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DRUGS USED IN HEART FAILURE, ANTIARRHYTHMICS

Heart Failure

Vital organs chronically suffer from inadequate blood perfusion (caused by dysfunction of the myocard of ventricles due to various diseases)…

ACUTE

- ✓ de novo
- ✓ decompensation of CHF

Acute Coronary Syndroma (AIM…)

- ✓ pulmonary oedema
- ✓ cardiogennic shock

Hypertension crisis

Acute arrhytmia…..

right, left ventricles

CHRONIC

- **Ischaemic Heart Disease**
- Cardiomyopathy
- Arterial hypertension
- Severe dysrrhytmias
- myocarditis

Systolic failure

(decreased contractility)

Diastolic failure

(more often in older patients)

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Heart Failure

Cardiac output CO = **Stroke volume SV** x **Heart rate HR**

Decreased CO…. ↓ SV or ↓ HR

Primary compensation by ↑ HR… leads to ↑ metabolic demand…vicious circle

Factors influencing SV…

Preload → **= fiber length-dependent activation…tension of the heart muscle before contraction (EDV)**

Afterload → **= Resistance to which the heart must pump blood**

Contractility → **= cardiac contractility (inotropy)**

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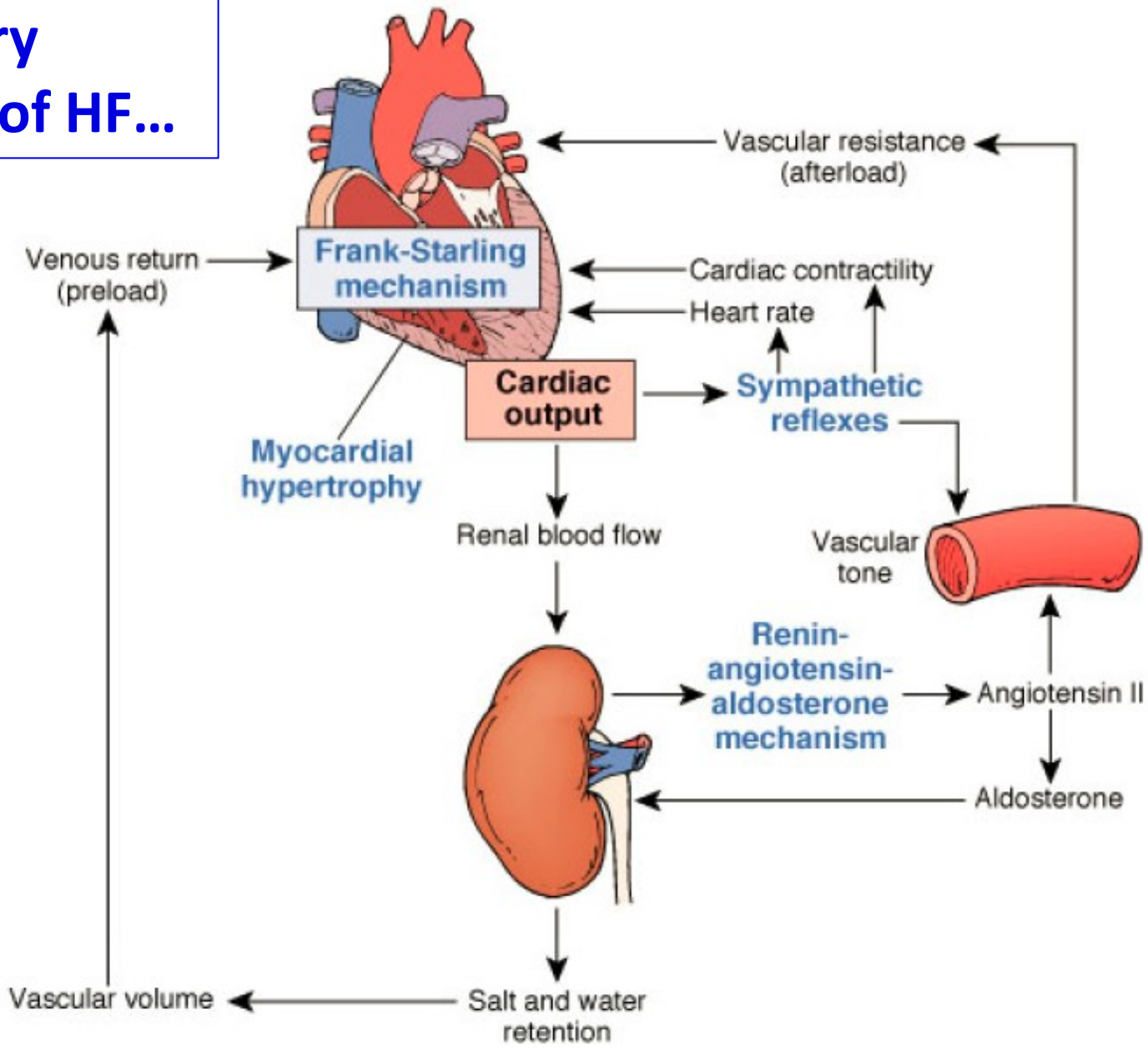
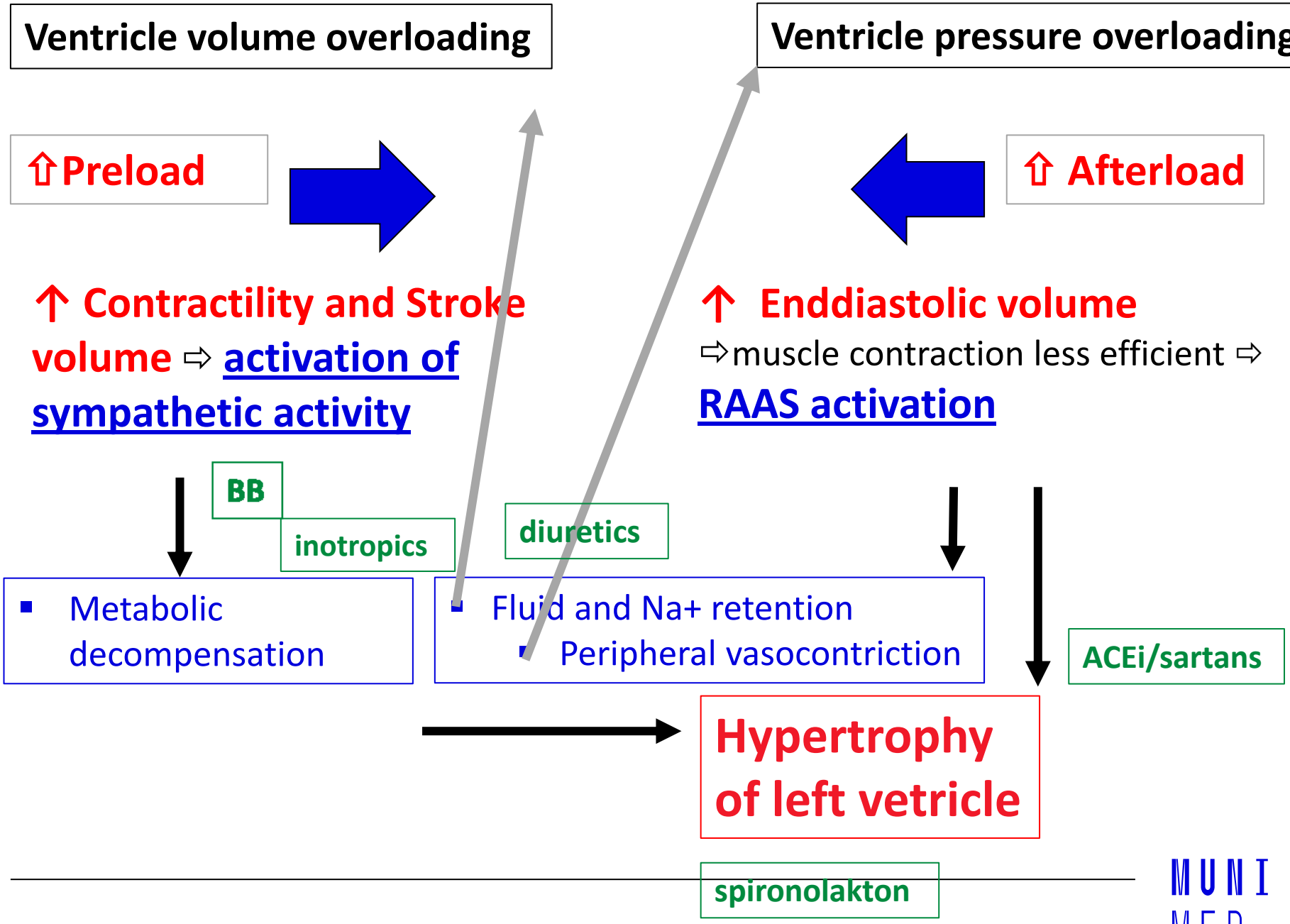
Compensatory mechanisms of HF…




Ventricle volume overloading
Ventricle pressure overloading
⇧Preload
⇧ Afterload
↑ Contractility and Stroke volume ⇨ activation of sympathetic activity
↑ Enddiastolic volume
⇨muscle contraction less efficient ⇨
RAAS activation
BB
inotropics
diuretics
Metabolic decompensation
Fluid and Na+ retention
Peripheral vasocontriction
ACEi/sartans
Hypertrophy of left vetricle
spironolakton

CHRONIC
HEART FAILURE

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Clinical symptoms…

- Shortness of breath (at rest or exertion)
- Fatigue
- Oedema

STAGE	DISABILITY
CLASS 1 MILD	No symptoms Can perform ordinary activities without any limitations
CLASS 2 MILD	Mild symptoms - occasional swelling Somewhat limited in ability to exercise or do other strenuous activities
CLASS 3 MODERATE	Noticeable limitations in ability to exercise or participate in mildly strenuous activities Comfortable only at rest
CLASS 4 SEVERE	Unable to do any physical activity without discomfort Some HF symptoms at rest

- tachycardia
- tachypnoe
- peripheral oedema
- hepatomegaly

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ACEi /sartans

RAAS inhibition

⇨ **affect heart remodelation**

⇨ **↓ vascular resistance**

(↓ volume + vasodilatation)

↓ preload

↓ afterload

THE DRUG OF FIRST CHOICE FOR HEART FAILURE

ARNI

Valsartan + sakubitril (inhibitor of neprilisin)

Nesiritide je rekombinant human natriuretic peptid type B

.

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Beta-blockers

Decreased sympathetic activity (indicated only in patients with compensated HF)

or **Bradins** ⇩ **SF**

⇩ **dromotropic effect**
⇩ **chronotropic effect**

The pacient have to be haemodynamically stabilised before BB teratment. Start with low dose, that incease if tolerated (1-2 weeks interval)

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Aldosteron – antagonists

- **Antagonists of AR**
- **Inhibit fibroblast proliferation**

Second line tretament (ACEi a BB as firt choice) – some RCT show decreased mortality (low dose add-on therapy)

spironolakton

Not combine with other potassium- sparing diuretics

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Drugs with positive inotropic effect

↑ contractility (inotropy)

1. ↑ Ca^{2+} v sarcoplasma

⇨ ↑ Ca^{2+} influx

Cardiotonics

⇨ beta-receptor stimulation

Katecholamins

⇨ signaling pathway interference

PDE-3 inhibitors

2. ↑ binding of troponin C to the action of Ca^{2+}

Calcium sensitizers

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ACUTE
HEART FAILURE

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ACUTE HEART FAILURE

Acute Coronary Syndroma

- ✓ pulmonary oedema
- ✓ cardiogenic shock

Hypertensive crisis

Acute arrhytmia

Acute myocarditis
cardiomyopathy
Aortic dissection
Acute valvular regurgitation...

Acute oedema

Strong diuretics – **furosemid** *i.v.*
Bolus, continual infusion

Hypertensive crisis

Nitrates (**nitroglycerin** *i.v.*) – BP monitoring !!

↑ contractility

Inotropics
levosimendan
dopamin ⇨ vasocontrction - incease BP + renovascular vasodilatation
dobutamin

Severe systemic hypotension

norepinephrin i.v.

Antiarrhytmics

beta blockers
amiodaron
digoxin

Cardial Intervention

PTCA, PCI (angioplasty, stents)

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DIURETICS and aldosteron antagonists

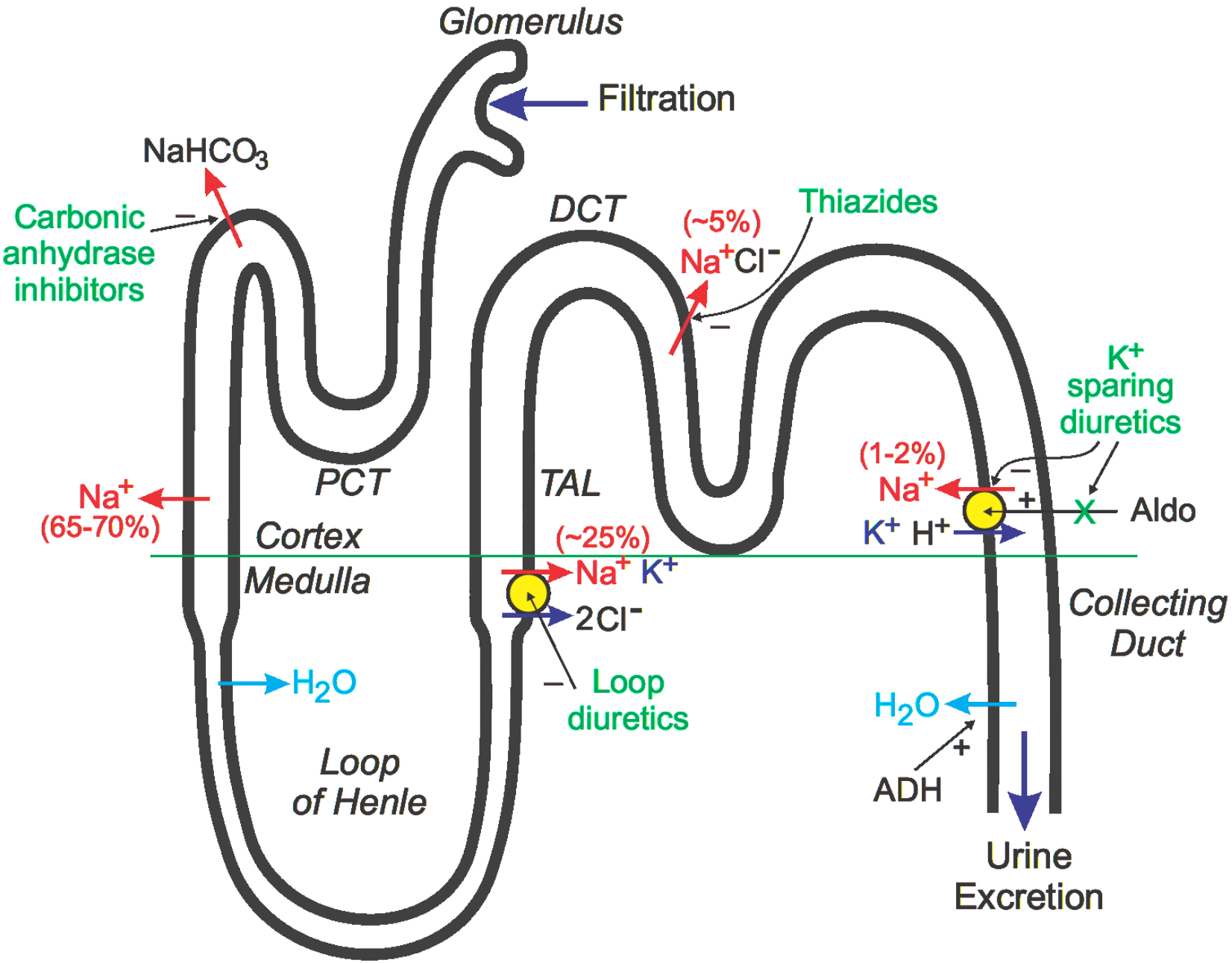
DIURETICS

Mechanism of antihypertensive action:

- decrease in plasma volume
- decrease in peripheral resistance
- vasodilatation

- act via several mechanisms directly in kidney on different parts of nephron:

proximal tubules
ascending limb of Henle loop
distal tubules
collecting ducts


Glomerulus
Filtration
NaHCO3
Carbonic anhydrase inhibitors
DCT
(~5%) Na+Cl-
Thiazides
K+ sparing diuretics
(1-2%) Na+
Aldo
K+ H+
Na+ (65-70%)
PCT
TAL
Cortex
Medulla
(~25%) Na+ K+
2Cl-
Collecting Duct
H2O
Loop diuretics
Loop of Henle
H2O
ADH
Urine Excretion

CLASSIFICATION

- **THIAZIDES** (distal tubules)
- **LOOP DIURETICS**
- **POTTASIUM-SPARING DIURETICS**

  ALDOSTERON RCP: ANTAGONISTS

- **CARBOANHYDRASE INHIBITORS** (proximal tubulus)
- **OSMOTIC DIURETICS**

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Thiazides (distal tubules)

MECHANIS OF ACTION

Cl^-/Na^+ symport inhibition in distal tubules. Inhibition of Na^+ resorbtion ⇨ inhibition of H2O reabsorbtion ⇨ ↑ diurhesis

Na^+ transport capacity in distal tubulus (5-8%) ⇨ lower diuretic effect

- if ↓ GFR 0,5ml/s…loop diuretics indicated
  slow onset af antihypertensive effect

PK

- well absorbed, excreted in proximal tubules
- diuretic effect lasts up to 12 hours, hypotensive effects with 3-4 days delay
- latency occurs also in withdrawal

INDICATION

- **Hypertension** (essential), manly in combination
- **Heart Failure** (prevention of cardial oedema)

AE

hypokalaemia, metabolic alkalosis, hyperuricemia, hypovolemia

DRUGS

- **hydrochlorothiazid**
- **chlortalidon**
  longer half-life than hydrochlorothiazid

- **indapamid**
- **metipamid**

indapamid in combination with ACEi in DM patients (prospective RCT)

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Loop diuretics

MECHANIS OF ACTION

Inhibition of 4 ions contransport (Na, K, 2xCl)

- very strong, short effects (significant loss of ions)

- RAA system activation – long-term treatment is not recommended

.

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Loop diuretics

DRUG

furosemid

Strong effect

Also in patients with ↓ GF

INDICATION

- lung oedema
- congestive heart failure
- hypercalcemia (furosemid)
- chronic renal failure
- forced diuresis (intoxications)
- post-operative anuria

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AE

- Ion imbalance (loss of Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+})
- Osteoporosis
- Hypovolemia ⇨ risk of trombosis

DRUG INTERACTIONS

Furosemid bounds to albumin ⇨ ↑ plasmatic level of metformin, amiodaron, digoxin,…

↑ Nephrotoxicity of cefalosporins

Potassium sparing diuretics

Antagonists of aldosteron receptors

MECHANISM OF ACTION

Na^+/K^+ antiport inhibition through direct channel affecting, or as aldosterone receptor inhibitors

Potassium sparing diuretics	Directly ion channel
aldosteron. rcp. antagonists	**aldosteron receptor** antagonisation

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- inhibition of **resorbtion** **Na^+ ionts + H2O**
- inhibition of **excretion** **K^+ ionts** → **potassium sparing**

Antagonists of aldosteron receptors:

- ✓ Extrarenal effect - **inhibition of fibroblast proliferation in myocard and vessels**
- ✓ **Mg^{2+} sparing**

→ **Indicated for pts. with HF**

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DRUG

Potassium sparing

amilorid

Weaker effect, used in combinations with other potassium-loss causing diuretics

INDICATION

Hypertension in combination
Prevention of cardial oedema

DRUG

Antagonist of aldosteron

spironolakton

(often combined with furosemide)

positive effects on remodelation → in heart failure also in monotherapy

Antiandrogenic effect

- ✓ Inhibition of bounding of testosteron to rcp.
- ✓ Inhibition of P-glp efflux pump

→ AE - gynecomastia, menstruation problems

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INDICATION

- Hypertension (in combination with furosemid, e.g. resistent HT form)
- Primary hyperaldosteronism
- **Heart failure**

eplerenon

MoA:

Selective antagonist of **mineralokortikoid** receptors

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Diuretics in general

Advantages:

- useful combinations with others AHT
- increase effect of other AHT effects
- no influence on CNS
- cheap

Disadvantages:

- metabolic effects (thiazides)
- low tolerance (elderly)

Diuretics

AE:

- potassium depletion (except K^+ sparing)
- hyperuricemia (thiazides, loop diuretics)
- weakness, nausea
- imbalance in glycid and lipid metabolism (thiazides)
- hypovolemia, hypotension (furosemid)
- hyperkalaemiaa (amiloride, spironolactone)
- Chronic therapy – disruption of kidneys functioning

CI:

- gout (thiazides)
- renal failure, hyperkalaemia (K^+ sparing)
- relative: pregnancy, metabolic syndrome

INDICATION of diuretics (general)

Thiazides

- HT older pts.
- Systolic isolated HT
- Chronic heart failure in combination

Loop diuretics

- HT in renal insufficiency
- Chronic heart failure Hyperkalcemia
- Pulmonary oedema

K-sparing + Aldosteron antagonists

- Resistent form of hypertension (spironolakton)
- HT and primary hyperaldosteronism (spironolakton)
- Chronic heart failure

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ACEi /sartans

Previous lecture

DRUGS with POSITIVE INOTROPIC EFFECTS

Cardiac glycosides (cardiotonics)

Katecholamines

PDE-3 inhibitors

Ca^{2+} sensitizers

Cardiac glycosides (cardiotonics)

MECHANISM OF ACTION:

- **Inhibition of Na+/K+ ATPasa pump**

  ⇨ increase intracellular sodium concentration (Na+/Ca+ exchange transporter

  ⇨ secondary rise of Ca^{2+} -

  ⇨ **increased contractility** ⇨ **↑inotropic effect efekt**

- **Activation of parasympatics (n. vagus)** and ACH release

  ⇨ SA node, AV conduction slow

  ⇨ ↓ chronotropy

  ⇨ ↓ dromotropy ⇨

  antiarrhytmic effect

DRUG

digoxin

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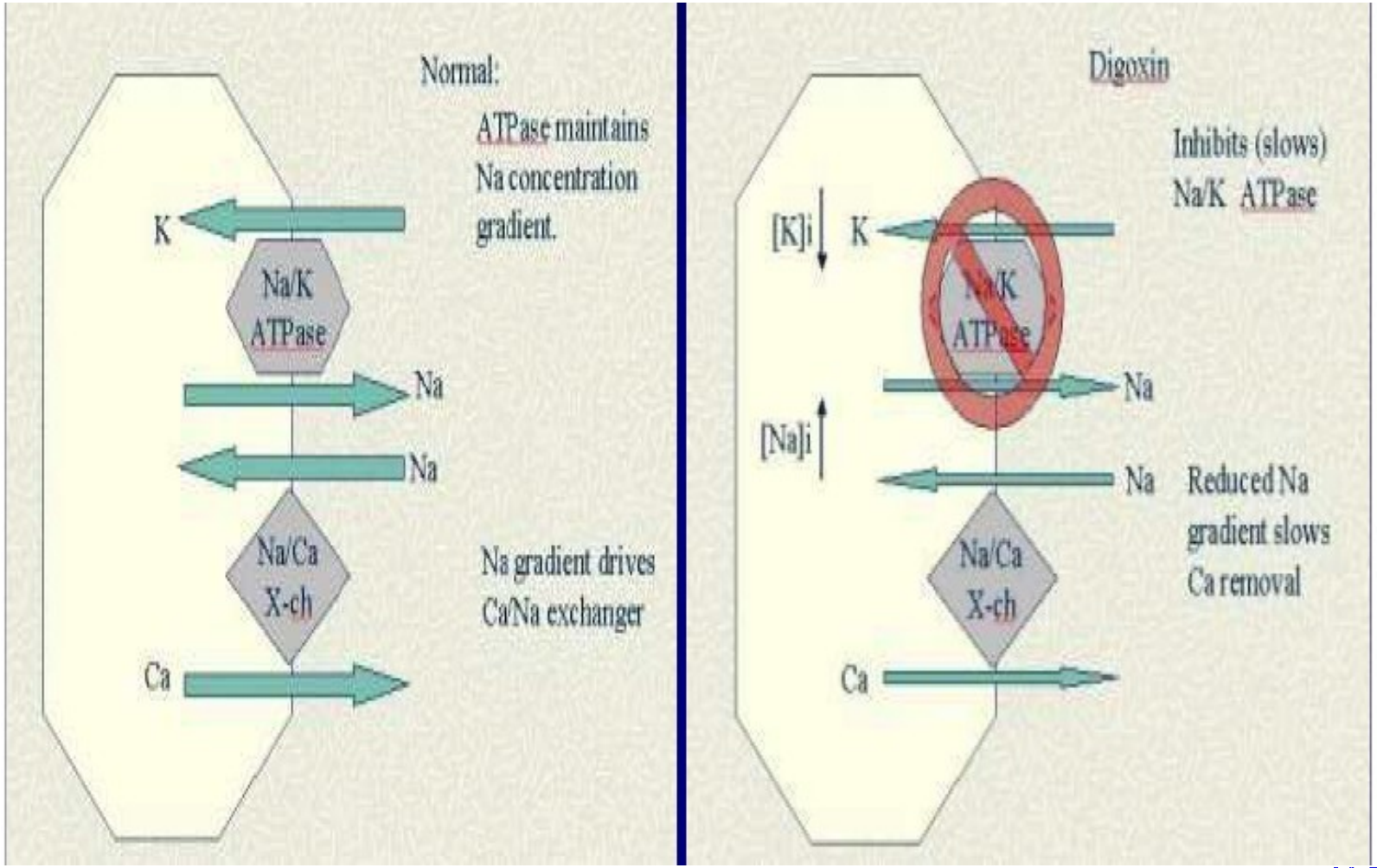
Cardiac glycosides (cardiotonics)



PHARMACOKINETICS

- $t_{1/2}$ = 36 hours
- TDM (plasma level 0,5–1,5 ng/ml)
- Variable bioavailability (50-70 %)
- P-glp pump substrate **(drug interaction !)**
- Binding to the albumin 20-40%
- Renal elimination, GFR depending
- Liver metabolization app. 20 %

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ADVERSE EFFECTS

Cardial, CNS and GI – clinically significant

→ **DIGITALIS INTOXICATION**

Cardial signs

- ↓ **intracelullar K+** leds to ↑ excitability (tachyarrhytmia)
- **Parasympatic activation** (sinus bradycardia, AV blocades)

Others :

CNS: Visual disturbance (yelow colors, disorientation, confusion

GI: Anorexia, nausea, vomiting

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DRUG INTERACTIONS

Strong or moderate Pglp pump inhibitors

verapamil, amiodaron, propafenon, telmisartan, cyklosporin, antimycotics (ketokonazol), macrolides ATB (clarithromycin)

…should increase plasmatic level of digoxin

→ **DIGITALIS INTOXICATION**

Hypocalemia should leads to digoxin intoxication

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INDICATION

- Chronic HF
- Sinoatrial tachyfibrilation

CONTRAINDICATION

- AV blockades
- Cardial insufficiency with bradycardia
- Digoxin intoxication

RELATIVE: aIM

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Catecholamines

norepinephrin

α_1 rcp. agonist ⟶ **increase BP**

dopamin

Dose-dependent

D rcp. ⇨ renovascular dilatation

β_1 rcp. ⇨ inotropic effect

↑ **dose** α_1 rcp. Agonist ⇨ **increase BP**

INDICATION

Severe hypotension (NA)

Vasodilatation of renal vessels (dopamin)

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Catecholamines

adrenalin, dobutamin

stimulation β_1 rcp. → ↑**contractility (inotropy)**

β_2 rcp. → vasodilatation

INDICATION

Acute HF, cardiopulmonal resuscitation

PK:

- Low bioavailability ⇨ i.v. administration
- Short half-life (2 minutes)

AE:

Arrhytmogenic effect

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PDE-3 inhibitors

MECHANISM OF ACTION

cAMP-dependent phosphodiesterase- myocardial isophorm3 - inhibitor

⇨ **arterial dilatation** (reduction of afterload)

⇨ **cardiostimulation** (+ chrono-, ino- a dromotropic effects)

DRUGS

milrinon

INDICATION

Treatment of acute and refractory HF

AE:

- Decreased BP, headache
- Proarrhytmogenic effect – less used

Calcium sensitizers agent

MECHANISM OF ACTION

- ↑ the force of contraction of the heart by binding troponin C and sensitising it to the action of Ca^{2+} ⇨
- Binds to the K_{ATP} channel – membrane hyperpolarization ⇨ ↓ opening of the Ca_L channel ⇨ **vasodilatation** (systemic, lung)

DRUG:

levosimendan

PK:

i.v. infusion

Metabolised to active metabolite with long half-life (80hrs)

INDICATION

Acute HF

ANTIARRHYTMICS

Antiarrhythmic agents

Vaughan-Williams classification (based on electrophysiological effects, 1970)

	Active agents	Clinical use	MoA
Class I a	Prajmalin	Limited use	Interfere with Na+ channel / effects on cardiac potentials
Class I b	Lidocain	Ventricular tachycardia	
Class I c	Propafenon	Atrial fibrilation, reccurent tachyarrhythmias	
Class II	B –blockers (metoprolol, atenolol	Tachyarrhythmias	decrease conduction through the AV node
Class III	Amiodaron, Sotalol Dronedaron Ibutilid	Vetnricular tachycardia Atrial fibrilation - the most effective AA	K+ channel blocker, prolong repolarisation (QT int.)
Class IV	Ca channel blockers	Atrial fibrilation - rate reduction Paroxysmal supraventricular tachycardia prevention	Ca++ channel blocker

Others…

Drug class	Mechanism of action	Drug
Cardiac glycosides	Parasympathetic activation	digoxin
Bradins	↓ depolarization of SA pacemaker	ivabradin
Agonists of β_1 rcp	positive chronotropic, dromotropic, bathmotropic effects	catecholamines
	↓ depolarization of SA and decreased AV conduction	adenosin

THE PHASE OF ACTION POTENCIAL

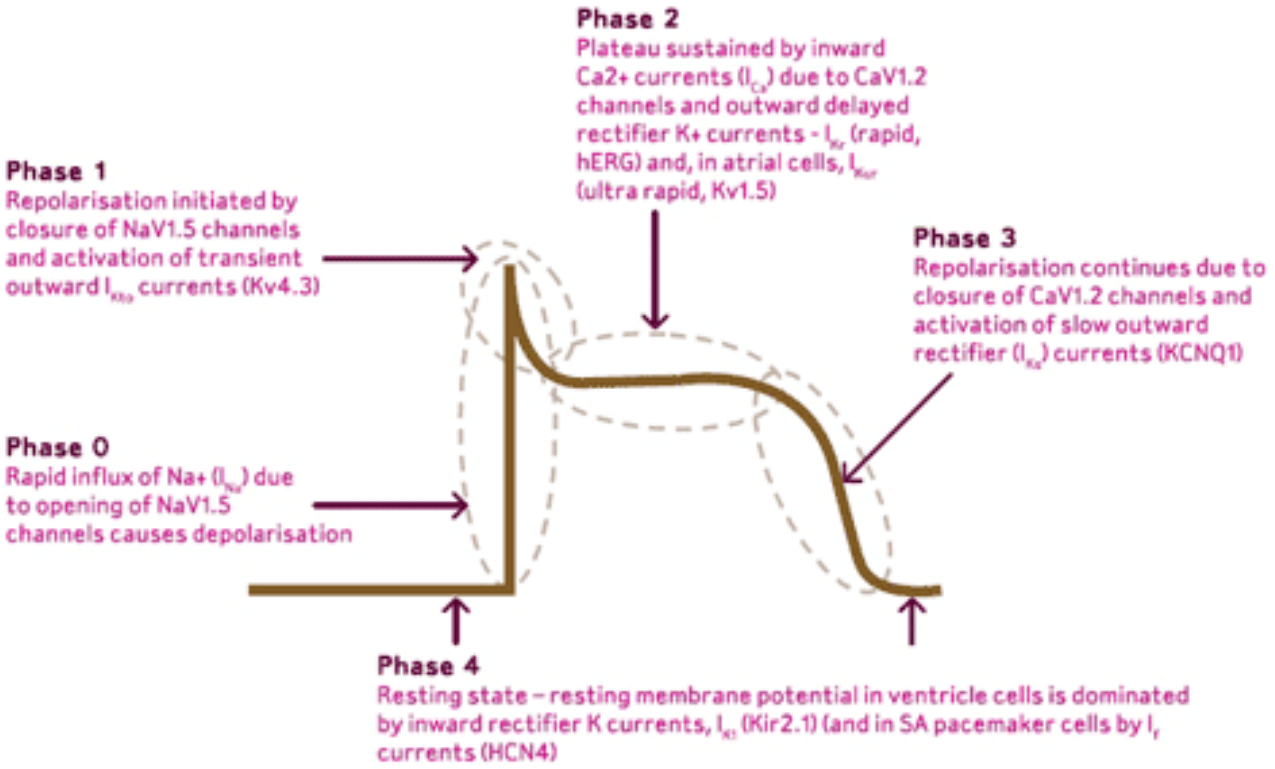
Phase 0: rapid depolarition

Phase 1: partial repolarization

Phase 2: plateau

Phase 3: final repolarization

Phase 4: resting stage



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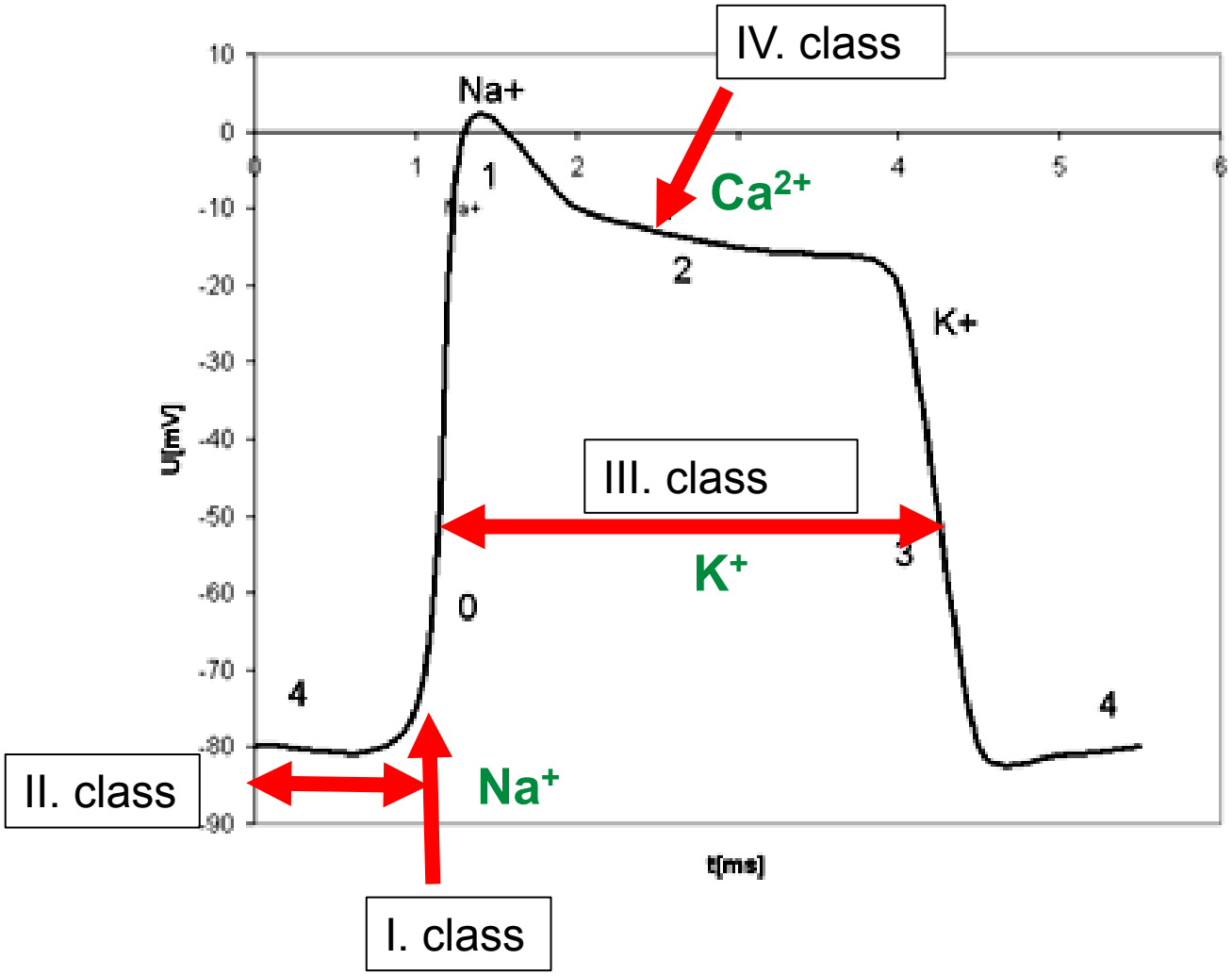
Four classes of antiarrhytmics



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ANTIARRHYTMICS class I

Class I drug block sodium channel

- Inhibit action potential propagation in excitable cells
- Membrane-stabilising activity

⇨ **reduce the maximum rate of depolarisation**

Subgroups:

IA prajmalin

Risk of torsade de pointes

Now seldom used

IB lidokain

IC propafenon

Prophylaxy and treatment of supraventricular arrhytmias

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ANTIARRHYTMICS class II

Antiarrhytmic effect caused by lowering of proarrhytmogenic effect of sympathetic activity **(negative chrono-,dromo- a bathmo-tropic effects)**

Leads to:

- **Increase the refractory period of the AV node**
- **Prevent reccurent attacks of SVT**
- ⇨ **prolongation of repolaritazion**

INDICATION:

- Prophylaxy of supraventrikular and ventricular tachyarrhytmias
- Sinoatrial fibrillation

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ANTIARRHYTMICS class III

Class III inhibit potassium channel involved in cardiac repolarization, mainly I_{kr} ⇨ **prolong the cardiac action potential**

⇨ **prolong repolarization**

DRUGS

amiodaron, sotalol

The most often used

superior in reducing the recurrence of ventricular arrhythmias and atrial fibrillation – but many Aes !

INDICATION

- Pharmacological cardioversion (fibrillation or flutter)
- Prophylaxy of fibrillation or flutter

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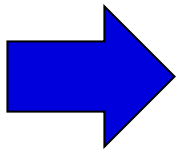
Amiodaron pharmacokinetic:

- Active metabolite (desmetylamiodaron) highly lipophilic ⇨ **accumulates in the liver, skin and fat**

Bioavailability of amiodarone is quite variable (ranges 22 to 95%, with better absorption when it is given with food)
Loaded dose (3-6x higher for weeks, orally)

Extensively bound in tissues
Long elimination half-life (40-50 days)

- Biotransformation - izoenzymes CYP (mainly CYP2C9, CYP2D6, CYP3A4)
- P glp inhibitor
- Liver elimination



Drug interaction

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DRUG INTERACTIONS

amiodaron x digoxin

P-glp. pump

↑ **digoxin** plasma level

Dose changes

amiodaron x statins
(simvastatin)

amiodaron x CCB

amiodaron x BB (lipophylic)

↑ plasma level – clinically significant

P-glp. pump + CYP3A4

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Adverse effects dose-dependent

1. **MoA**
   - **dysrrhytmia**
   - **decreased heart contractility**

All antiarrhytmics

2. **Specific AEs**
   - **reverzible** corneal deposits
   - blue discoloration of the skin is (10%)
   - **irriversible severe lung fibrosis**

to avoid sun exposure due to photosensitivity

3. **Thyreoid toxicity**
   - **Hypothyreosis** (10%)
   - **Typerthyreosis** (less common)

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ANTIARRHYTMICS class IV

Blocking voltage-sensitive calcium-channel

- **Slow conduction in the SA and AV nodes**
- **Shorten the plateau of the action potential**
- **Reduce the force of contraction**

Antiarrhytmic effect of **verapamil is** better than **diltiazem**

Not indicated for patients with left vetricle dysfunction of heart failure

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Other antiarrhytmics

atropin (parasympatolytic effect)

MoA: competitive inhibition of M_2 rcp in SA a AV nodes

I: **treatment of** sinus bradycardia

PK: i.v. administration

adenosin

MÚ: activation of adenosin rcp. A_1 in SA a AV nodes slow conduction
Activation of rcp. A_2 – vasodilatation

I: re-entry arrhytmias

PK: i.v. bolus centrally

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Thank you for your attention

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