Antihypertensives

Definition of ARTERIAL HYPERTENSION

- Definition : repeated increase of blood pressure (systolic-diastolic) 140/90 mmHg or higher in patients older than 18 years in at least two of three measurements in two different checks

  - The most often disease of cardiovascular system
  - AH + hyperlipidemia +DM + nicotine addiction

  premature atherosclerosis & ischemic heart disease

- prevalence in elderly 20-50 %, 35 % in CZ

Classification

- **Ethiology**
  - **Primary – essential**
  - **Secondary**

- **Primary – essential**
  - App. 90 % of all patients with HT
  - Multifactorial disease without organic reason

Classification

- **Ethiology**
  - **Primary – essential**
  - **Secondary**

Secondary hypertension

- **Nephropathy** – the most often
- **Endocrine** – suprarenal gland (hyperaldosteronismus)
- **Renovascular** – renal arthery disease
- **Iatrogenic** – long-term use of corticosteroids, NSA, sympatomimetics, HAT
- **Gestation** – HT in pregnancy

Treatment goals in hypertensive patients

SBP < 140 mm Hg

low- moderate CV risk

diabetes

previous stroke or TIA

SBD between 150 and 140 mm Hg

elderly < 80 years

elderly > 80 years in good condition

DBP < 90 mmg Hg

always recommended, except diabetes (< 85 mm Hg)

Blood Pressure regulation

- **decrease / increase**

Peripheral resistence
(vasoconstriction/vasodilatation)

- **decrease / increase**

Blood volume, cardiac output

THERAPY OF ARTERIAL HYPERTENSION

1. **NON-PHARMACOLOGICAL**
2. **PHAMACOLOGICAL**

decrease the risk of cardiovascular disease /
target BP ↓ **140/90 mm Hg (high-risk 140/85 mm Hg)**

2. PHARMACOLOGICAL

- **WHEN ?**
- **WITH ?**

- **MONOTHERAPY** (app. 30 % of the patients)
- **COMBINATION, lower doses /Fixed combination -** better compliance, *more problematic titration* **/**

Next steps

✓ + drug

✓ Increase the dose

Changes - 4-6 weeks interval, urgent situation immediatelly

Drug classes

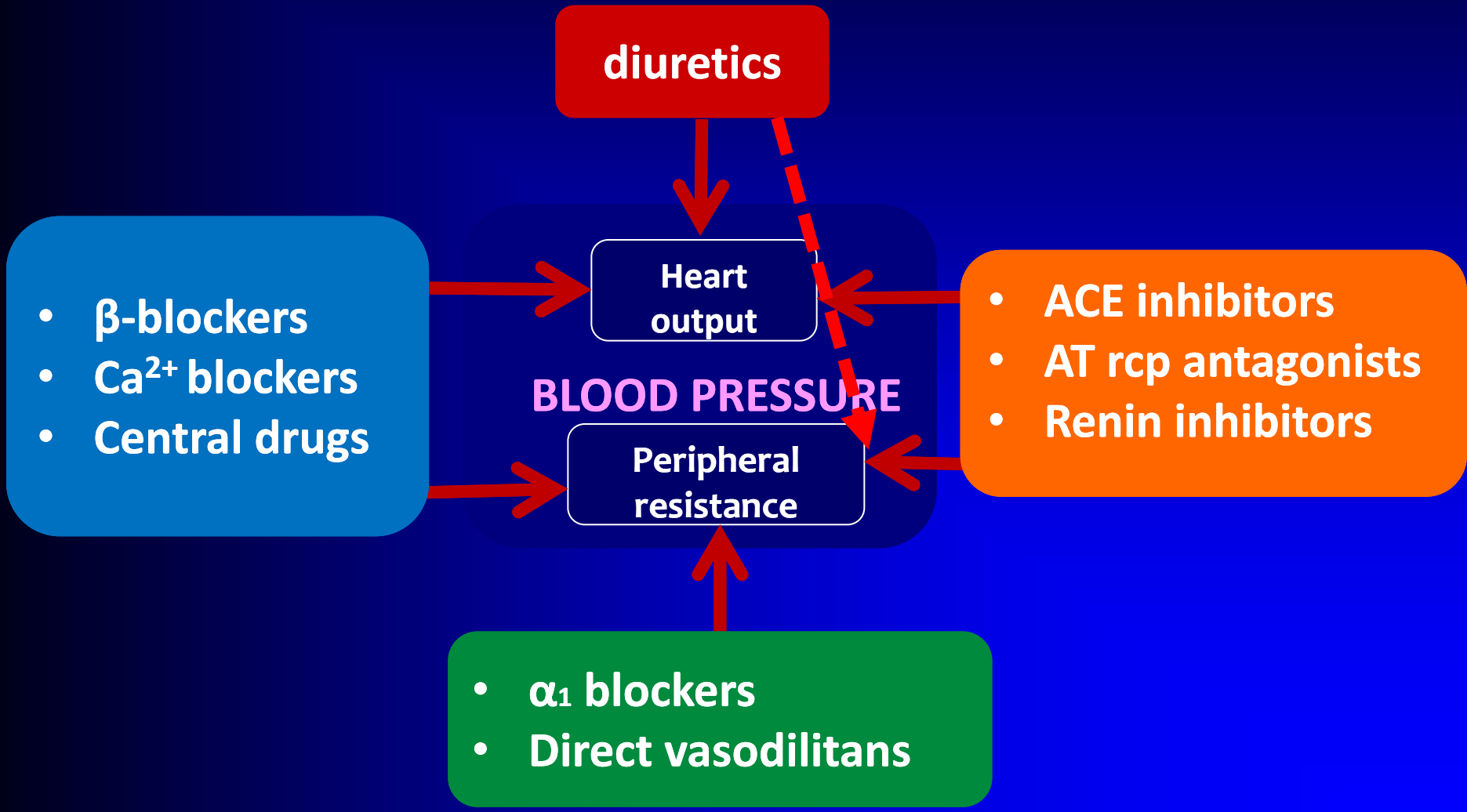
1st line treatment

- ACEi
- AT-II inhibitors
- CCB
- Diuretics
- BB

2nd line treatment

- Central acting drugs
- α_1-lytics
- Renin inhibitors

PHARMACOTHERAPY



1. ACEi
2. AT_1-antagonists

R-A-A-S

Hyperactivation leads to ↑ TK

✓ ↑ blood volume **(aldosteron) +**

✓ ↑ peripheral resistence **(A II)**

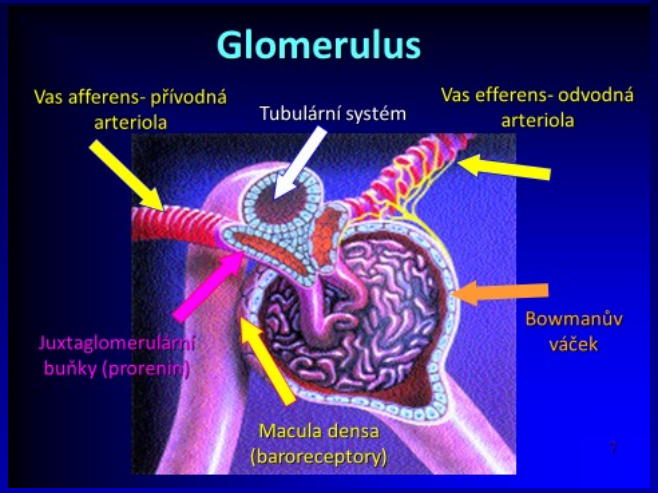
AT II actions include also…

induction of growth, cell migration, mitosis of vascular smooth muscle cells, increased synthesis of collagen type I and III in fibroblasts, leading to thickening of the vascular wall and myocardium, and fibrosis.

Physiology

RENIN

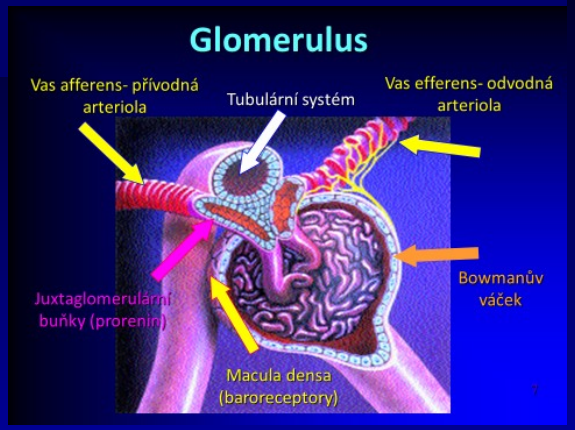
juxtaglomerular apparatus; as prorenin



- Signal from baroreceptors *(decreased BP)*
- Signal from chemoreceptors *(decreased Na load)*
- Stimulation of β_1 adrenergnic receptors

RENIN / **PRORENIN** are hormons

Physiology



RENIN

PD effect

❖ **PROTEOLYTIC ENZYME**

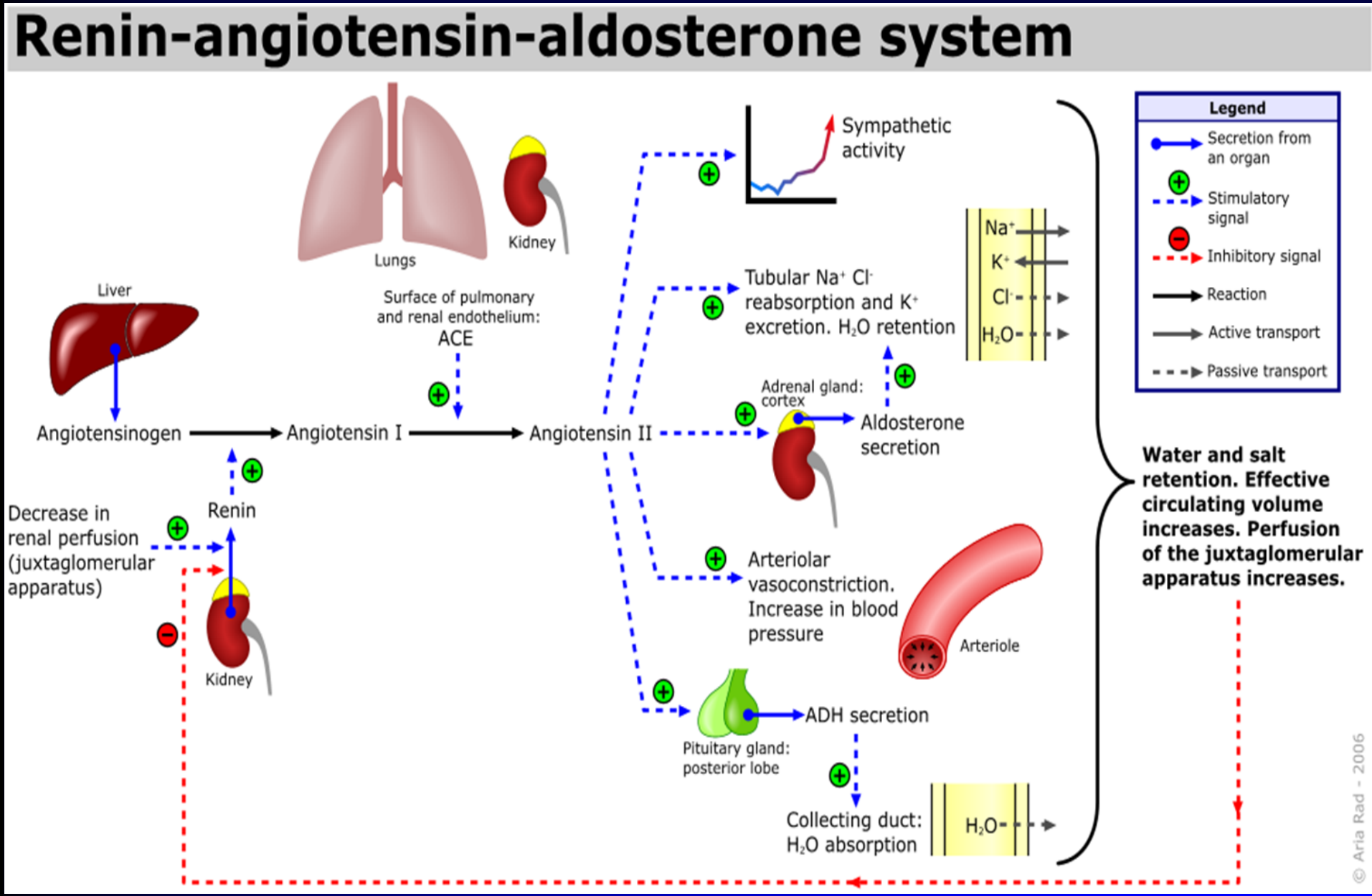
endopeptidase acts on **angiotensinogen splitting off a decapeptid angiotensin I**

inactive, but converted to AT II (potent vasoconstrictor)

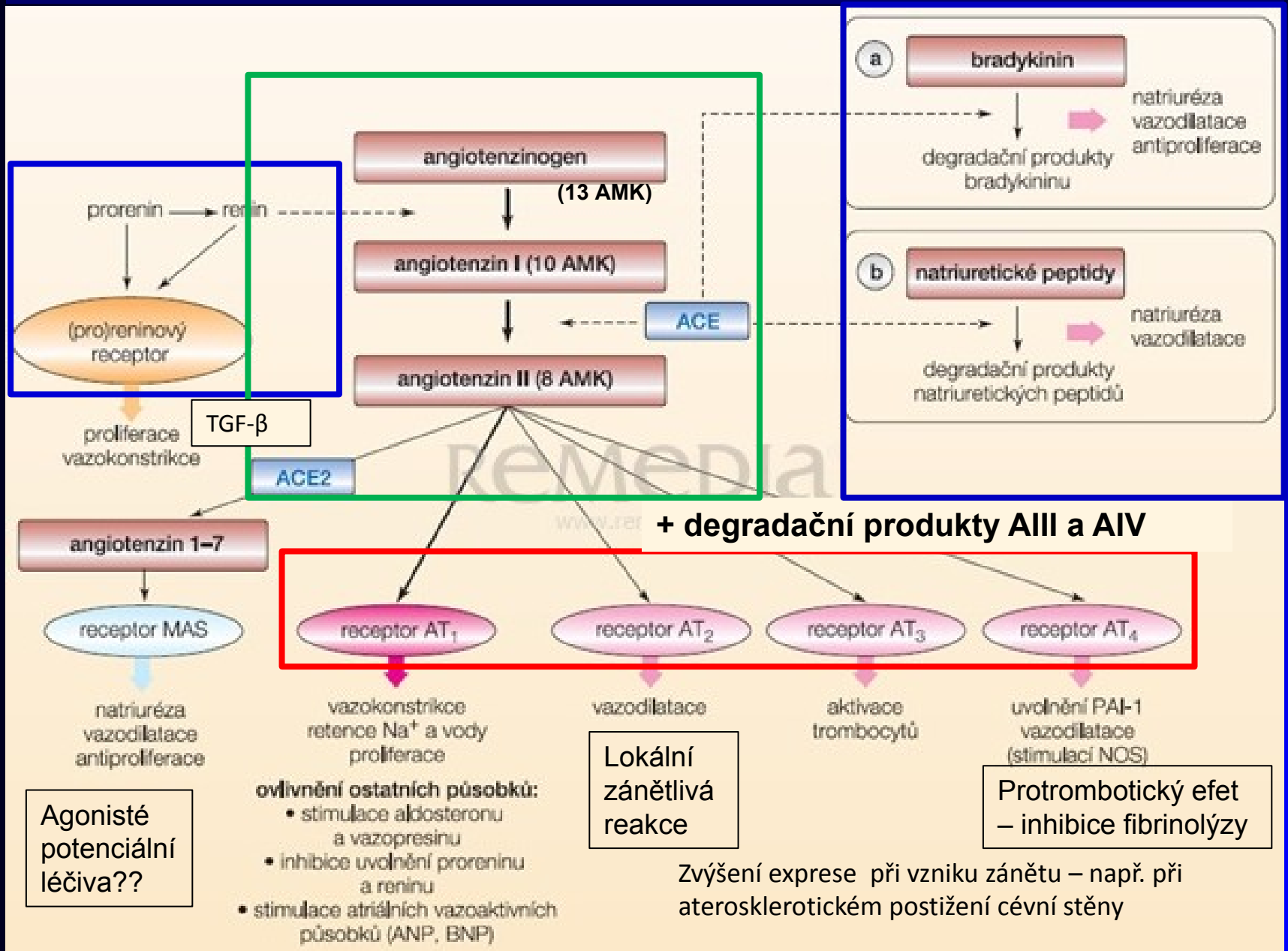
❖ **NON-PROTEOLYTIC ACTIVITY**

induction of synthesis of **TGF-β a PAI-1** ⇨ fibroproduction and remodelation of tissues ⇨ etiopathogenesis of CVD (!)

RAAS


Renin-angiotensin-aldosterone system
Lungs
Kidney
Liver
Surface of pulmonary and renal endothelium:
ACE
Angiotensinogen
Angiotensin I
Angiotensin II
Renin
Decrease in renal perfusion (juxtaglomerular apparatus)
Kidney
Sympathetic activity
Tubular Na+ Cl- reabsorption and K+ excretion. H2O retention
Na+
K+
Cl-
H2O
Adrenal gland: cortex
Aldosterone secretion
Arteriolar vasoconstriction. Increase in blood pressure
Arteriole
ADH secretion
Pituitary gland: posterior lobe
Collecting duct: H2O absorption
H2O
Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Legend
Secretion from an organ
Stimulatory signal
Inhibitory signal
Reaction
Active transport
Passive transport
© Aria Rad - 2006

R-A-AS


a
bradykinin
natriuréza
vazodilatace
antiproliferace
degradační produkty
bradykininu
b
natriuretické peptidy
natriuréza
vazodilatace
degradační produkty
natriuretických peptidů
angiotenzinogen
(13 AMK)
prorenin
renin
angiotenzin I (10 AMK)
ACE
(pro)reninový
receptor
angiotenzin II (8 AMK)
proliferace
vazokonstrikce
TGF-β
ACE2
+ degradační produkty AIII a AIV
angiotenzin 1–7
receptor MAS
receptor AT1
receptor AT2
receptor AT3
receptor AT4
natriuréza
vazodilatace
antiproliferace
vazokonstrikce
retence Na+ a vody
proliferace
ovlivnění ostatních působků:
• stimulace aldosteronu
a vazopresinu
• inhibice uvolnění prorenina
a reninu
• stimulace atriálních vazoaktivních
působků (ANP, BNP)
vazodilatace
aktivace
trombocytů
uvolnění PAI-1
vazodilatace
(stimulací NOS)
Agonisté
potenciální
léčiva??
Lokální
zánětlivá
reakce
Protrombotický efet
– inhibice fibrinolýzy
Zvýšení exprese při vzniku zánětu – např. při
aterosklerotickém postižení cévní stěny

R-A-AS - final step ALDOSTERON

the main mineralocorticoid hormone

produced by the zona glomerulosa of the adrenal gland
by acting on the mineralocorticoid receptors in the distal tubules and collecting ducts of the nephron

- Na^+ + H_2O reabsorption
- Tubular secretion K^+ (antiport Na-K)

Stimulation of aldosteron production:

- ACTH
- AT II
- ↑ K^+ ionts

Inhibition of production:

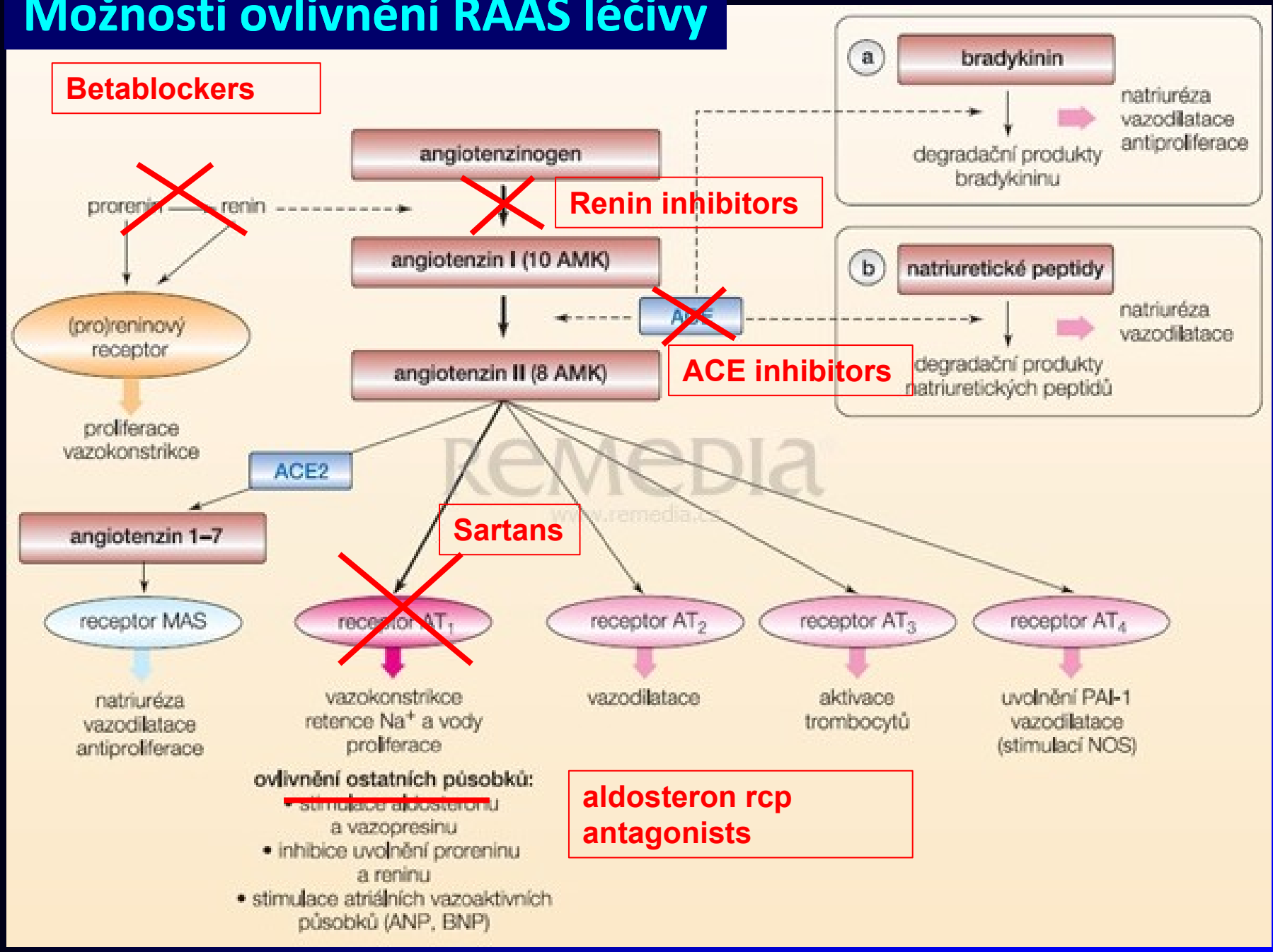
- Negative feadback regulation

Inhibition of R-AA-S

Different level…

- **Beta – blockers** (inhibition of renin secretion)
- **Renin inhibitors** (inhibition of conversion angiotensionogen to AT I)
- **ACEi** (inhibition of conversion of AT I to AT II)
- **sartans** (antagonization of AT_1-rcp)
- **Antagonisation of aldosteron receptor**

Možnosti ovlivnění RAAS léčivy

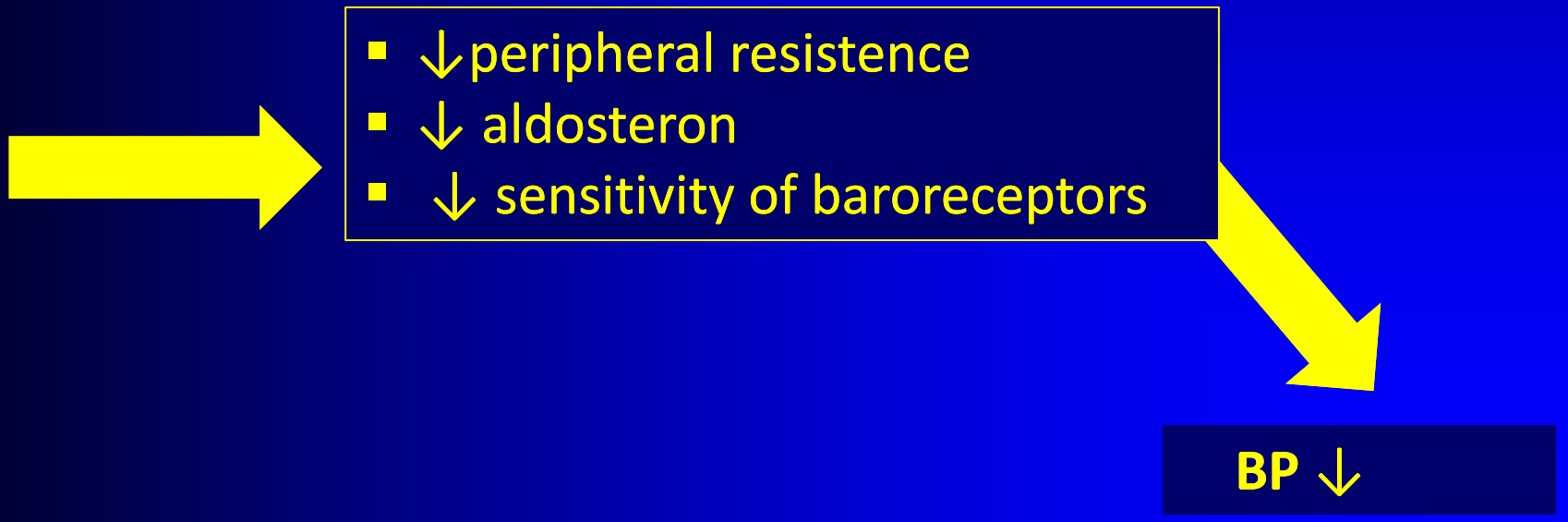


1. ACEi

MECHANISM OF ACTION

1. Reversible antagonisation of ACE (dipeptidase)

2. Block od bradykinine degradation ⇨ prolongation of vasodilatation and natriuretic effect



PK

- Given orally
- Bioavailability 50-75 %
- Liver metabolisation (to the active metabolite)
- Renal elimination /glomerular filtration/

- Variable half-life

  13-36 hrs ramipril(ate)

  30-120 hrs perindopril(ate)

ACEi

ADVANTAGE

- Safe and effective drugs in monotherapy as well as combination
- **Favorable profile on carbohydrates** (diabetic patients)
- **Cardioprotective effect**
- **Renoprotective effect** (↓ albuminuria)

Classification accoring to $t_{1/2}$:

- **Short-acting** (3x/ per day)
  $t_{1/2}$ = app. 2 hrs, effect app. 8 hrs
  CAPTOPRIL (not used)

- **Intermediatte** (1-2x/ per day)
  $t_{1/2}$ = app. 6-12 hrs, effect app. up to 24 hrs
  ENALAPRIL*, LISINOPRIL, FOSINOPRIL

- **Long-acting (1x/ per day)**
  $t_{1/2}$ = app. 13-36 hrs (perindopril 120 hrs)
  TRANDOLAPRIL♦, RAMIPRIL, PERINDOPRIL

---

* **i.v.** (hypertensive crisis) ♦ **lowest onset of action**

ADVERSE EFFECTS

ACEi

- **Dry irritant cough.** **The most common**
  ↓ degradation of bradykinin

- **Hyperkalemia.** (↓ aldosteron ⇨ inhibition of Na/K antiport)
  lab monitoring K, urea and kreatinine level (mainly during the first period of tretament)

- **Angiooedema.** allergic/ hereditary angioedema

- **Teratogenity.** KI in gravidity *(second and third trimestr)*

- **(hypotension)**

ACEi

INDICATION

- **Arterial hypertension*** /suitable in DM pts. /
- **Chronic Heart Failure*** – /↓ LVF, remodelation and **hypertrophy** of left ventricule/
- **Secondary prophylaxy of trombotic complication** * (IM, stroke)
- **Diabetic /non-DM/ nephropathy**

Long-time administration of ACEI for clinical benefit

* The best RR in RCT: **PERINDOPRIL, RAMIPRIL**

ACEi

CONTRAINDICATION

- **GRAVIDITY ***
- **Hypercalemia**
- **Bilateral stenosis of renal arteries** with clinically significant ↓ GF (relative KI)
- **Angioedema in anamnesis**
- **Primary hyperaldosteronism** (non-responders)

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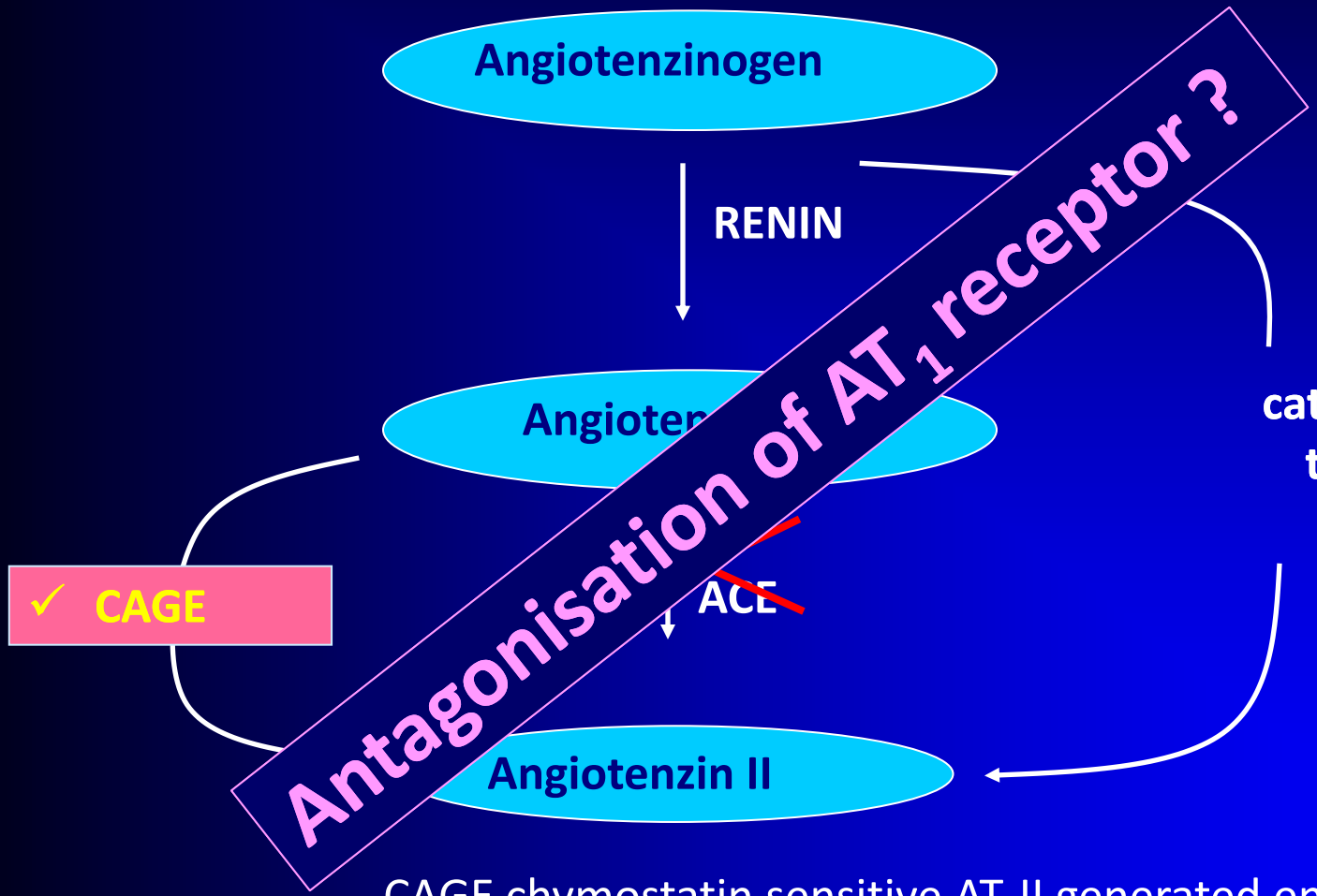
* All RAAS acting drugs

Alternative synthesis of AT-II not inhibited by ACEi



CAGE chymostatin sensitive AT-II generated enzyme (veins)
t-PA – tissue plazminogen activator
catepsin – serum protease

2. AT_1 RECEPTOR ANTAGONISTS – SARTANS (ARB)

MECHANISM OF ACTION

Non-competitive/competitive antagonisms of AT_1 receptor (selective)

⇨ **↓ peripheral vascular resistance**
⇨ **vazodilatation**
⇨ **↓ volume**

↓ BP

ACE not affected – cough not present

PHARMACOKINETICS

Sartans

Biological half-life

EPROSARTAN

LOSARTAN - prodrug - CYP2C9 metabolisation. Drug interaction!!

VALSARTAN – nephroprotective drug

CANDESARTAN – EBM efficacy in CHF

OLMESARTAN

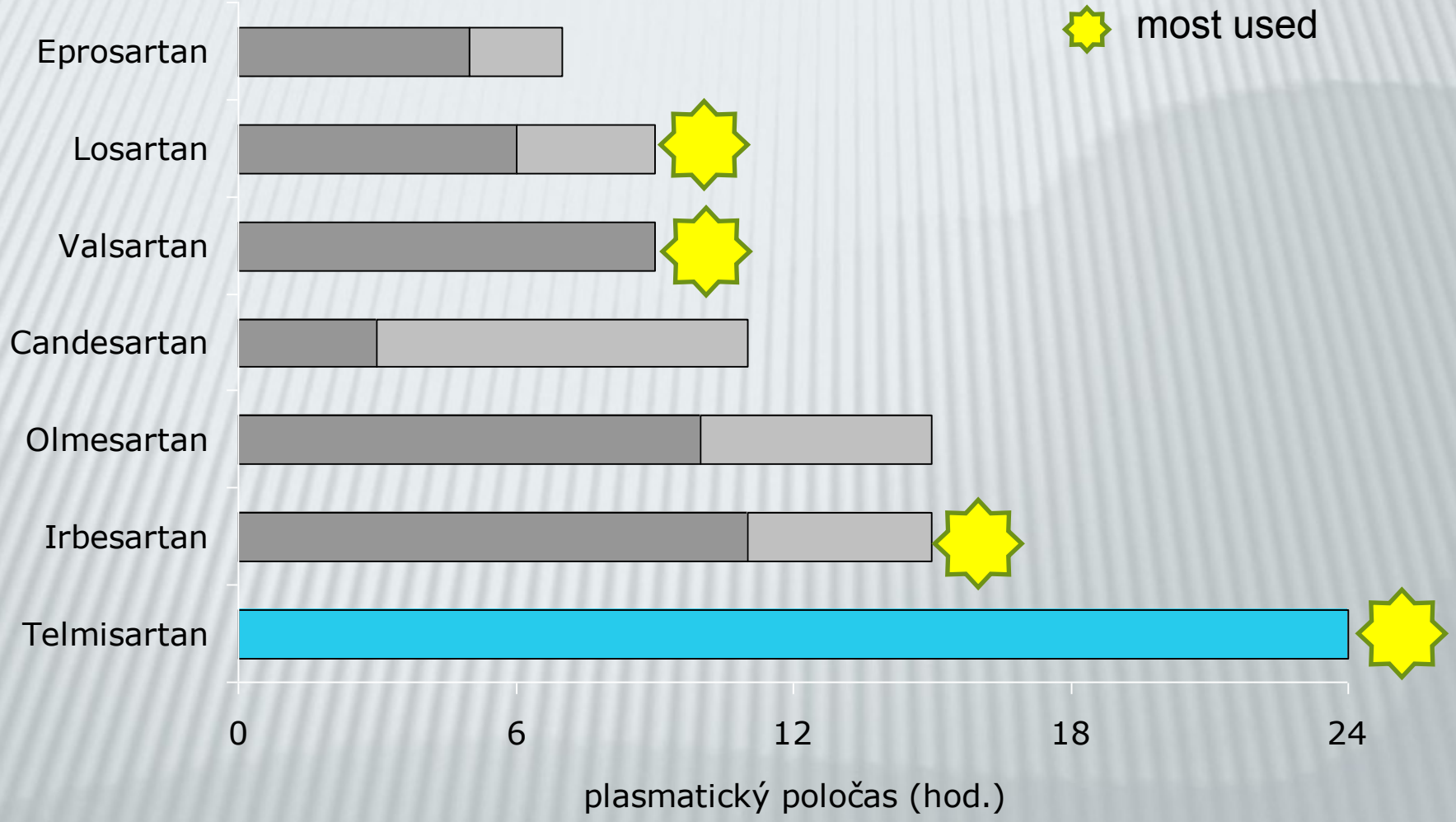
IRBESARTAN

TELMISARTAN - long half-life

Strong inhibitor of P-glp, hepatal elimination

Partial agonist of PPAR-γ receptor → better metabolic profile

Angiotensin receptor blockers (ARB)



ADVERSE EFFECT

- (hypotension)
- Hyperkalemia
- angioedema less common

At the beginning and during the treatment lab monitoring – kalium, urea and creatinine

Sartans

INDICATION

- **Arterial Hypertension** (ACEI a sartans, both effective)
- **Chronic Heart Failure** (ACEi better, only for – pouze pro candesartan EBM data for ↓cardiovascular complications)
- **Diabetic nephropathy with proteinuria** (data for telmisartan and valsartan)
- **Cough after ACEi**

CONTRAINDICATION

- **Pregnancy, lactation**
- Hyperkaemia
- Angioedema in anamnesis
- Bilateral stenosis of renál arteries (relative contraindication)

DRUG INTERACTION of RAAS drugs

- **LITHIUM** ⇨ ↑ plazmatic level of **LITHIUM** (based on PK)

- **NSAID, ASA (more than 3g/day)**
  - ⇨ ↓ antihypertensive effect
  - ⇨ ↑risk of renal function
  - ⇨ ↑risk hyperkalemia

  (PD interaction)

LOSARTAN + **strong** inhibitor of CYP2C9 (**FLUCONAZOL**) ⇨ ↓ level of active metabolitace (50%)

TELMISARTAN (strong inhibitor of P-glycoprotein) + **DIGOXIN** ⇨ ↑digoxin level

Combination - dual effect

Entresto®

ARNI =

Angiotenzin receptor blocker / neprilysin inhibitor

VALSARTAN + **SACUBITRIL** ⇩ prodrug

NEPRILYSIN = enzyme catalysed degradation of endogenous vasodilatative natriuretic petides

neprilysine inhibition ⇨ prolongation of effects

⇨ ↓ **BP**

INDICATION:

Hypertension + symptomatic chronic heart failure with ↓left ventricular fraction in adult patients

CONTRAINDICATION:

- Hypersensitivity
- Concomitant therapy with ACE inhibitors
- Angioedema
- Concomitant therapy with renin inhibitors

RENIN INHIBITORS

Second line treatment of hypertension !

MECHANISM OF ACTION

Selective direct renin inhibitor

Binds to active site of renin, changes its steric confirmation and inhibits its binding to angiotensinogen

⇨ **block conversion of angiotenzinogen to angiotensin I**

DRUGS

ALISKIREN

Registered

Oral form, non-peptide, LW

Combination with diuretics, ARBs – additive effect

PHARMACOKINETICS

- Bioavalability 15%, effect is not influenced by food
- long T1/2 (about 24 hrs)
- **First pass efect**
- **Biliary excretion** (78 %) and **kidney excretion** (< 10%)

INDICATION

Essential hypertension

CONTRAINDICATION

- Hypersensitivity, allergic reaction in anamnesis
- Gravidity (mainly 2. a 3. trimester), lactation
- Bilateral stenosis of arteria renalis
- Severe nephropathy

ADVERSE EFFECTS

- **diarhhoea** (the most often)
- **veretigo**
- **atralgia**
- **Hyperkalemia**
- **Oedema** (< 1%)

In combination with sartans ↑ stroke in older patients

3. Ca CHANNEL BLOCKERS

Previous lecture

For the treatment of hypertension:

DIHYDROPYRIDINES

- ↓peripheral vascular resistance (vazodilatation)
- vasoselective (relatively)

4. DIURETICS

Next lecture

5. β blockers β sympatolytics)

From previous lecture…

Drugs for second line treatment of hypertension

CENTRAL ANTIHYPERTENSIVES

- Central α_2-agonists
- Imidazolin I_1 receptor agonists
- Central α_2-agonists + peripheral α_1-antagonists

α_1-receptor antagonists

VASODILATANS (direct)

- Nitrates
- PDE-5 inhibitors
- Endotelin-1 antagonists
- Syntetic analogs of prostacyclines

Previous lecture

CENTRAL ANTIHYPERTENSIVES

Indirectly acting vasodilatators – the central control of sympathetically mediated vasoconstriction:

METHYLDOPA
KLONIDIN

- **central α_2 rcp. (brain stem)**
- **imidazoline rcp. (ventrolateral medulla)**

ACTIVATION ⇨ reducing sympathetis activity

MOXONIDIN
RILMENIDIN

Peripheral activation:

- **peripheral presynaptic α_2 rcp.**
  ⇨ ↓NA
- **Imidazolin receptors in kidney**
  ⇨ stimulation of Na^+/H^+ pump in proximal tubulus

CENTRAL ANTIHYPERTENSIVES

❖ Central α_2 agonists

METHYLDOPA

MoA:

- Activation of central α_2 rcp. in brain stem and peripheral presynaptic α_2 rcp.
- indirect sympatholytic activity - false NRA precursor/ prodrug
  α –metyldopa → α –methylnorepinephrine → activation of α_2 adrenergic receptors

CLONIDIN

MoA:

- Activation of central α_2 rcp and imidazolin I_2 receptors

METHYLDOPA

Disadvantages:
Short half-life ⇨ more time daily

INDICATION:

- Hypertension **in pregnancy**
- Hypertension in patient with **renal insufficiency**

GF is not affected

- Patients with anxiety
- Without metabolic effect - in combination for patients with **DM, HLP**

ADVERSE EFFECT:

Sedation, nasal congestion, dry mouth, orthostatic hypotension

Methyldopa combined with diuretics

CLONIDIN

INDICATION:

Hypertensive crisis (ICU) – *on request*

Essential hypertension - obsolent

ADVERSE EFFECTS:

- **rebound fenomen**

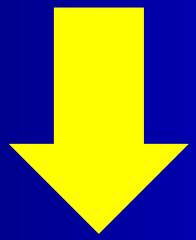
CENTRAL ANTIHYPERTENSIVES

❖ Imidazoline I_1 receptor agonists

MOXONIDIN, RILMENIDIN

Mechanism of action:

I_1 receptor stimulation (medulla oblongata, kidney)



- Inhibition of sympathetic stimulation of heart, veins and kidney
- ↓renin secretion
- ↓ vasopresin secretion

ADVERSE EFFECTS

Selective agonists of I_1 receptors ⇨ minimal effect on **α_2 – rcp.** ⇨

- less AE

Positive metabolic profile

- Stimulation of Na excretion
- ↓ insulin resistence
- ↑glucose tolerance

INDICATION: prevention of diabetic nephropathy

CONTRAINDICATION: chronic heart failure

CENTRAL ANTIHYPERTENSIVES

❖ Central α_2 –rcp agonists + peripheral α_1 – rcp antagonists

URAPIDIL MoA:

Agonistic effect
α_2 a $5HT_{1A}$ rcp. in CNS

Antagonistic effect
α_1 rcp. in vessels

Dual action

↓ sympatic tonus

vasodilatation

⇨ **↓peripheral resistence without reflex tachycardia**

- Significant antihypertensive effect
- i.v. administration – rapid onset

INDICATION:

- Rezistant hypertension
- Severe hypertension (stroke)
- **Emergent hypertension crisis (ICU)**
- Perioperative hypertension

- Well titrated (i.v. infusion)
- Rapid onset (maximal effect 2-5 minutes)

AE:

- Sedation (higher dosis)
- Bradycardia

CONTRAINDICATION:

Pregnancy, lactation

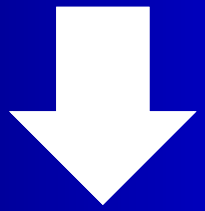
Liver insufficiency

PERIPHERAL α_1-receptor antagonists

MoA

Selective reversible antagonisation of peripheral α_1 receptors – **relaxation of vascular smooth muscle**

⇨ ↓peripheral vascular resistence



Slight increase of hert output

TERAZOSIN
DOXAZOSIN

INDICATION

- In combination – severe hypertension
- Vasospasm (Raynaud fenomen)

uroselective, blocks α_{1A}
TAMSULOSIN
ALFUZOSIN

INDICATION

- BHP
- Not used for hypertension

CONTRAINDICATION

- heart failure

ADVERSE EFFECTS

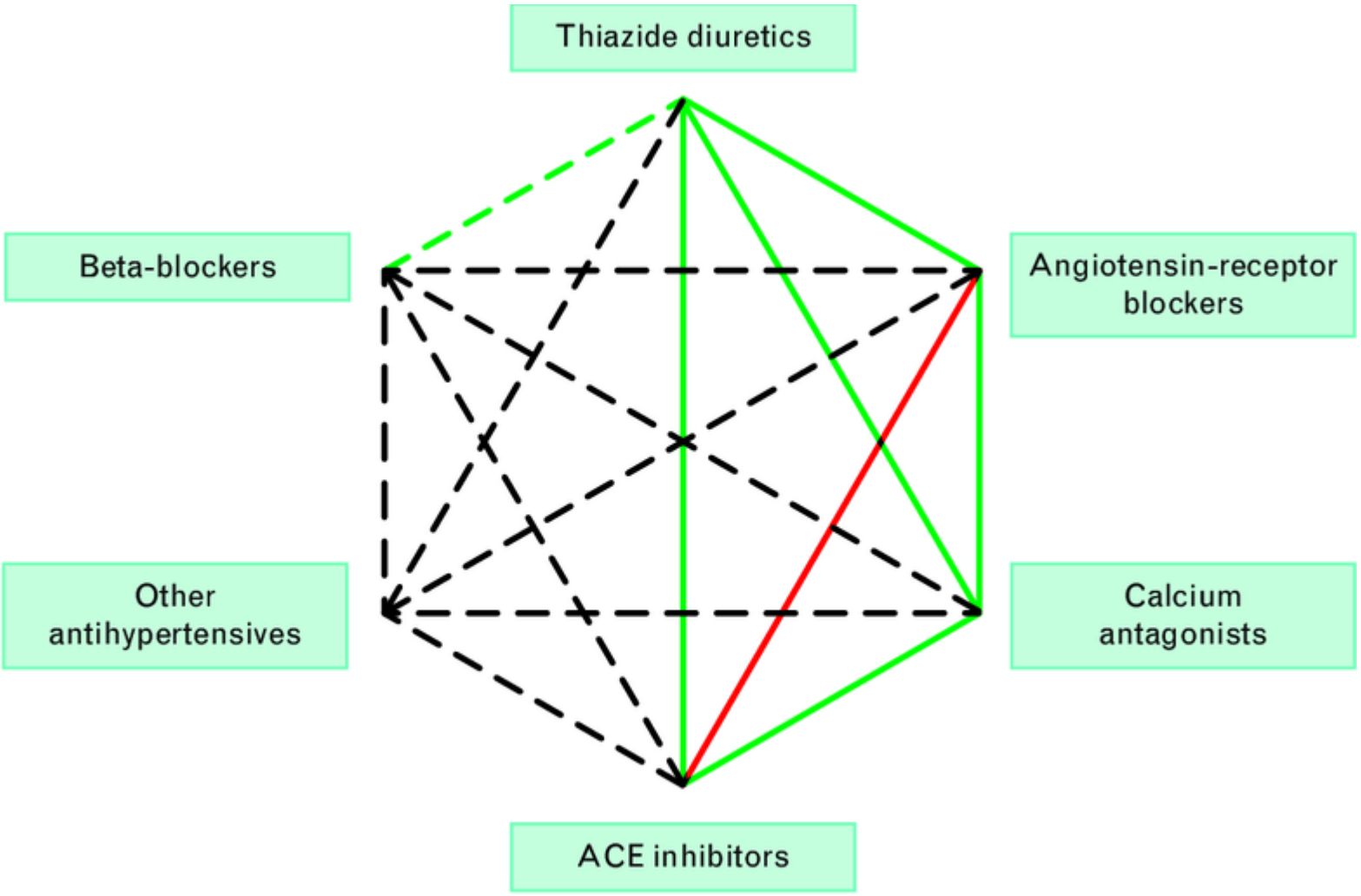
- Ortostatic hypotension
- Reflex tachycardia
- Impotency
- Oedema, cephalea, fatigue

COMBINATION OF DRUGS

MONOTHERAPY - 30 % of the patients
Combination - two or more drugs

fixed combination (2 v 1) - better compliance

COMBINATION OF DRUGS



ACE = angiotensin-converting enzyme.

HYPERTENSION IN GRAVIDITY

HT: Systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg

If systolic BP ≥ 170 mm Hg or diastolic BP ≥ 110 mm Hg – emergent situation with hospitalisation

PHARMACOTHERAPY

ACEi and sartans are contraidicated !
Relative contraindication – thiazide diuretics

- **Pre-existing hypertension**
  chronic medication, if not contraindicated

- **Gestational hypertension**
  METHYLDOPA (1st line)
  Metoprolol, atenolol – third trimester
  Pre-eclampsia – diuretics not recommended
  Severe hypertension LABETALOL i.v.

Thank you for your attention