types of dyslipidaemia are STATINS!!



STATINS

1st choice drug in atherosclerosis

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

→ ↑ LDL clearance

▪ **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 patients) 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 \uparrow catabolism of VLDL
 \rightarrow decrease export of TG to peripheral tissues

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

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

fenofibrate

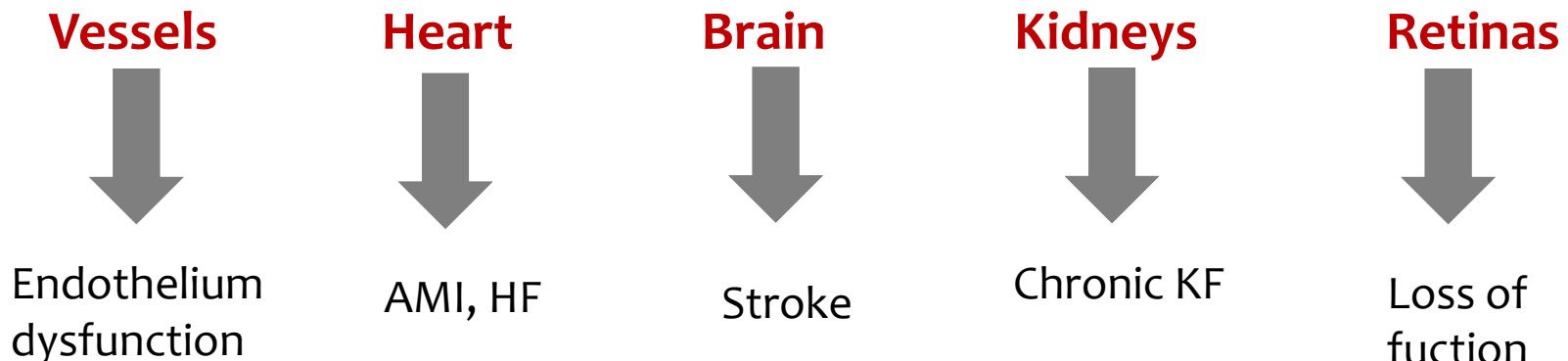
ciprofibrate, bezafibrate



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?



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 \uparrow 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 resistance (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 vasodilant 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



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 AT₁

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 \uparrow bradykinin)
- decrease intravascular volume
- specific dilatation of vas efferens
- positive glycometabolic effects
- antiproliferative activity



ACEi

Kinetics: liver microsomal metabolisms (enalapril = prodrug)
VARIABLE 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
- remodeling 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
vasodilators

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

Smooth muscle cells
(vessels, bronchi, GIT, uterus)
⇒ **decrease in peripheral
resistance**

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
vasodilators

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

Smooth muscle cells
(vessels, bronchi, GIT, uterus)
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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

Antiarrhythmics
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 metabolism
- AE:** **gum hyperplasia**
oedema, hypotension, headache
bradycardia (Non-DHP), reflexive tachycardia (DH pyridines)
negative inotropic effects
constipation
- I:** hypertension
angina pectoris
local vasodilation in interventions (i.a. application)
tachyarrhythmia (non-dihydropyridines)
- CI:** AV block, heart failure (verapamil, diltiazem)
tachycardia (DH pyridines)



Diuretics and aldosterone antagonists

- drugs increasing excretion 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).

hydrochlorothiazide, indapamide

Insufficient efficacy when
impaired kidney function ⇒
loop diuretics are indicated

Loop diuretics

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

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

The strongest, short effect

+ vasodilant 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: Resistant hypertension and hyper-aldosteronismus

amiloride
Potassium-sparing diuretic

Aldosterone antagonist
spironolaktone

Increased diuresis

- Na⁺ goes out
- K⁺ stays in

positive effects on remodelation → in heart failure also in monotherapy
AE: gynecomastia, 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



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 depletion

hyperurikemia

weakness, nausea

dysbalance in

hypovolemia, hypotension (furosemid)

hyperkalemia, hypomagnezemia (amilorid, spironolakton)

All AE are strongly dose-dependent

⇒ If possible, the lowest effective doses are preferred

⇒ Usually combined with other AHT

CI:

gout (thiazides)

renal failure, hyperkalemia (K⁺ sparing)

Relative: pregnancy, metabolic syndrome

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 (inhibit release of renin) \Rightarrow **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	WITH ISA	carteolol
	timolol <i>antiglaucomatic</i>		<i>antiglaucomatic</i>

Not used in
CV therapy

CARDIOSELECTIVE β_1 rec

W/O ISA	metoprolol	WITH ISA	
	atenolol		acebutolol
	esmolol $t_{1/2} = 2-10$ min.		nebivolol $t_{1/2} = 30-50$ hod + mild vasodilatant

celiprolol = $\beta_1, \alpha_1, \alpha_2$, vasodilatation (β_2 ISA)

labetalol, carvedilol = $\beta_1, \beta_2, \alpha_1$



Beta blockers with combined effects

Apart from β_1 and β_2 act on

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

carvedilol

!: hypertension, IHD, HF

labetalol

!: 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)
- bradyarrhythmia (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

Farmacotherapy of hypertension

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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 I₁ receptor in medulla oblongata

I₁- in CNS and kidney

I₂- pain modulation, neuroprotection

I₃- insulin secretion

↓ heart + vessels + kidney stimulation by sympathetic NS

↓ renin and vasopressin secretion

great positive effect on glycaemia and insulin resistance

Unlike central α_2 -agonists

- **DO NOT CAUSE** sedation
- rebound phenomenon

moxonidine

rilmenidine



Centrally acting antihypertensives

Central α_2 agonists

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

clonidine - α_2 stimulation, sedation, strong **rebound phenomenon**
Indicated in hypertension crisis (ICU)

Central α_2 agonist + peripheral α_1 antagonist

urapidil – very strong anti HT



Alpha blockers

- selective reversible α_1 -lytics
- no effect on α_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 vasodilators

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

sodium nitroprusside - for acute attacks

isosorbid dinitrate (ISDN) – infusion in HT crisis, prophylaxis

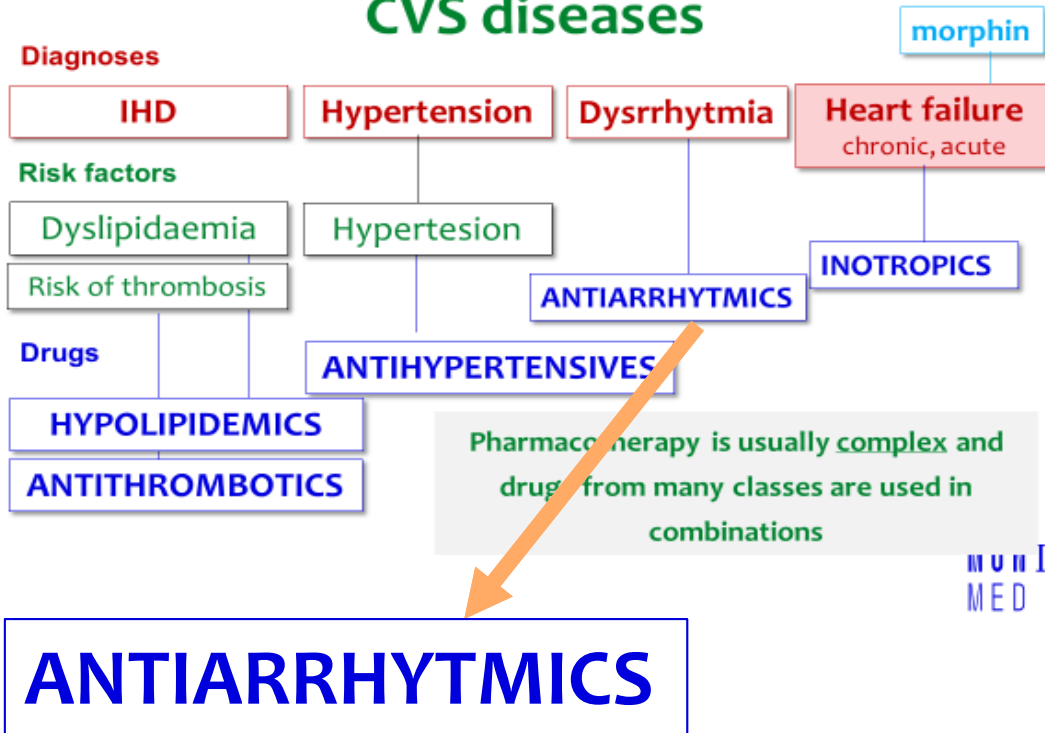
isosorbid 5-mononitrate (ISMN) – active metabolite, chronic AP

molsidomin – different structure, fibrinolytic

minoxidil – vasodilatatory and prevention of hair loss



COMPLEX THERAPY of CVS diseases



1. Classification by Vaughan-Williams

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

2. Others AA

Catecholamines, digoxin, atropine,.....

Drugs, which DIRECTLY or INDIRECTLY affect electrophysiological processes on membranes, thus influencing generation and length 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-dependent 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 fibrillation or flutter of atrium (in CHF)
- Pharmacological cardioversion of fibrillation 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 + antiarrhythmic drug

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

INDICATION:

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

Narrow therapeutic window (TDM)

Large volume of distribution

Renal elimination

Lots of interactions (P-g/p.)

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

AV blockades, sinus bradycardia, excitability

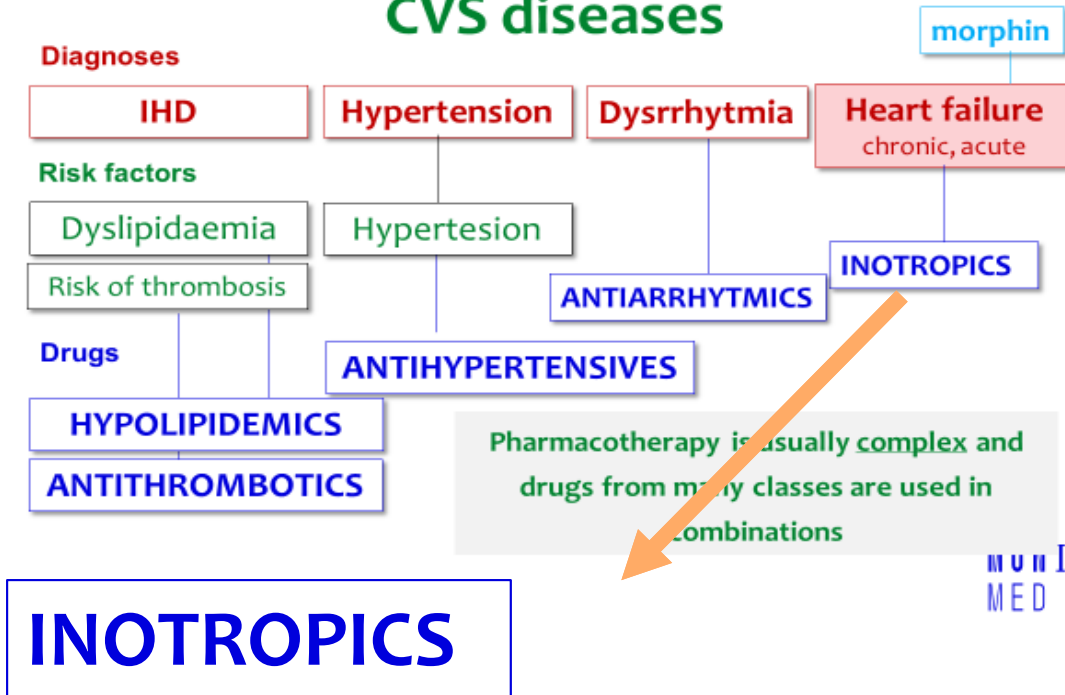
Digitalis intoxication

Weakness, depression, hallucinations, yellow color perception

Nausea, vomiting, diarrhoea, sweating

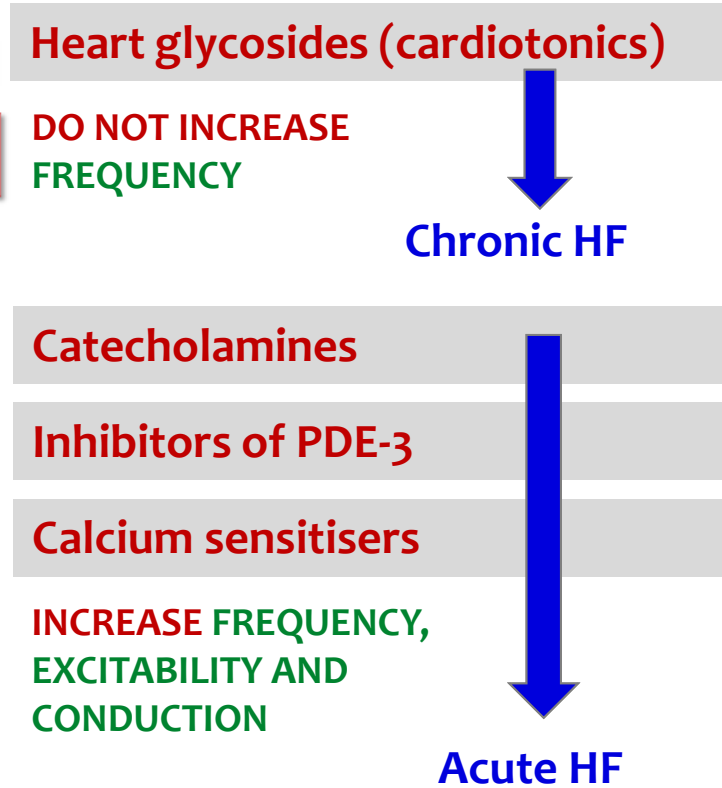


COMPLEX THERAPY of CVS diseases



INOTROPICS

DRUGS WITH POSITIVE INOTROPIC EFFECT



MUM I
MED



INOTROPICS

Heart glycosides (cardiotonics)

digoxin

Catecholamines

adrenaline, dobutamine,
noradrenaline, dopamine

Inhibitors of PDE-3

milrinone

Calcium sensitisers

levosimendan

DRUGS WITH POSITIVE INOTROPIC EFFECT

MoA: inhibition of Na/K ATP-ase pump \Rightarrow influx of Ca^{2+} into sarcoplasm

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

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

MoA: stronger binding of myofilaments to troponin C \Rightarrow **increased contractility**



Conclusions

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

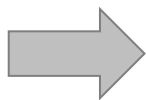
(dyslipidemia, hypertension, obesity, DM2, thrombosis prevention)

⇒ **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)



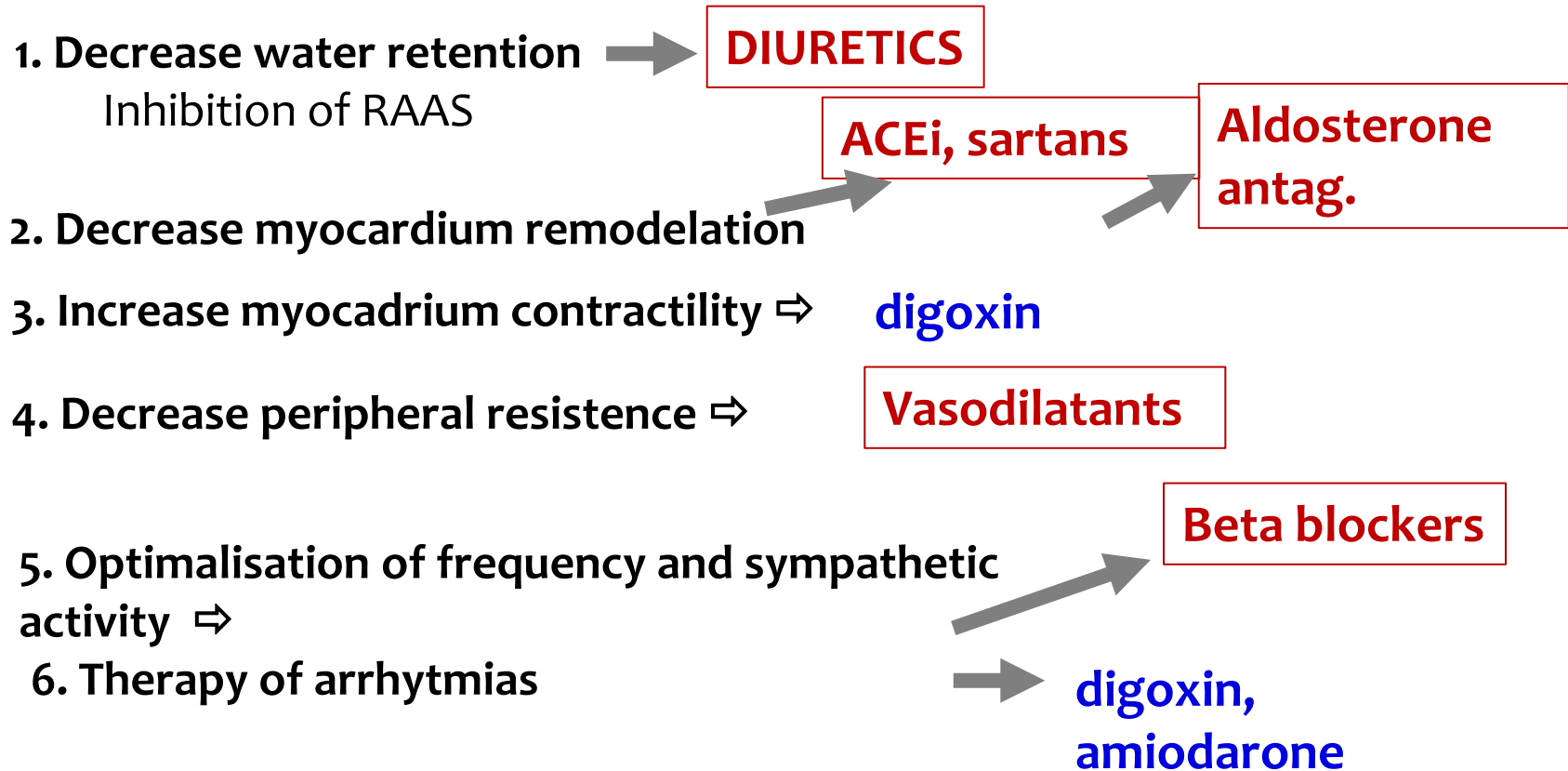
slower frequency
and conduction

⇒ **BETABLOCKERS**

⇒ **Non-dihydropyridines**



Pharmacotherapy of chronic HF



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. ARRHYTHMIAS ⇒

**Choose of AA according to the type of
dysrrhythmia**

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



Thank you for your attention

