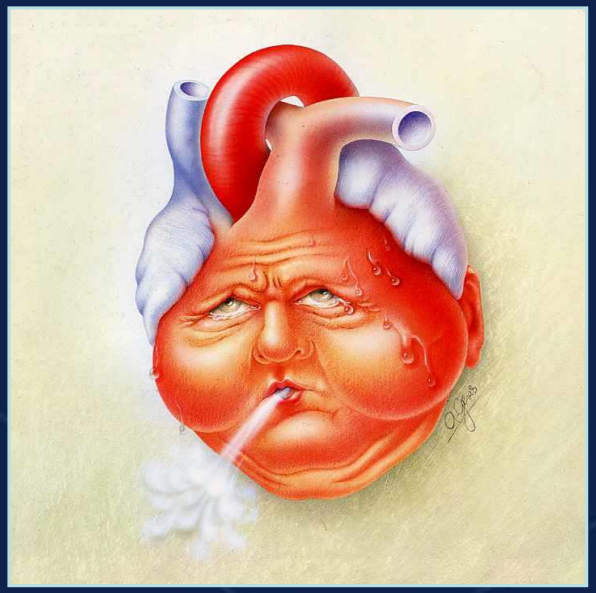
Drugs used to treat heart failure



J. Mojžiš

Heart failure (HF)

- is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body
- its cardinal symptoms are dyspnea, fatigue, and fluid retention
- HF is due to an impaired ability of the heart to adequately fill with and/or eject blood
- it is often accompanied by abnormal increases in blood volume and interstitial fluid, hence the term "congestive" HF because symptoms include dyspnea from pulmonary congestion in left HF, and peripheral edema in right HF

HEART FAILURE (HF)

insuficient cardiac output

⇧ central venous pressure (⇧ pre-load)

⇧ peripheral vasoconstriction

(⇧ after-load)

Causes of HF

- **aterosclerotic disease, MI, hypertension, valvular heart disease, dilated cardiomyopathy, and congenital heart disease**

- **left systolic dysfunction secondary to coronary artery disease is the most common cause of HF, (nearly 70% of all cases)**

- **the number of newly diagnosed patients with HF is increasing, because more individuals now survive acute myocardial infarction**

Causes of HF

- **primary myocardial damage:**
  - **diffuse in inflammation**
  - **local in MI**
- **blood pressure overload - hypertension**
- **volume overload – valve damages**
- **defects in heart filling:**
  - **constrictive pericarditis**
  - **heart tamponade**
- **cardiac arrhythmias**
  - **extreme bradycardia or tachycardia**

Compensatory mechanisms in HF

- the failing heart evokes three major compensatory mechanisms to enhance cardiac output

- although initially beneficial, these alterations ultimately result in further deterioration of cardiac function

Increased sympathetic activity

- ⇩ in blood pressure ⇨ activation the sympathetic NS ⇨ stimulation of β-adrenergic receptors in the heart
- this results in an ⇧ heart rate and a greater force of contraction of the heart muscle
- in addition, vasoconstriction (α_1-mediated) enhances venous return and increases cardiac preload
- these compensatory responses increase the work of the heart and, therefore, can contribute to further decline in cardiac function

Activation of the RAAS

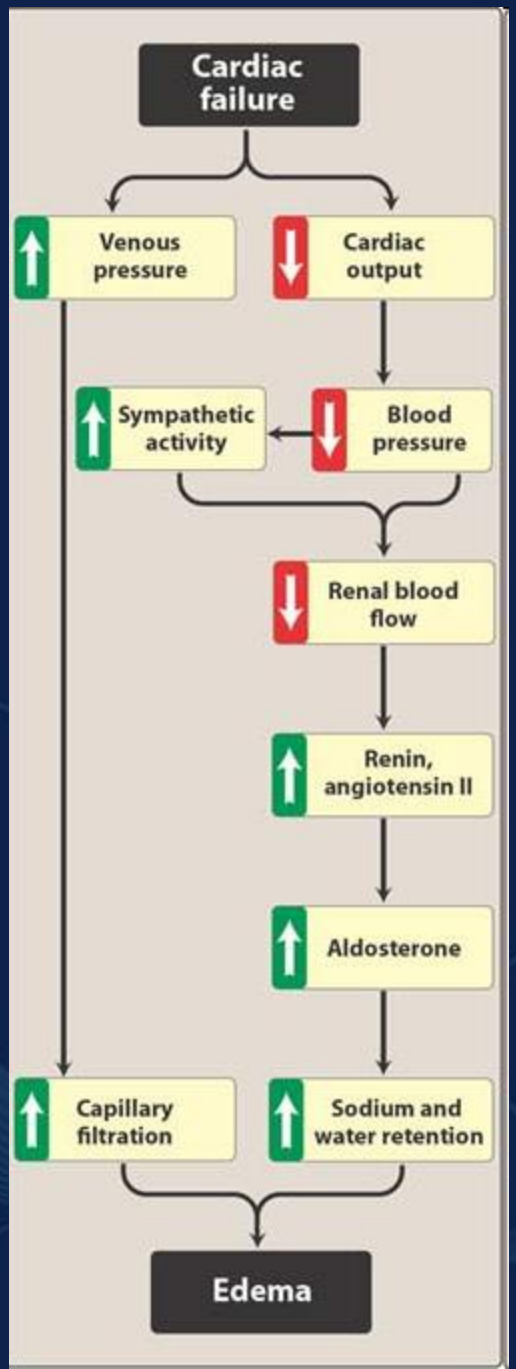
- a fall in cardiac output - ⇩ blood flow to the kidney ⇨ release of renin ⇨ formation of A II and release of aldosterone
- ⇧ peripheral resistance and retention of sodium and water
- blood volume ⇧, and more blood is returned to the heart
- if the heart is unable to pump this extra volume, venous pressure increases and peripheral edema and pulmonary edema occur
- these compensatory responses increase the work of the heart and, therefore, can contribute to further decline in cardiac function

Myocardial hypertrophy

- the heart increases in size, and the chambers dilate and become more globular
- initially, stretching of the heart muscle leads to a stronger contraction of the heart
- however, excessive elongation of the fibers results in weaker contractions, and the geometry diminishes the ability to eject blood

Decompensated HF

- if the mechanisms mentioned above adequately restore cardiac output, the HF is said to be **compensated**
- however, these compensations increase the work of the heart and contribute to further decline in cardiac performance
- if the adaptive mechanisms fail to maintain cardiac output, the HF is termed **decompensated**



Cardiovascular consequences of heart failure

Lippincot´s Pharmacology, 2009

Chronic left HF

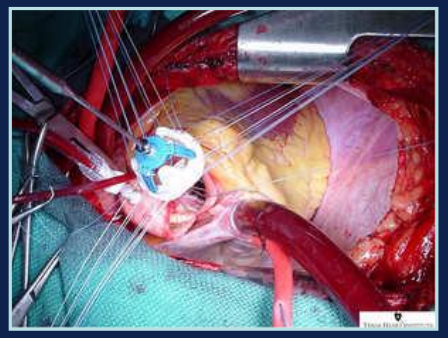
- **Cardial dyspnea**
- **Fatigue, muscle weakness, sweting, oliguria**
- **Tachycardia**

Chronic right HF

- ⇧ jugular vein filling
- Hepatomegalia
- Cardial edema
- Latent edema – fluid retention 2-5 l
- Chronic edema
- Hydrothorax, hydropericard, ascites
- Cyanosis

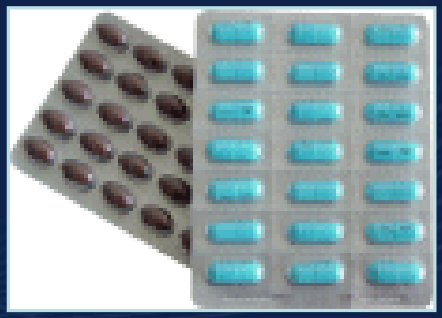
Basic therapy of HF

- cause elimination



- diet

- pharmacotherapy



Pharmacotherapy

- ACE-I/ARBs
- Diuretics
- β-blockers
- Cardioglycosides

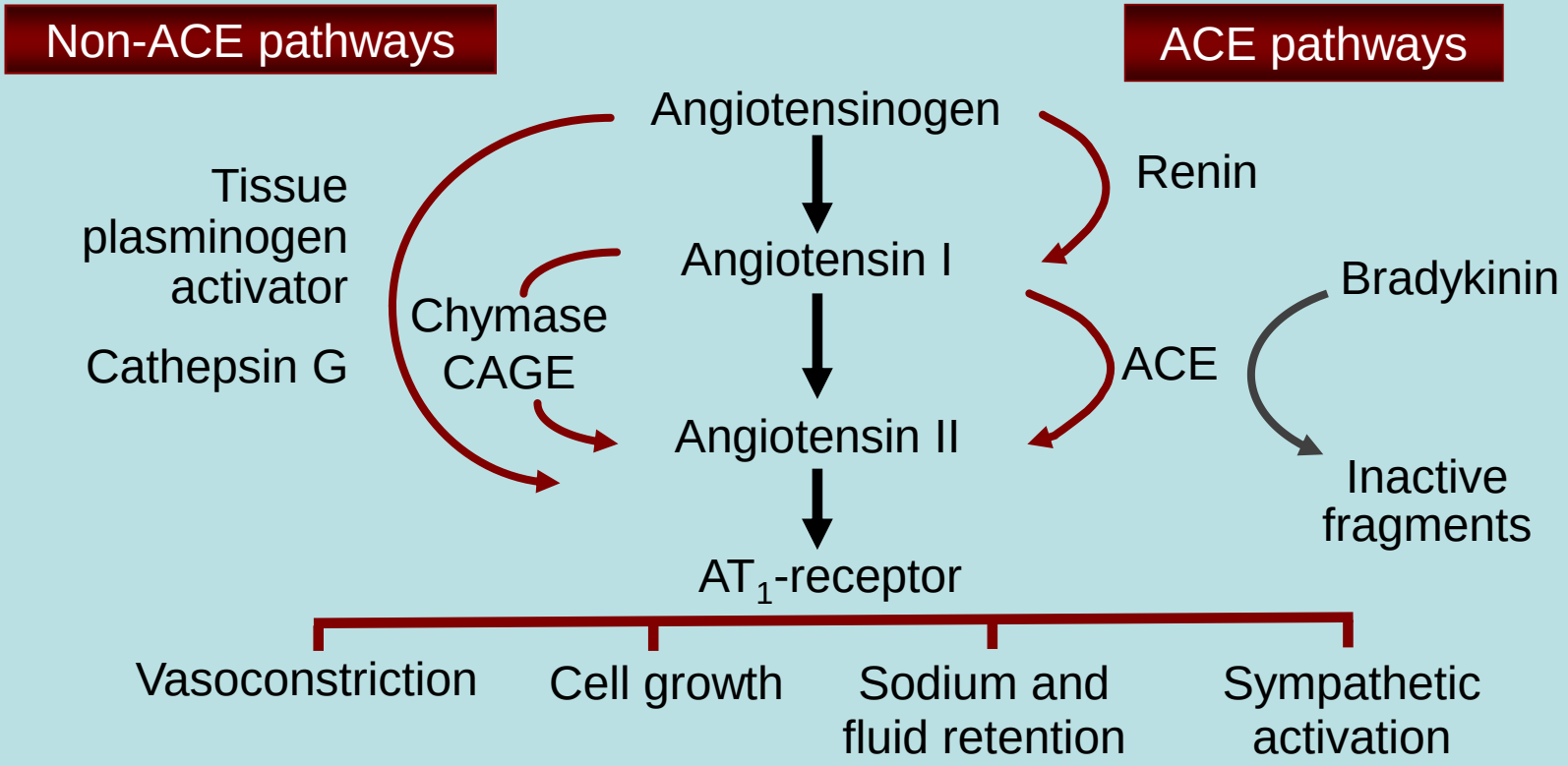
Angiotensin converting enzyme inhibitors (ACE-I)

ACE-I

- **RAAS – BP, water and mineral ion regulation**

- **angiotensin II – main role in patophysiology of CVS diseases:**
  - **hypertension**
  - **chronic HF**

Renin-Angiotensin-Aldosterone System



ACE, angiotensin converting enzyme; CAGE, chymotrypsin-like angiotensin-generating enzyme
Hollenberg NK, et al. *Hypertension.* 1998;32(3):387-392.

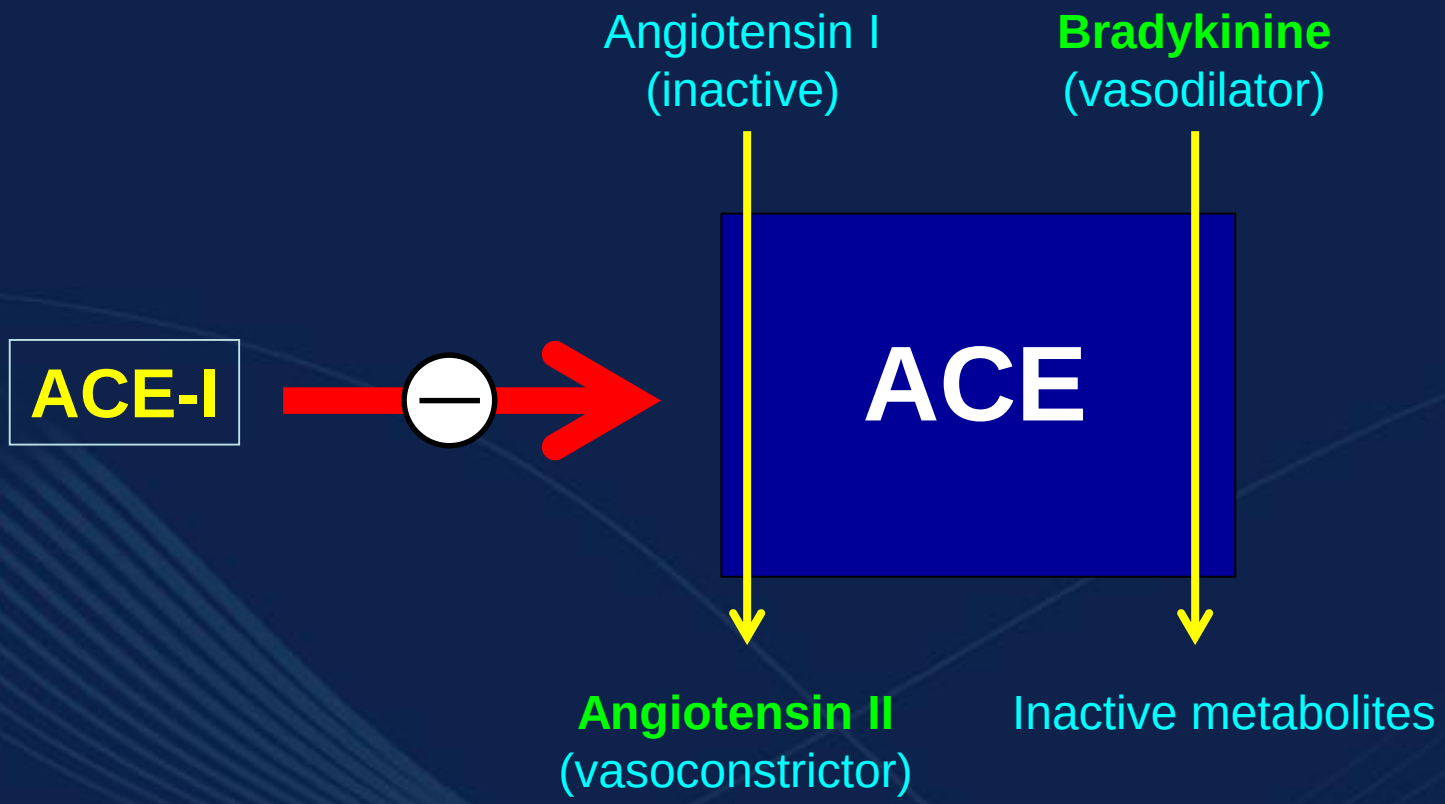
SUBSTANCE	DESCRIPTION-EFFECTS
angiotensinogen	α-2 globuline from liver
renin	protease - juxtaglomerular cells
angiotensin I	decapeptide – no biological effect
ACE (kininase II)	conversion of AT I to AT II degradation of bradykinin
angiotensin II	octapeptide – potent vasoconstrictor, aldosterone release, secretion of growth factors
aldosterone	mineralocorticoid

RAAS can be inhibited on...:

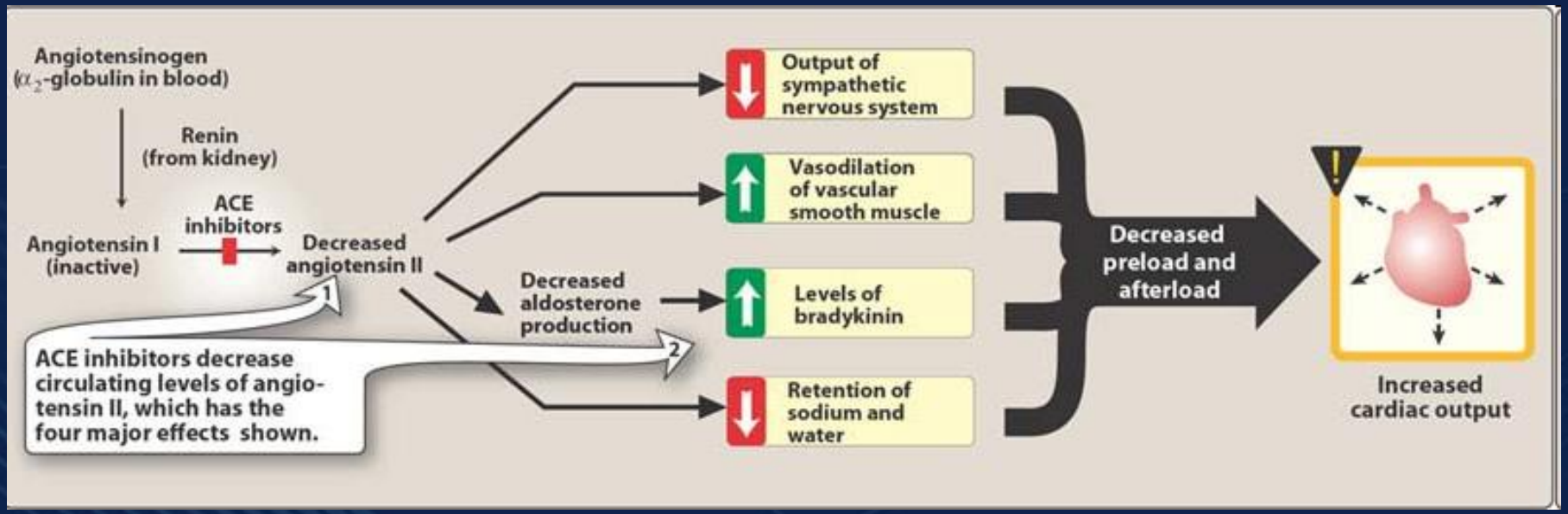
- **Release of renin *(β-blockers)***
- **Renin inhibitor *(aliskiren?)***
- **ACE – inhibitors *(captopril, enalapril, lisinopril, perindopril)***
- **AT1 receptor blockers *(losartan)***
- **Aldosterone antagonists *(spironolacton)***

ACE inhibition

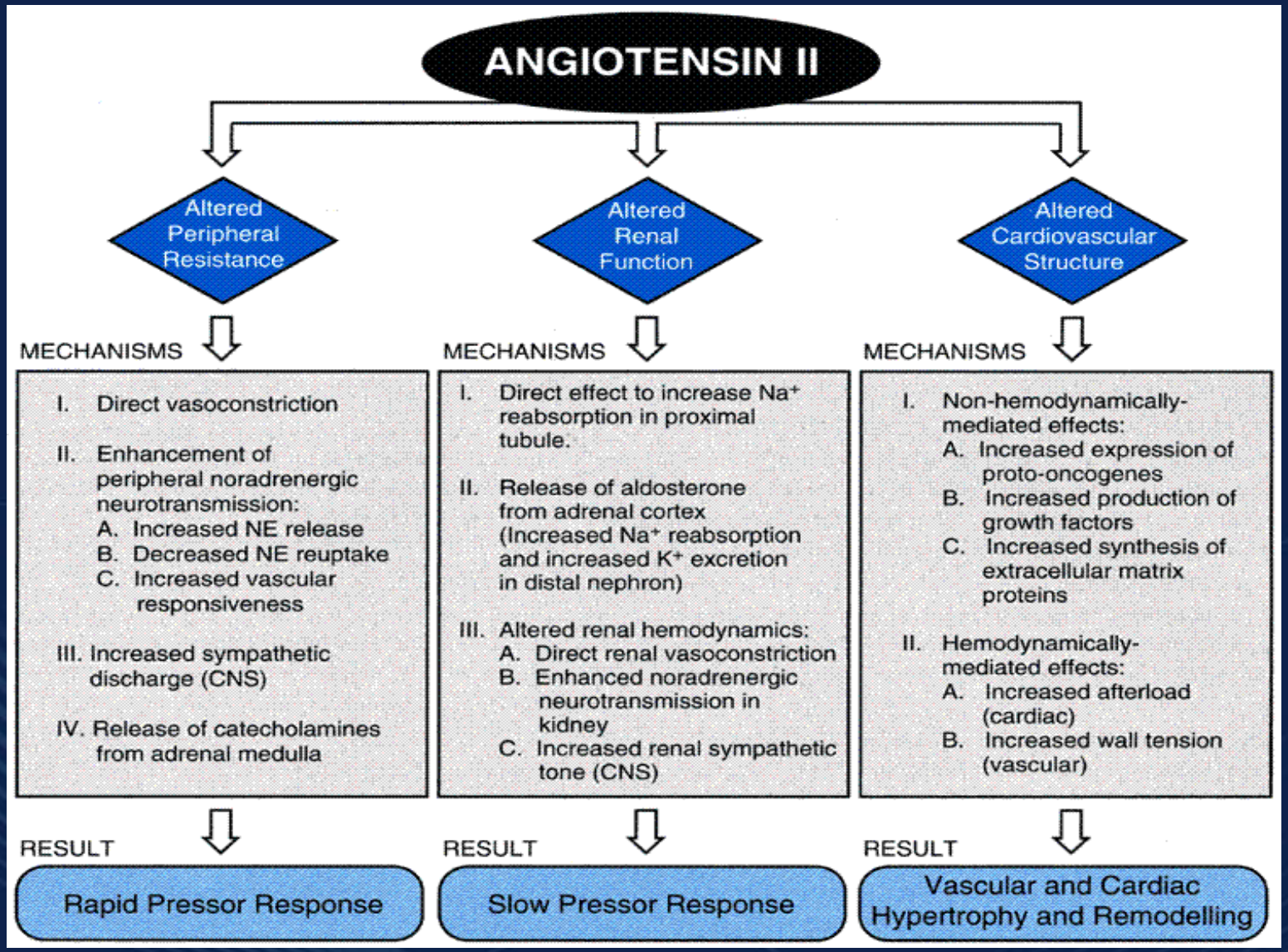
- inhibition of AT II production
- inhibition of bradykinine degradation
- ⇩ in stimulation of aldosterone secretion
- ⇩ of NA release from nerve terminals
- ⇩ in production of vasoconstricting endotheline by damaged endothelium


Angiotensin I
(inactive)
Bradykinine
(vasodilator)
ACE-I
ACE
Angiotensin II
(vasoconstrictor)
Inactive metabolites

Effects of ACE inhibitors



Lippincot´s Pharmacology, 2009



Summary of the three major effects of angiotensin II and the mechanisms that mediate them.

Effect of ACE-I

Effect of ACE-I dependes on renine levels:

- **high level -** 
- **low level -**  **(old people, afroamericans)**

Major ACE-I

- sulfhydryl group – captopril, zenopril
- carboxyl group - cilazapril, enalapril, lisinopril, quinalapril
- phosphoryl group - fosinopril

Pharmacokinetics

- all ACE inhibitors are adequately but incompletely absorbed following oral administration
- the presence of food may decrease absorption, so they should be taken on an empty stomach
- some ACE inhibitors (e.g. enalapril) are prodrugs that require activation by hydrolysis via hepatic enzymes
- renal excretion of the active moiety is important for most ACE inhibitors
- plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer
- the newer compounds such as ramipril and fosinopril require only once-a-day dosing

ACE-I

Effect	Drug	Hours
Short-acting	*captopril*	*6-8*
Moderate-acting	*enalapril*	*12*
	quinapril	
Long-acting	*perindopril*	*24*
	lisinopril	
	spirapril	
	ramipril	

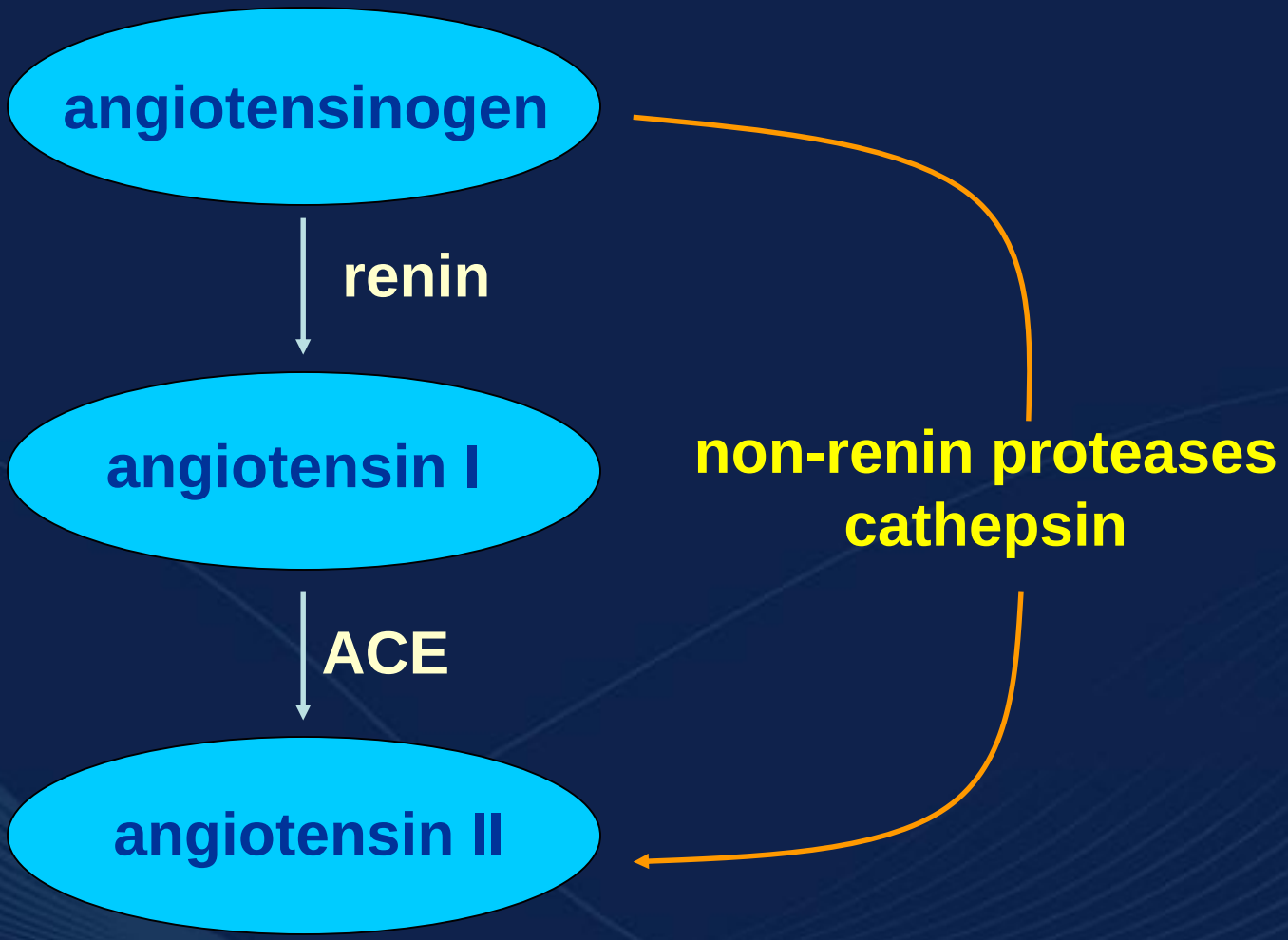
Benazepril 10 mg
Captopril 50 mg (25 mg bid)
Enalapril 5 mg
Fosinopril 10 mg
Lisinopril 10 mg
Perindopril 4 mg
Quinapril 10 mg
Ramipril 2.5 mg

ACE-I side effects

- **cough (10-15% of patients) ⇨AII blockers**
- **hypotension, headache, vertigo**
- **fatigue, GI disturbances, allergies**

Angiotensin-receptor blockers (ARBs)

- **ARBs are nonpeptide, orally active compounds that are extremely potent competitive antagonists of the angiotensin II receptor, type 1 (AT1)**
- **losartan is the prototype drug**
- **ARBs have the advantage of more complete blockade of A II action, because ACE inhibitors inhibit only one enzyme responsible for the production of A II**
- **ARBs do not affect bradykinin levels**
- **ARBs are a substitute for ACE inhibitors in those patients who cannot tolerate the latter.**

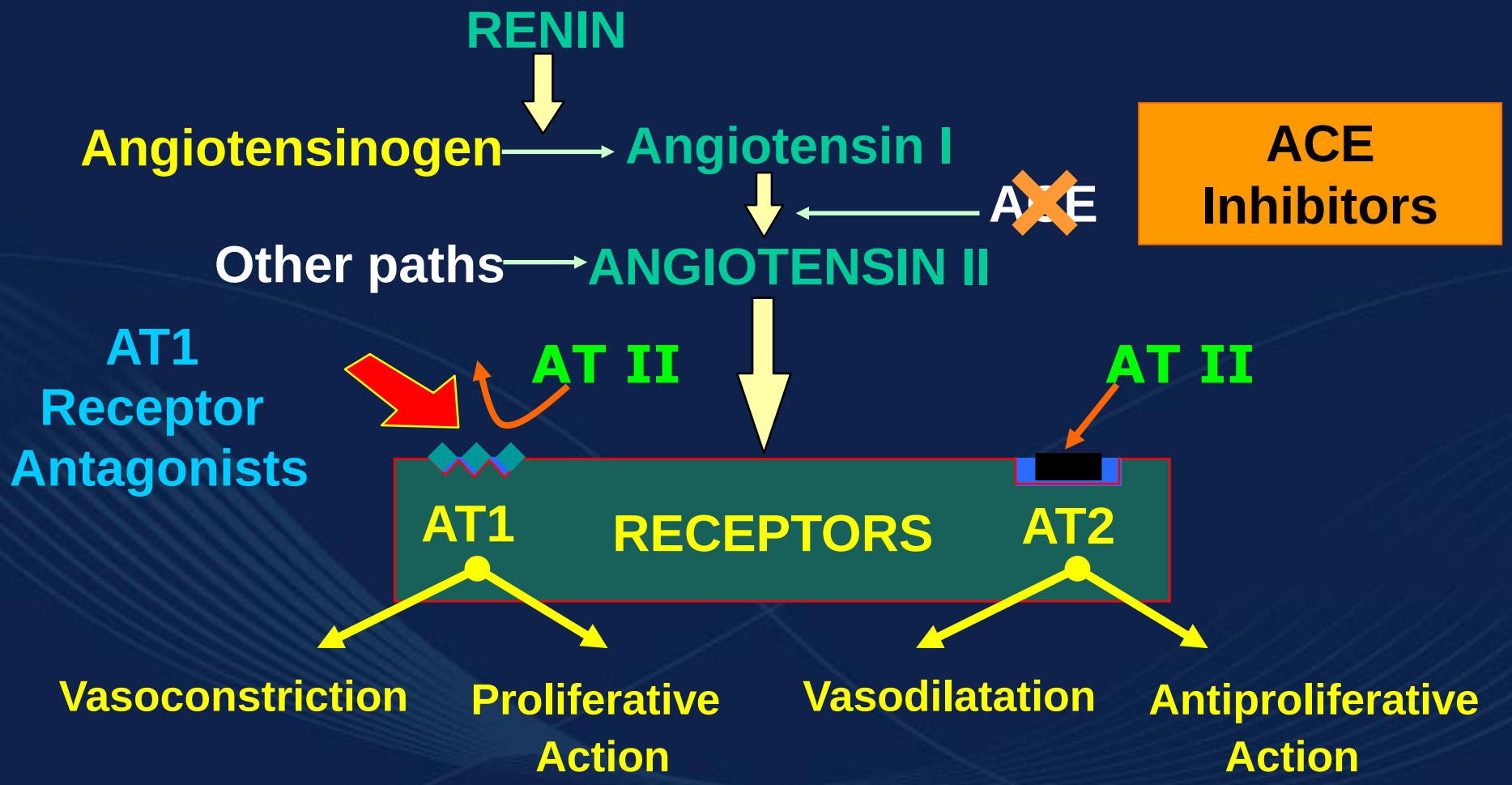

angiotensinogen
renin
angiotensin I
ACE
angiotensin II
non-renin proteases
cathepsin

Actions on the cardiovascular system

- all the ARBs are approved for treatment of hypertension based on their clinical efficacy in lowering blood pressure and reducing the morbidity and mortality associated with hypertension

- as indicated before, their use in HF is as a substitute for ACE inhibitors in those patients with severe cough or angioedema

Inhibition of the effects of angiotensin II



Pharmacokinetics

- all the drugs are orally active and require only once-a-day dosing
- Losartan differs from the others in that it undergoes extensive first-pass hepatic metabolism, including conversion to its active metabolite
- the other drugs have inactive metabolites
- excretion of metabolites and parent compounds occurs in the urine and feces
- all are highly plasma protein–bound (over 90%)

losartan

- prodrug (metabolite is 10-40x potent than losartan)

- rapid absorption, food has minor effect on the absorption, bound to albumin

valsartan

- active drug (40, 000 x greater affinity to AT-1 than AT-2)

rapid absorption, food has minor effect on the absorption, bound to albumin

Renin Inhibitor

- 1st agent FDA approved in 2007: aliskiren
- Inhibits angiotensinogen to angiotensin I conversion
- Does not block bradykinin breakdown - less cough than ACE Inhibitors
- Aliskiren failed to improve outcomes for patients hospitalized for HF and is not presently recommended as an alternative to an ACEI or ARB.
- Combination with ACEIs/ARBs – contraindicated in patients with DM and renal failure (EMA) – *(hypotension, stroke, hyperkalemia, renal failure)*
- Adverse effects: orthostatic hypotension, hyperkalemia

Adverse effects

- ARBs have an adverse effect profile similar to that of ACE inhibitors
- however, ARBs do not produce cough
- ARBs are contraindicated in pregnancy.

New drugs

Sacubitril

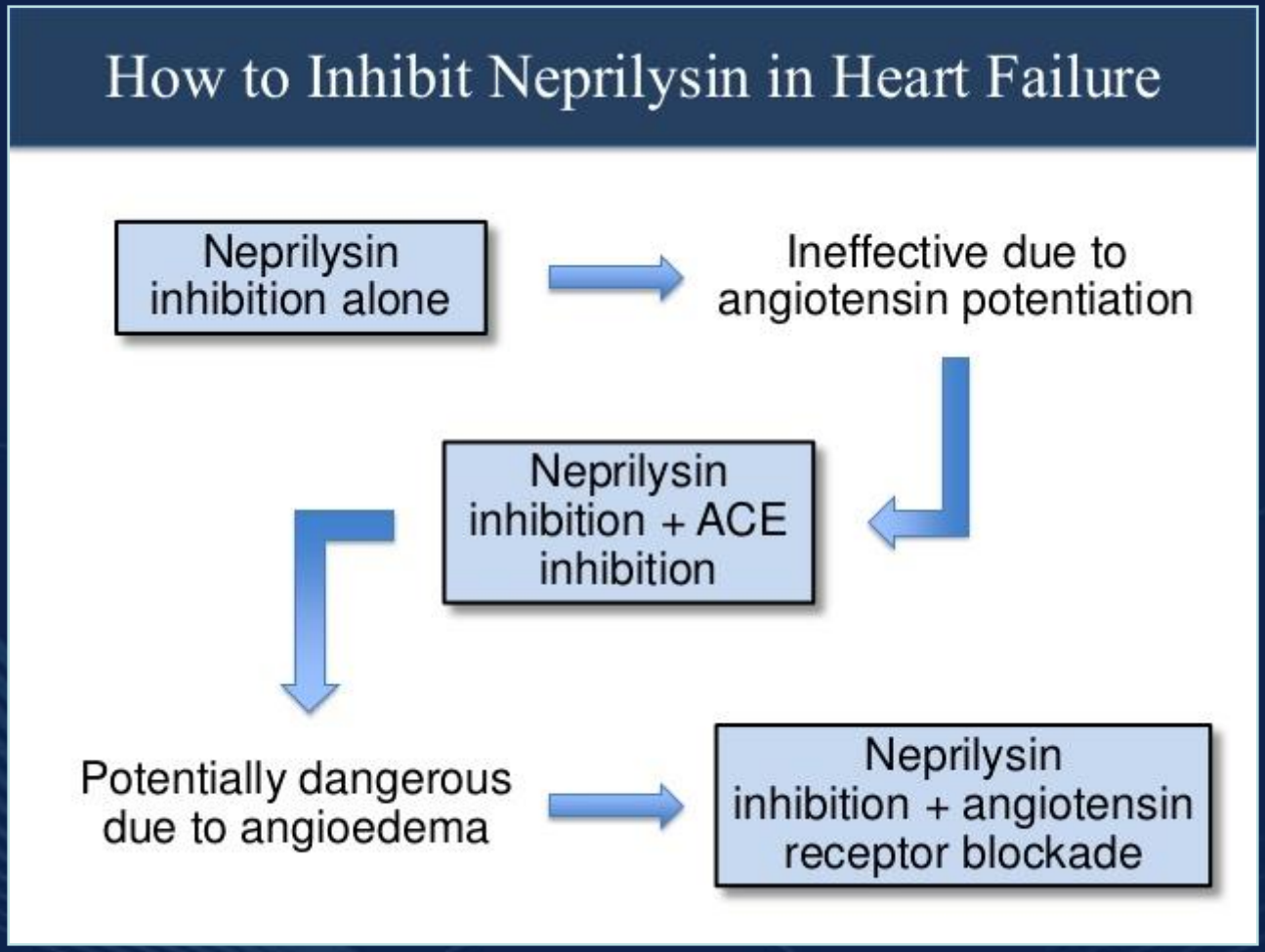
- **Inhibitor of neprilysin**
- **Neprilysin catalyzes the degradation of natriuretic peptides (ANP, BNP).**
- **NP are produced in response to volume overload and cardiac dysfunction, and exert a beneficial response in HF.**

- **Sacubitril – prodrug**

- **active metabolite (sacubitrilat) inhibits neprilysin, thus allowing NP to persist longer and promote vasodilation, diuresis, and natriuresis, as well as prevent cardiac hypertrophy.**

- **AR: ortostatic hypothension**

- **Contraindicated with ACE-i, in pregnancy**



combination with valsartan

Ivabradine

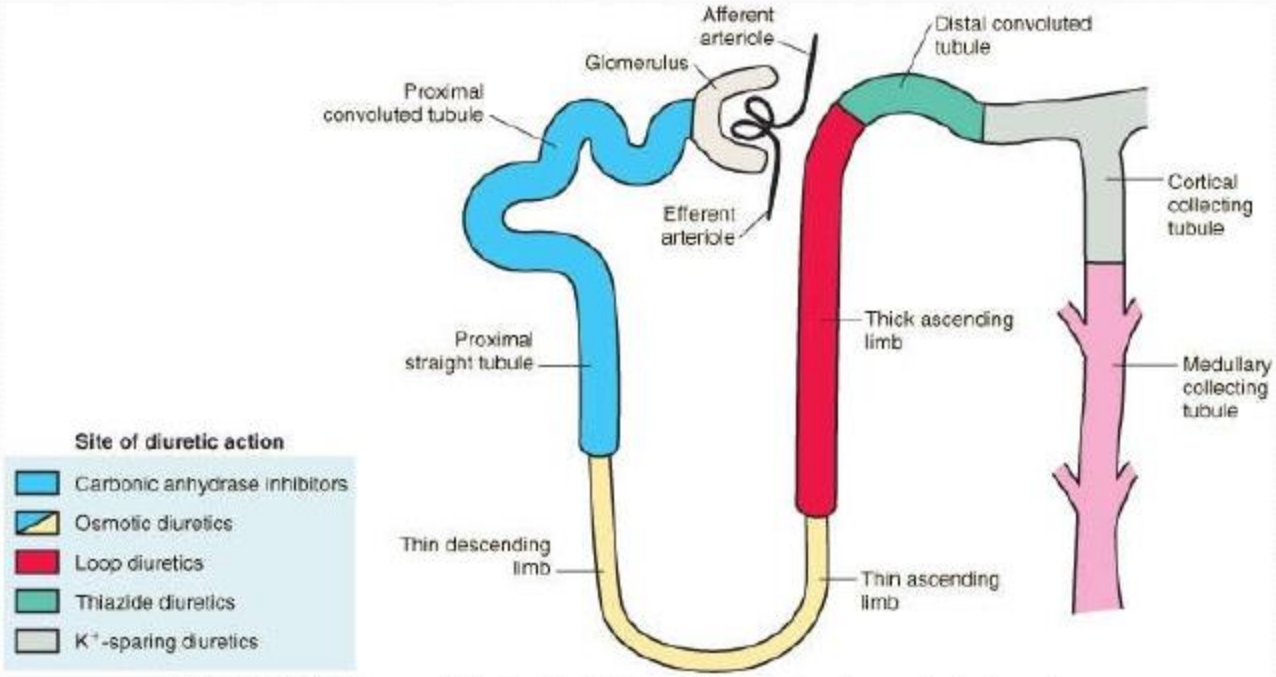
- it acts on the I_f channels(f is for "funny„) in SA node ⇨ reduced cardiac pacemaker activity, and slowing the heart rate ⇨ more time for blood to flow to the myocardium.

- opposite to BB and CB, ivabradine does not decrease cardiac contractility

- AR: bradycardia, ⇧ BP, atrial fibrillation

Diuretics

Nephron sites of action of diuretics



DIURETICS

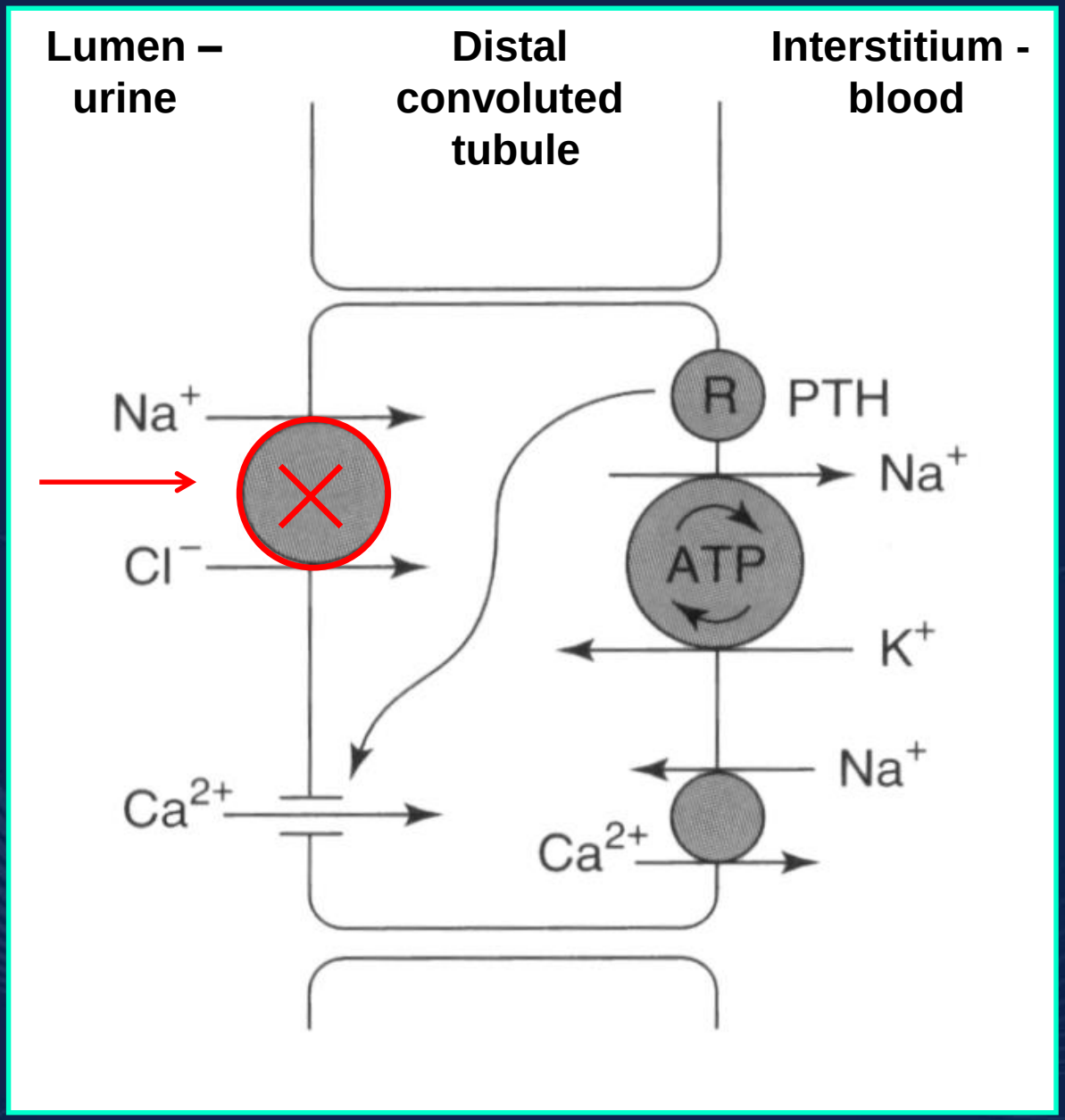
- drugs of first choice for treating patients with ***mild hypertension*** often combined with another drug in treatment of more severe hypertension

THIAZIDES

hydrochlorothiazide, clopamid, chlorthalidone
indapamid, metipamid

- preferable (to loop diuretics) for the treatment of uncomplicated hypertension
- given by mouth as a single morning dose
- begin to act within 1-2 hours and work for 12-24 hours
- treatment should be started using a low dose

Thiazides


Lumen – urine
Distal convoluted tubule
Interstitium - blood
Na+
Cl−
Ca2+
R
PTH
Na+
ATP
K+
Na+
Ca2+

Mechanism of action:

lower blood pressure by reduction of blood volume and by direct vascular effect

- inhibition of sodium chloride transport in the early segment of the distal convoluted tubule → ↑***natriuresis, decrease in preload and cardiac output - renal effect***

- slow decrease of total ***peripheral resistance*** (raised initially) during chronic treatment, suggesting an action on resistance vessels - ***extrarenal effects***

compensatory responses to pressor agents including angiotensin II and noradrenaline are reduced during chronic treatment with thiazides

- used with loop diuretic - synergistic effect occurs

Adverse effects

- **metabolic and electrolyte changes**

  hyponatremia

  ***hypokalemia (*combine with potassium-sparing diuretics)**

  hypomagnesemia

  ***hyperuricemia* (most diuretics reduce urate clearance)**

  hyperglycemia

  ***hypercalcemia* (thiazides reduce urinary calcium ion clearance)**

- **idiosyncratic reactions (rashes - may be photosensitivity, purpura)**

LOOP DIURETICS

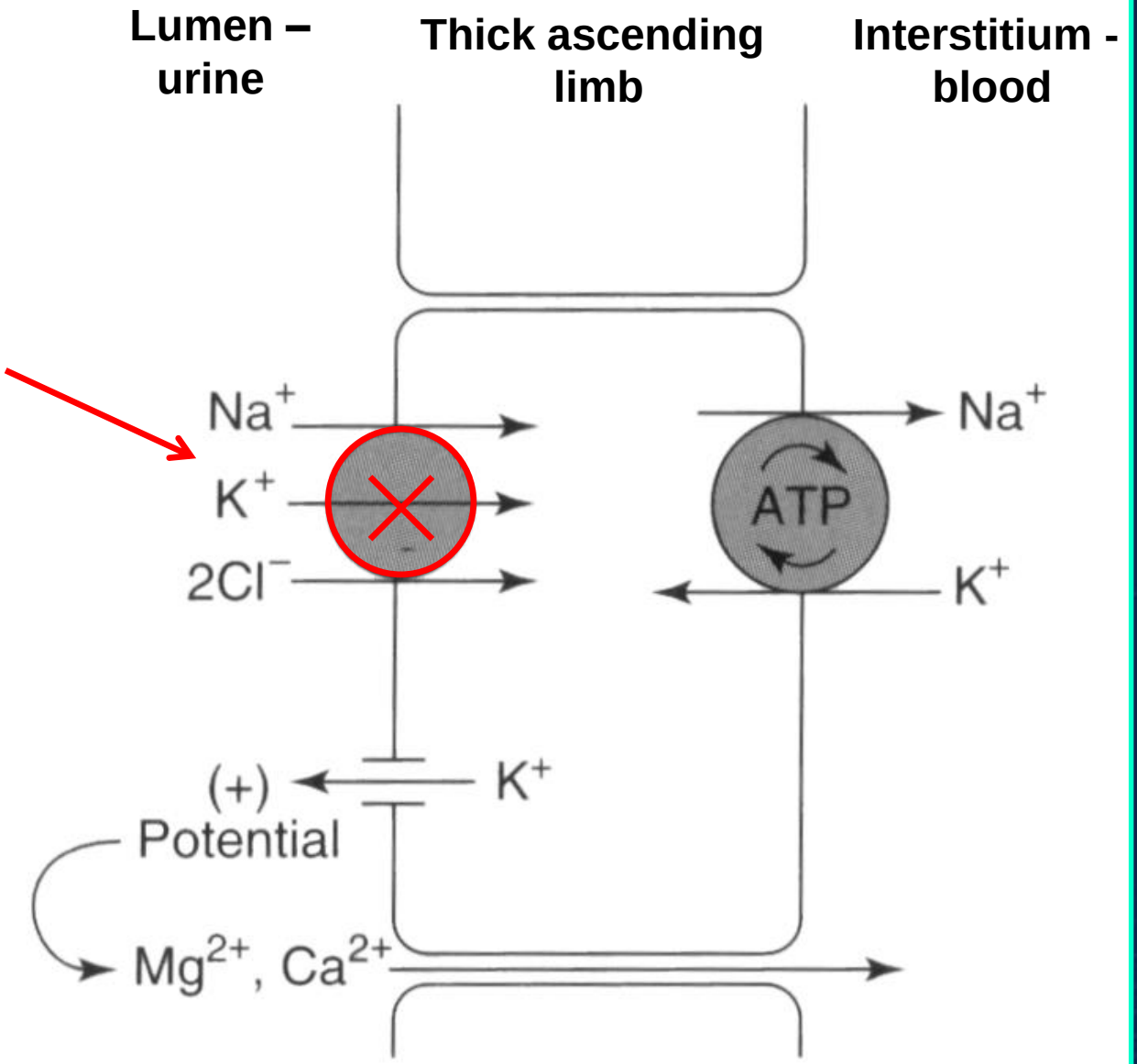
furosemide, bumetanide, torsemide

- useful in hypertensive patients with moderate or severe renal impairment, or in patients with hypertensive heart failure
- relatively short-acting (diuresis occurs over the 4 hours following a dose) → used in hypertension if response to thiazides is inadequate

Mechanism of action:

- they inhibit the co-transport of Na^+, K^+ and $2Cl^-$
- ↑ of Ca^{2+} and Mg^{2+} excretion
- they have useful pulmonary vasodilating effects (unknown mechanism)

Furosemide


Lumen – urine
Thick ascending limb
Interstitium - blood
Na+
K+
2Cl−
ATP
Na+
K+
(+) Potential
K+
Mg2+, Ca2+

Adverse effects

- hypokalemic metabolic alkalosis (↑ excretion of K^+)
- ototoxicity (dose dependent, reversible)
- hypomagnesemia
- hyperuricemia (block of uric acid tubular secretion)
- sulfonamide allergy
- risk of dehydration (> 4 L urine/ 24 h)

Important drug interaction may occurs if loop diuretic is given with Li^+ (antimanic drug). Decrease of Na^+ reabsorption can lead to increase of Li^+ reabsorption → toxicity.

Potassium-sparing diuretics

act in the distal tubule and the collecting tubule to inhibit Na^+ reabsorption, K^+ secretion, H^+ secretion

they are often used with a thiazide diuretic to spare potassium

Spironolactone, *(eplerenone)*

- it is an aldosterone antagonist
- is useful in patients with high level of aldosterone
- it has low diuretic efficacy ⇨ its advantage is sparing of potassium
- it is often used with loop or thiazide diuretics

.

Amiloride

- it has similar potassium-spring action to that of spironolactone

- its efect is independent on aldosterone concentration

- it si also frequently used with other diuretics

β-Blockers

- **several clinical studies have clearly demonstrated improved systolic functioning and reverse cardiac remodeling in patients receiving β-blockers**

- **the benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of the chronic activation of the sympathetic nervous system, including decreasing the heart rate and inhibiting the release of renin**

- **in addition, β-blockers also prevent the direct deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy and cell death**

- **two β-blockers have been approved for use in HF: carvedilol, and long-acting metoprolol**

- **Carvedilol is a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors, whereas metoprolol is a β_1-selective antagonist**

- **carvedilol and metoprolol reduce morbidity and mortality associated with HF**

- **treatment should be started at low doses and gradually titrated to effective doses based on patient tolerance**

β-blockers – immediate effects

- ⬇ heart rate
- ⬇ BP
- ⬇ heart ejection fraction
- vasoconstriction

β-blockers – chronic application

⇩myocardial O_2 consumption

⇩ heart rate & better myocardial blood supply by the increased blood flow duration in diastole

metabolism amelioration –

⇩ anaerobic glycolysis

⇧oxidative phosphorylation

⇧ energy reserve =

⇧ systolic function

⇧ sensitivity of β-receptors

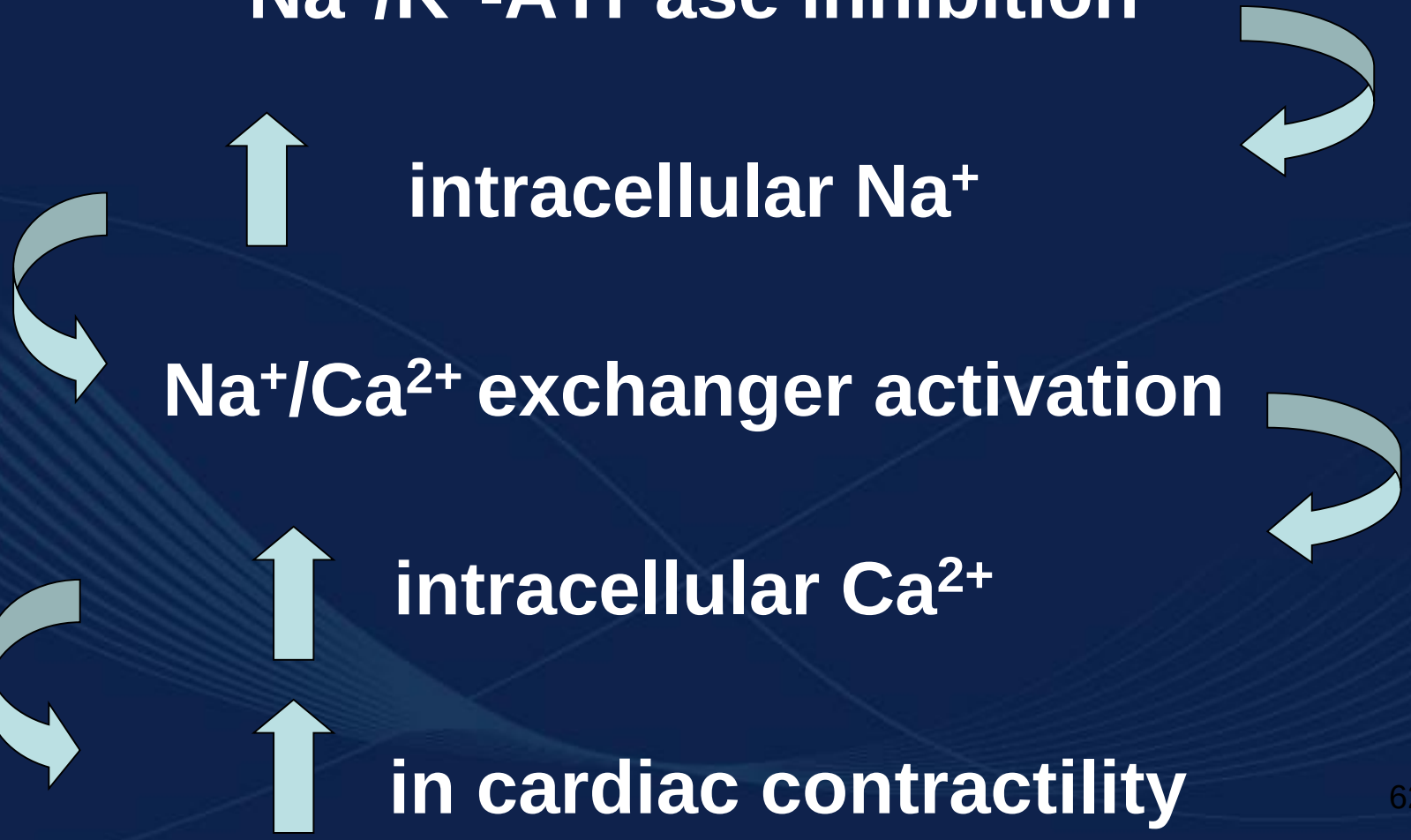
myocardial protection against toxic effects of catechoamines

⇩ renin release

Cardioglycosides

- **digitoxin** – ***Digitalis purpurea***
- **digoxin** – ***Digitalis lanata***
- **strophantin (ouabain)** – ***Strophantus gratus***

Mechanism of action



Cardioglycoside side effects
(approx. 20%)

Cardiac

- arrhythmias (ventricular extrasystole, atrial tachycardia, SA & AV block, ventricular tachycardia)

GIT

- anorhexia, nausea, vomitus, diarrhea

CNS

- headache, drowsiness, fatigue, disorientation
- visual disturbances (yellow-green vision)

Cardioglycosides - CI

Absolute

- ventricular tachykardia in recent IM
- AV-block II. a III. degree
- i.v. calcium application

Relative

- HF with mechanical obstacle without atrial fibrilation
- gravidity, breast feeding

Cardioglycosides - intoxication

Symptoms

a) mild intoxication

- anorhexia, nausea, vomitus
- bradycardia
- headache

b) severe intoxication

- visual disturbancies, disorientation
- diarrhea
- ventricular tachycardia, fibrilation
- SA & AV block

Intoxication therapy

- discontinue drug application
- stomach lavage + activated charcoal
- kalium chloratum
- in case of arrhythmias – fenytoin, lidocain
- antiobodies
- ECG & serum electrolyte control

Factors increasing risk of intoxication

1. Disturbancies in electrolyte homeostasis
   - hypokalemia
   - hypercalcemia
   - hypomagnesemia
2. Drugs
   - chinidine - ⇩clearance of digoxin - accumulation
   - diuretics
   - corticosteroids
3. Diseases
   - hypoxia, renal failure, myocarditis

Chronic HF therapy 1

- ACE-I - “gold standard"
- β-blockers regularly after MI
- ARB – in case of cough after ACE-I
- in fluid retention - diuretics (thiazide, later loop)
- in atrial fibrilation - digoxin
- digoxin in NYHA II-III in case of side effects during ACE-I, diuretics, β-blockers therapy

Chronic HF therapy 2

- in ventricular arrhythmia - amiodaron
- do not use β-blockers with ISA, prefer blockers with vasodilating effects (carvedilol)
- control of other diseases (DM, hyperlipoproteinemia)
- life style