

Inhibitorii Enzimei de Conversie a Angiotensinei I

Ovidiu Bedreag

Universitatea de Medicina si Farmacie "Victor Babes" Timisoara

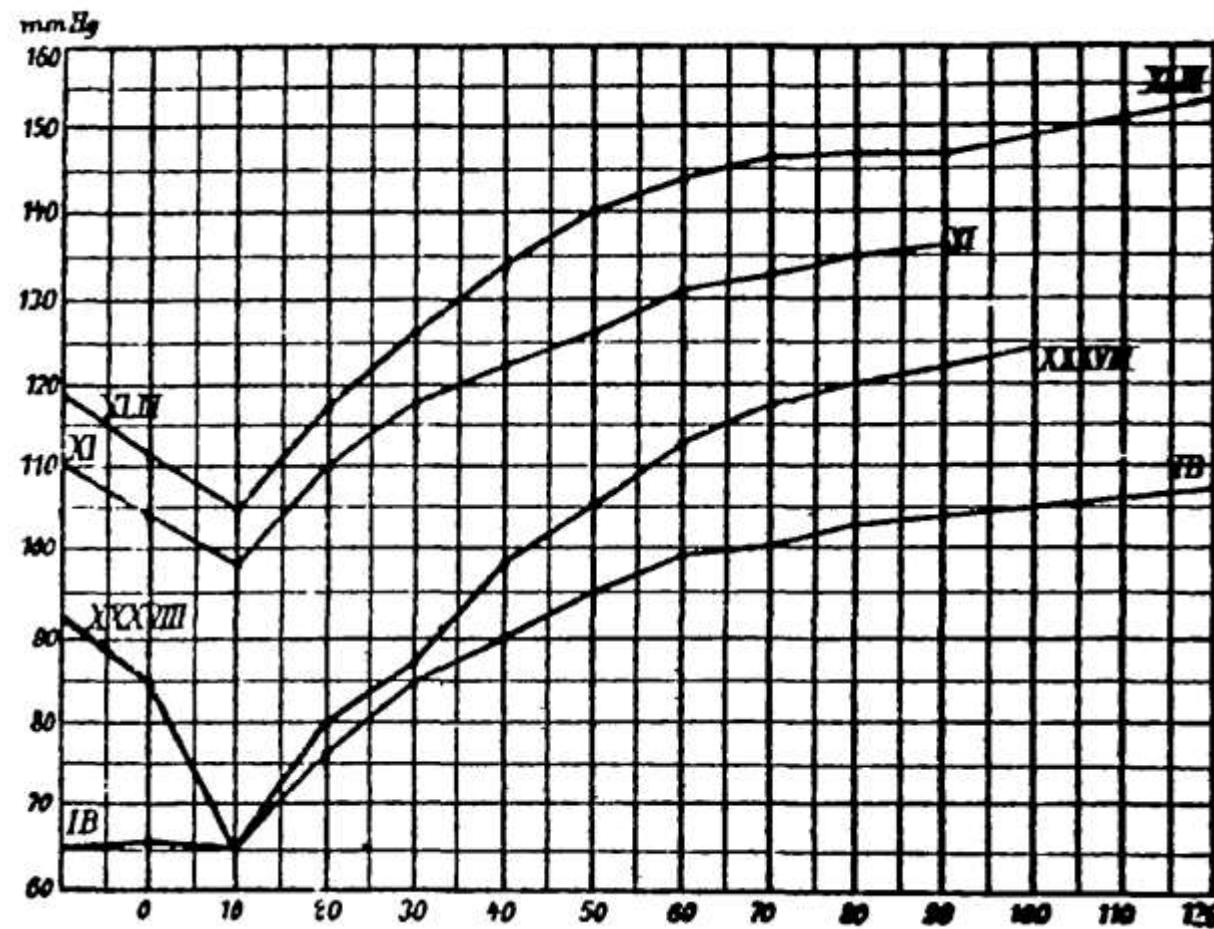
Inhibitorii Sistemului Renina-Angiotensina-Aldosteron

Istoric

Tigerstedt R, Bergman PG. Niere und kreislauf. Scand Arch Physiol **1898**; 8: 223.

- Ipoteza
“A blood-pressure raising substance is formed in the kidneys and passed into the blood”
- Metode
 - rinichi de iepure omogenizat in solutie salina
 - centrifugat
 - supernatantul injectat i.v. la alti iepuri a determinat hipertensiune

“For the sake of brevity we will call it Renin”



Tigerstedt R, Bergman PG. Niere und kreislauf. Scand Arch Physiol 8: 223, 1898

Istoric

Page IH, Helmer OM. **1939**. A crystalline pressor substance, angiotonin. *Proc Center Soc Clin Invest* 12:17.

Braun-Menendez E, Fasciolo JC. **1939**. La substancia hipertensora de la sangre del riñon isquemiado. *Rev Soc Argent Biol* 15:420–425.

- Extrasul purificat de renina are efect limitat asupra tensiunii arteriale
- Necesita

“substrat de renina”=“hipertensina” sau “angiotonina”



ANGIOTENSINA

Istoric

- 1970 Ferreira si col., 1971 Ondetti si col. izoleaza din veninul de sarpe peptide cu 5 pana la 9 resturi de aminoacizi, cu o actiune specifica de inhibare a conversiei angiotensinei I si de potentare a bradikininii.

Ferreira SH, et al. (June 1970). *Isolation of bradykinin-potentiating peptides from *Bothrops jararaca* venom*. *Biochemistry* **9** (13): 2583–2593.

Ondetti MA, et al. (October 1971). *Angiotensin-converting enzyme inhibitors from the venom of bothrops jararaca. Isolation, elucidation of structure, and synthesis*. *Biochemistry* **19** (22): 4033–4039.



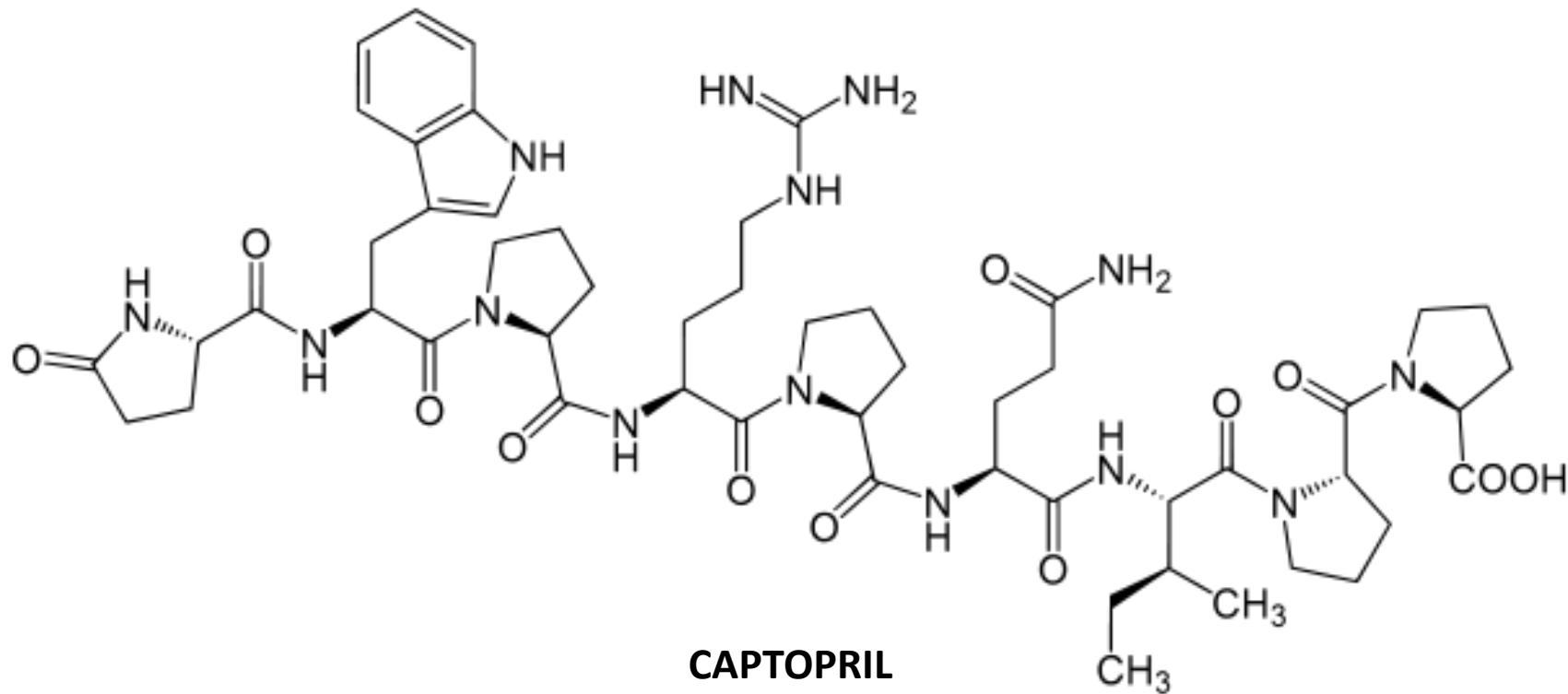
Istoric

- În 1974, Gavras a demonstrat că nonapeptidul *TEPROTIDE* era cel mai puternic și cel mai stabil dintre acești inhibitori și cel mai eficient medicament pentru tratamentul HTA la om.
- Nu era activ pe cale orală ci doar i.v.
- Nu a fost introdus în tratamentul cronic al HTA.

Istoric

- În 1977, Cushman și Ondetti au sintetizat primul *IECA* activ pe cale orala: captoprilul.

Istoric



Istoric

- De atunci si pana in prezent au fost sintetizati cel putin 16 blocanti ai enzimei de conversie.

CAPTOPRIL

ENALAPRILUM

BENAZEPRIL

CILAZAPRIL

FOSINOPRILUM

IMIDAPRIL

LISINOPRIL

MOEXIPRIL

PERINDOPRIL

QUINAPRIL

RAMIPRIL

TANDOLAPRIL

ZOFENOPRIL

Istoric

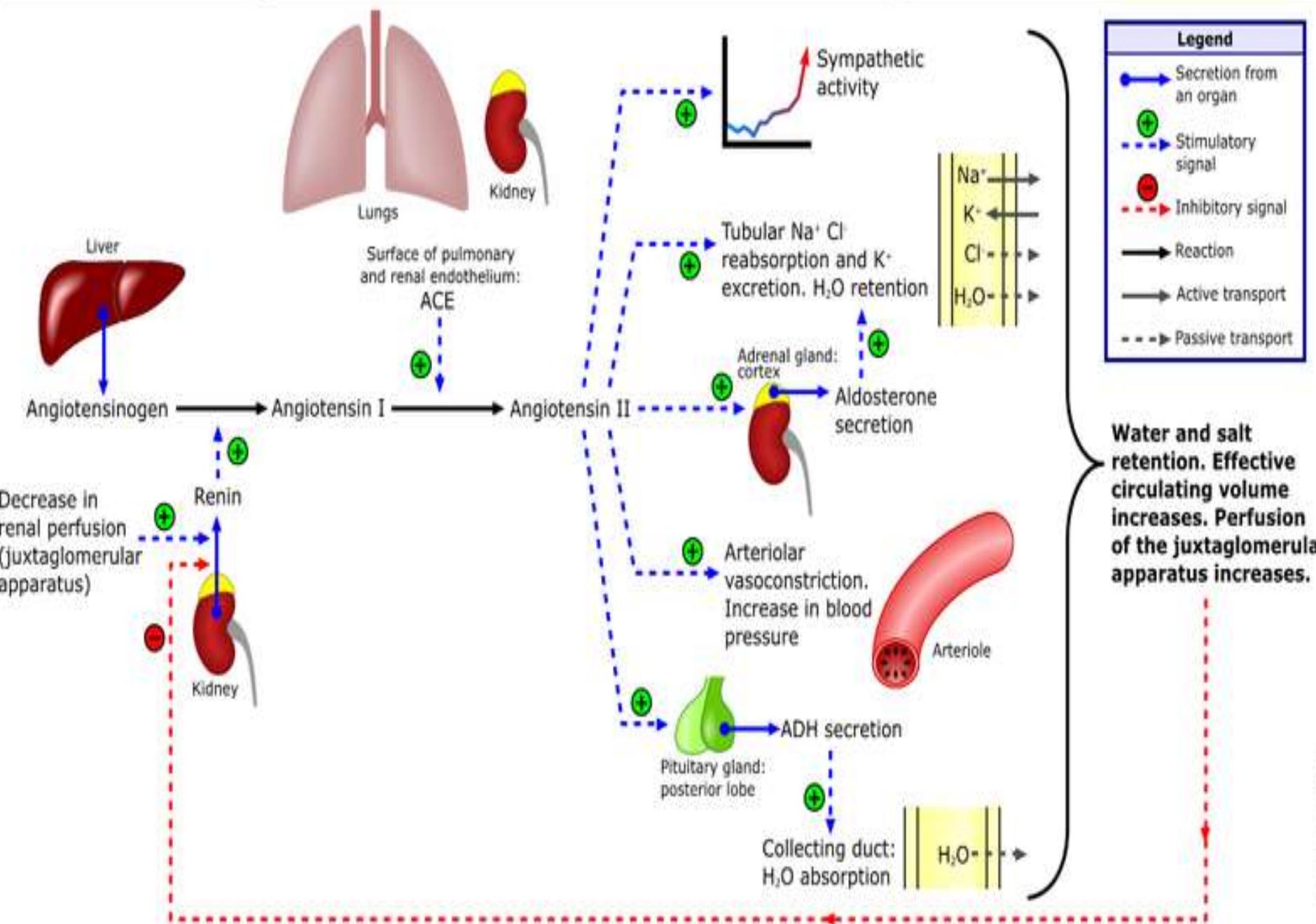
Mult mai recent:

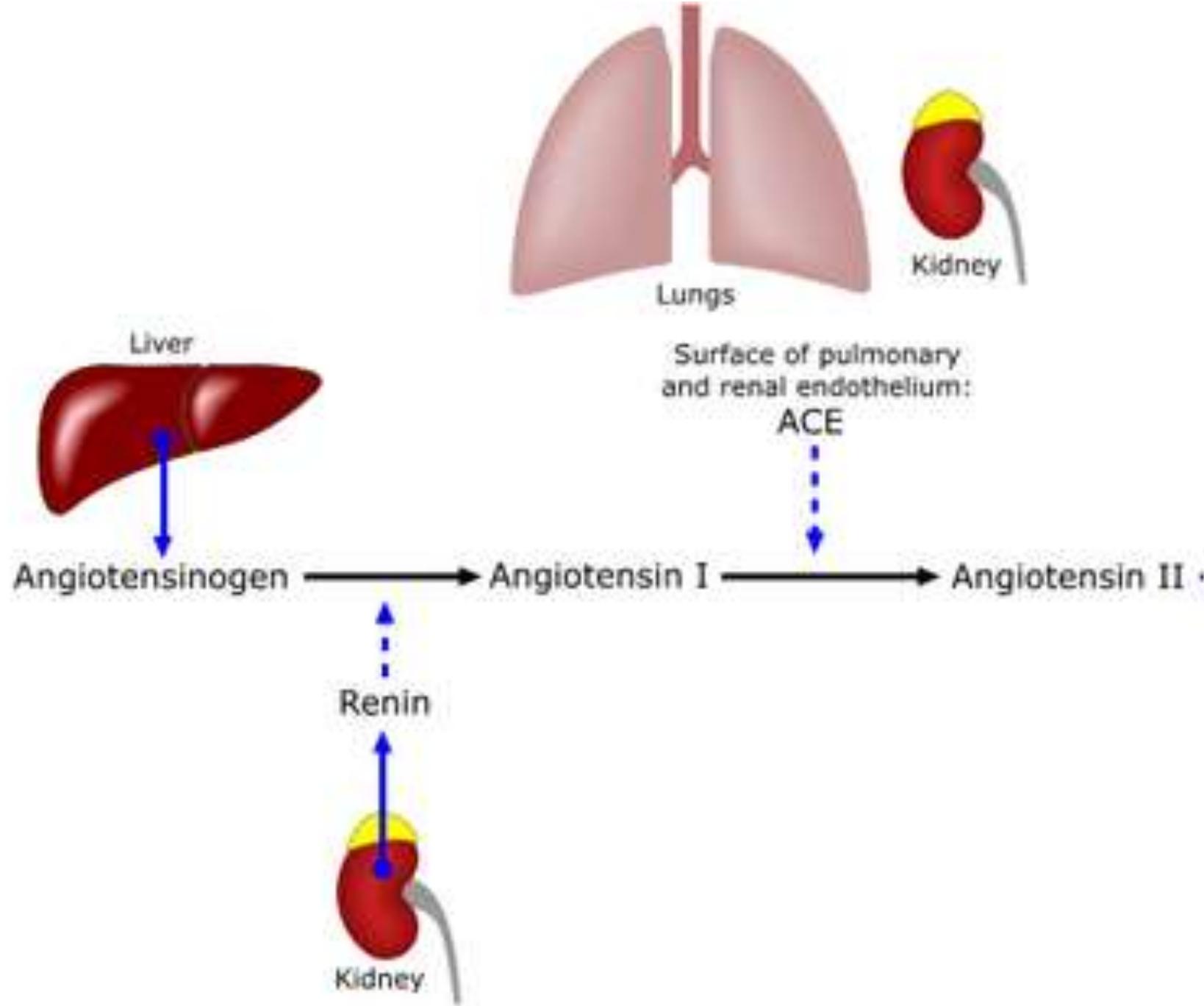
- 1991 – blocantii receptorilor AT1 ai angiotensinei II (losartan)
- 1994 – inhibitorii directi ai reninei (aliskiren)

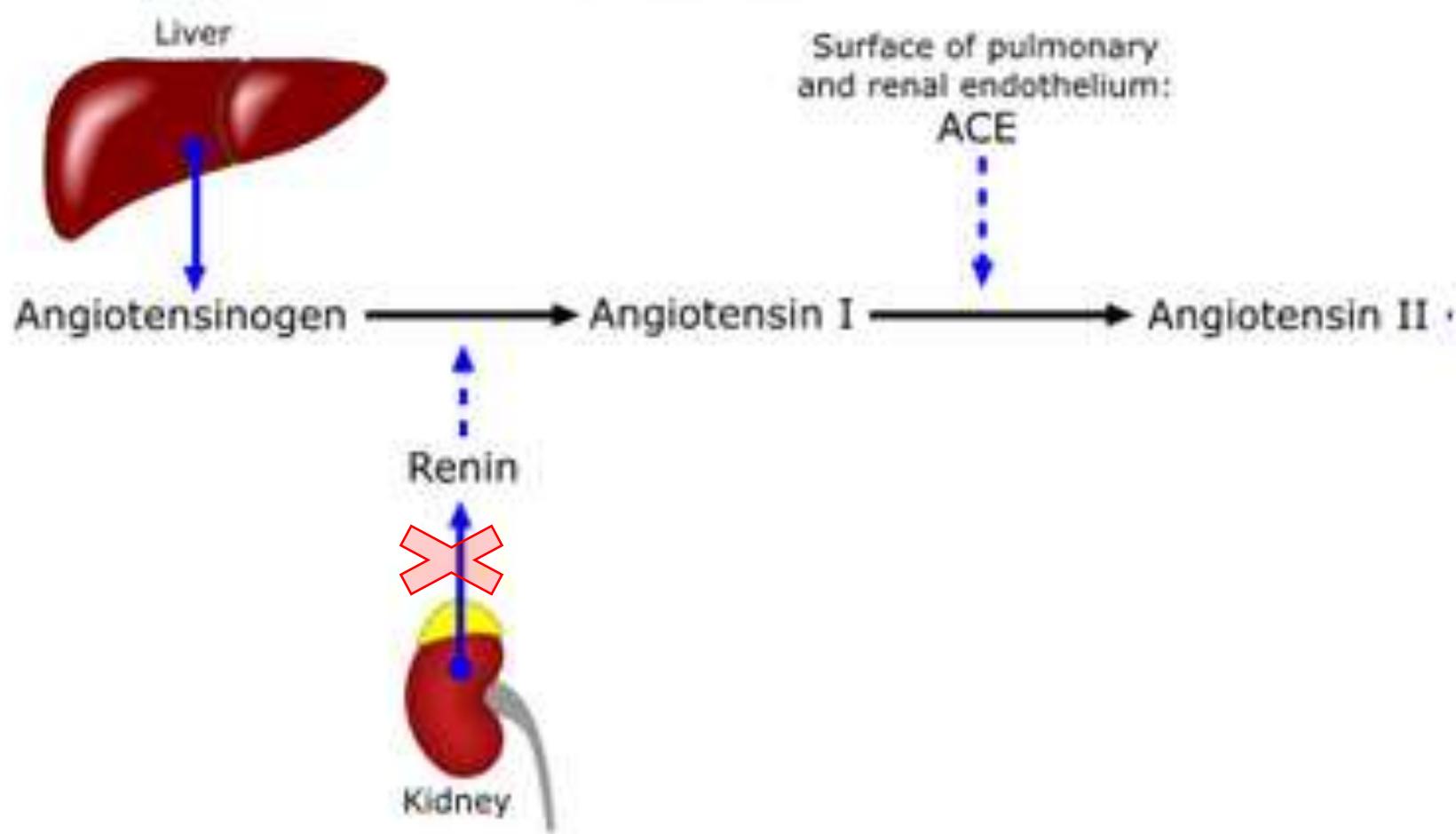
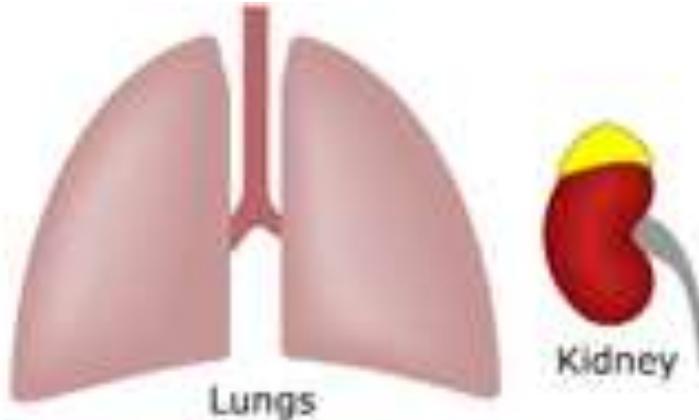
Nelson E, Merrill D. **Efficacy and safety of oral MK-954 (DuP753), an angiotensin receptor antagonist, in essential hypertension.** J Hypertens. 1991; 9:468S-9S.

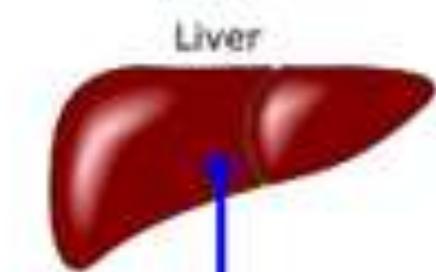
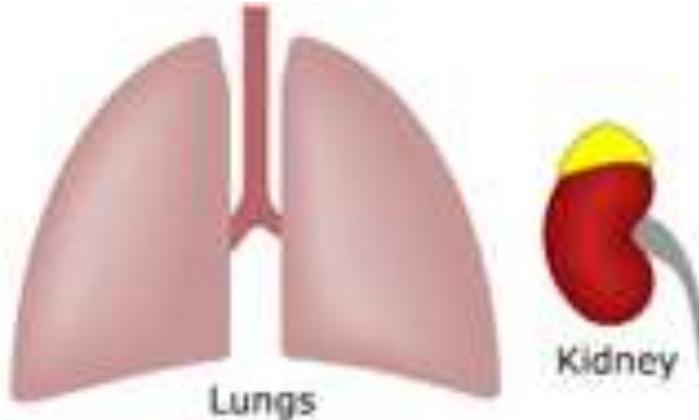
Frishman WH, Fozailoff A, Bin C et al. **Renin inhibition: a new approach to cardiovascular therapy.** J Clin Pharmacol. 1994; 34: 837-80.

Renin-angiotensin-aldosterone system









Angiotensinogen —————→ Angiotensin I —————→ Angiotensin II

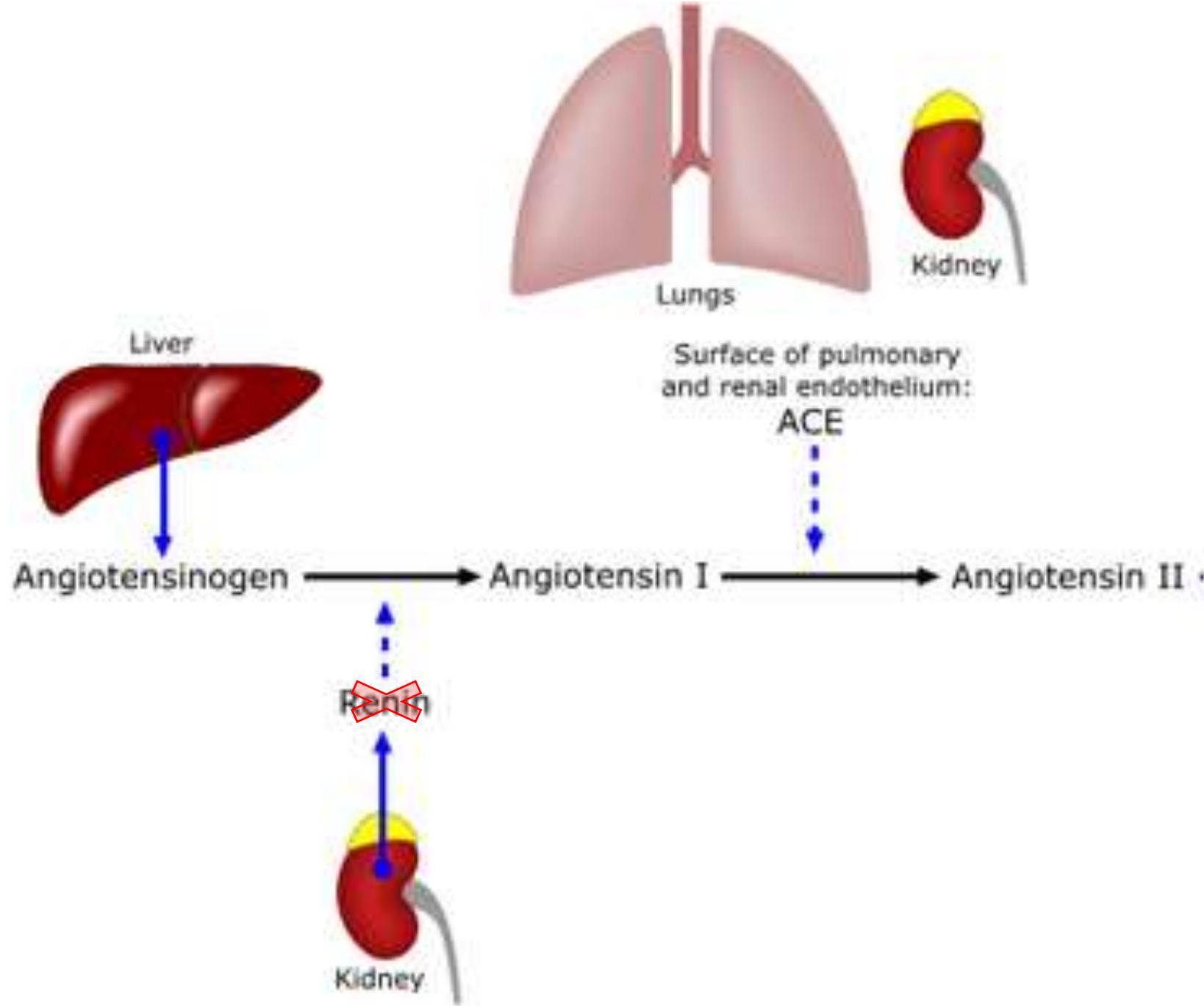
Renin

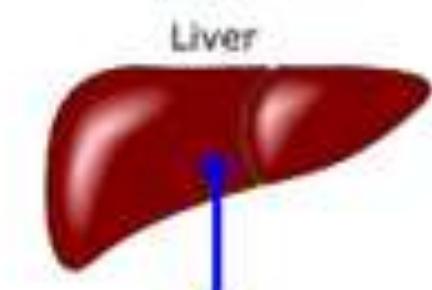
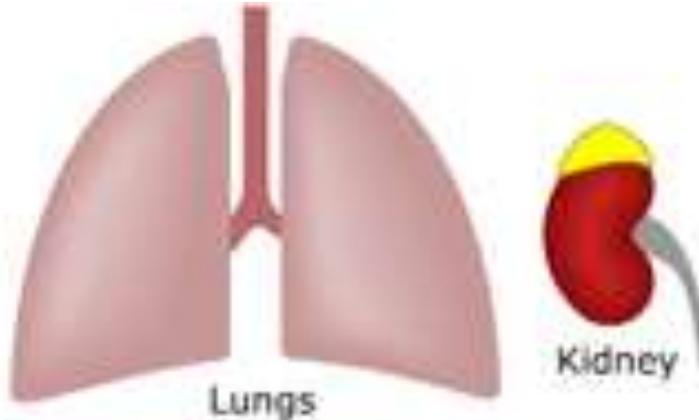


Kidney

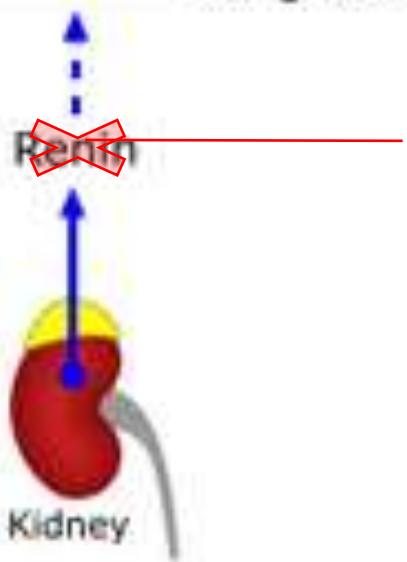
Surface of pulmonary
and renal endothelium:
ACE

beta blocante





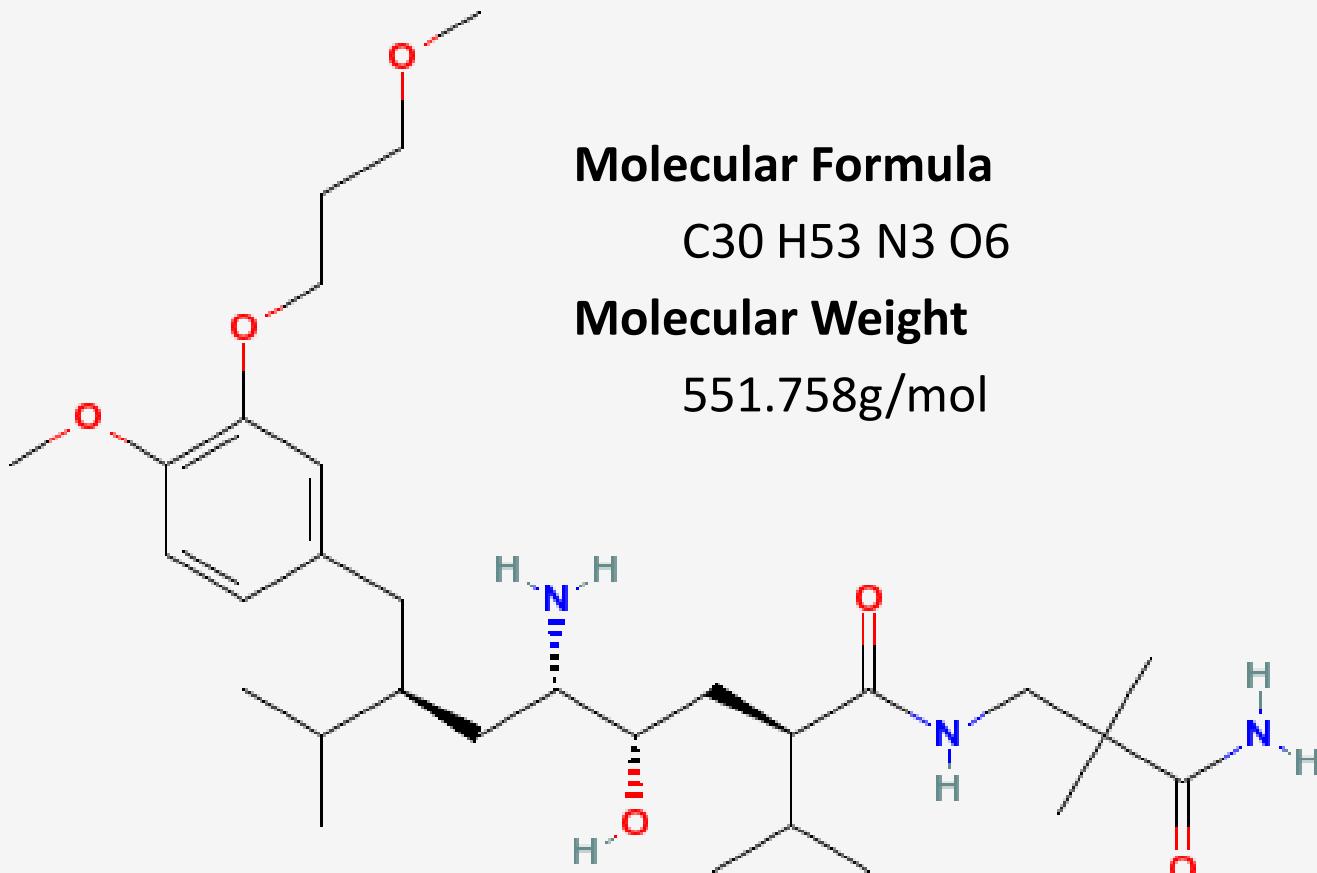
Angiotensinogen —————→ Angiotensin I —————→ Angiotensin II



**Inhibitori de renina
(ex. aliskiren)**

Aliskiren

Direct Renin Inhibitor



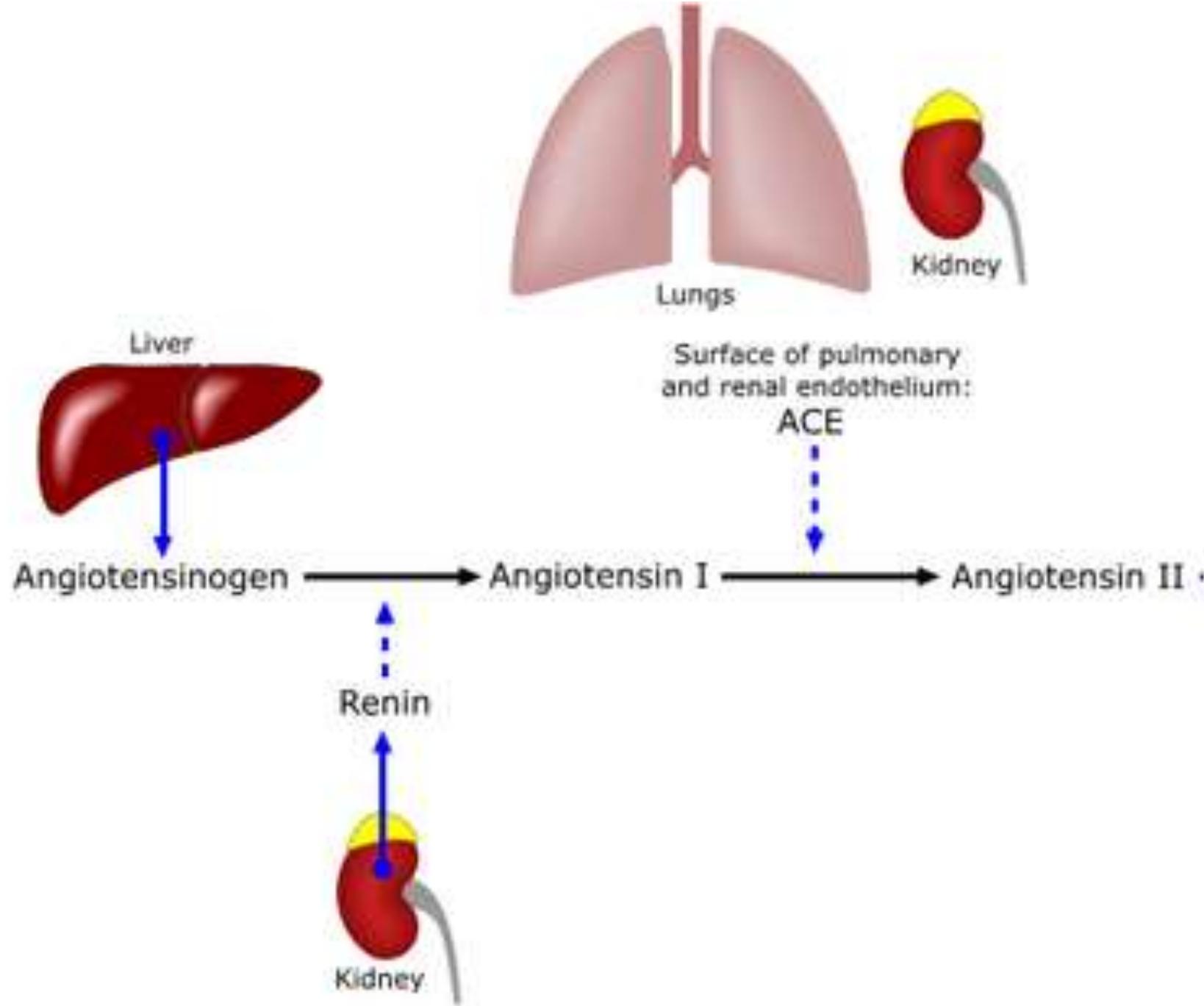
Molecular Formula

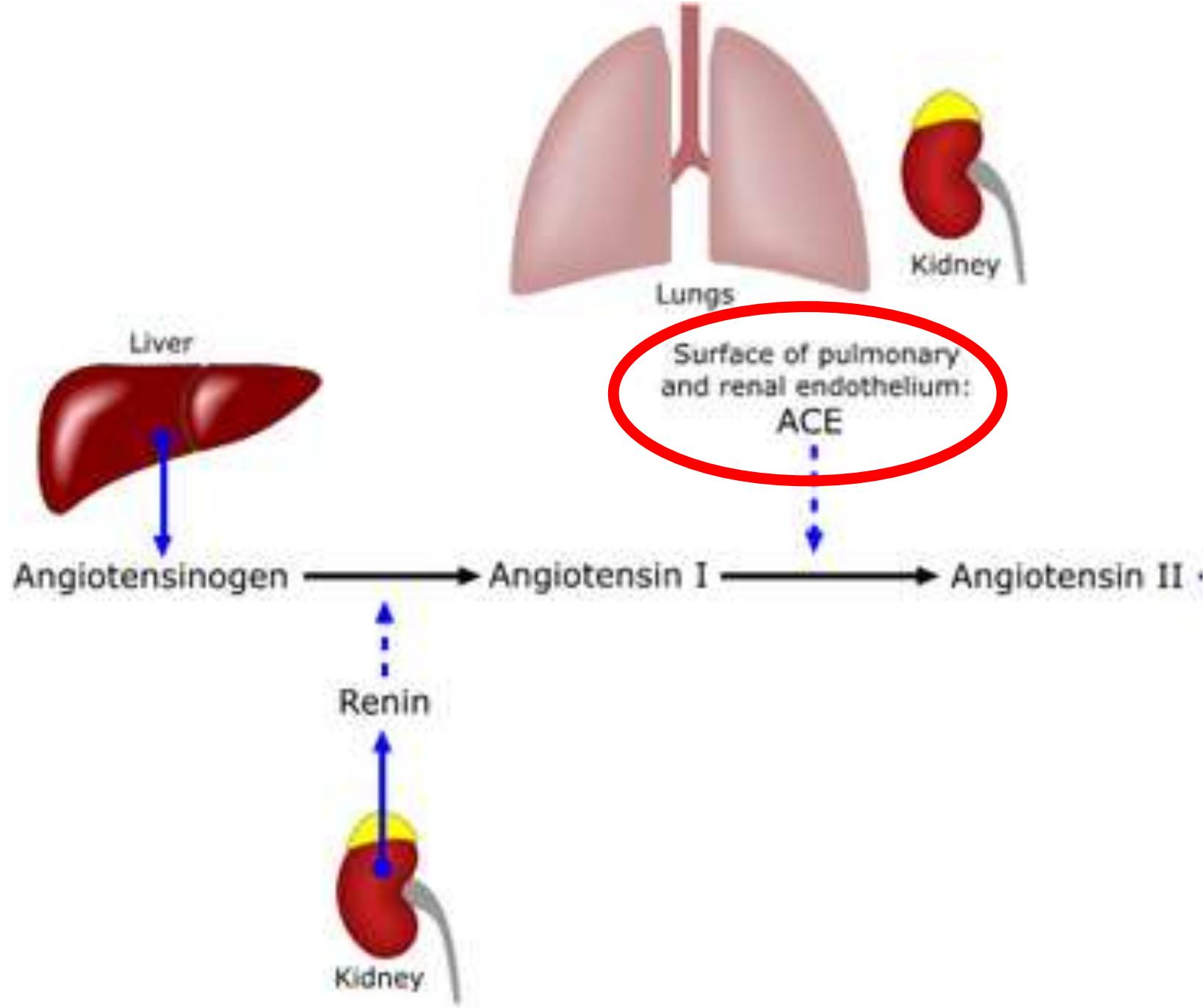
C₃₀ H₅₃ N₃ O₆

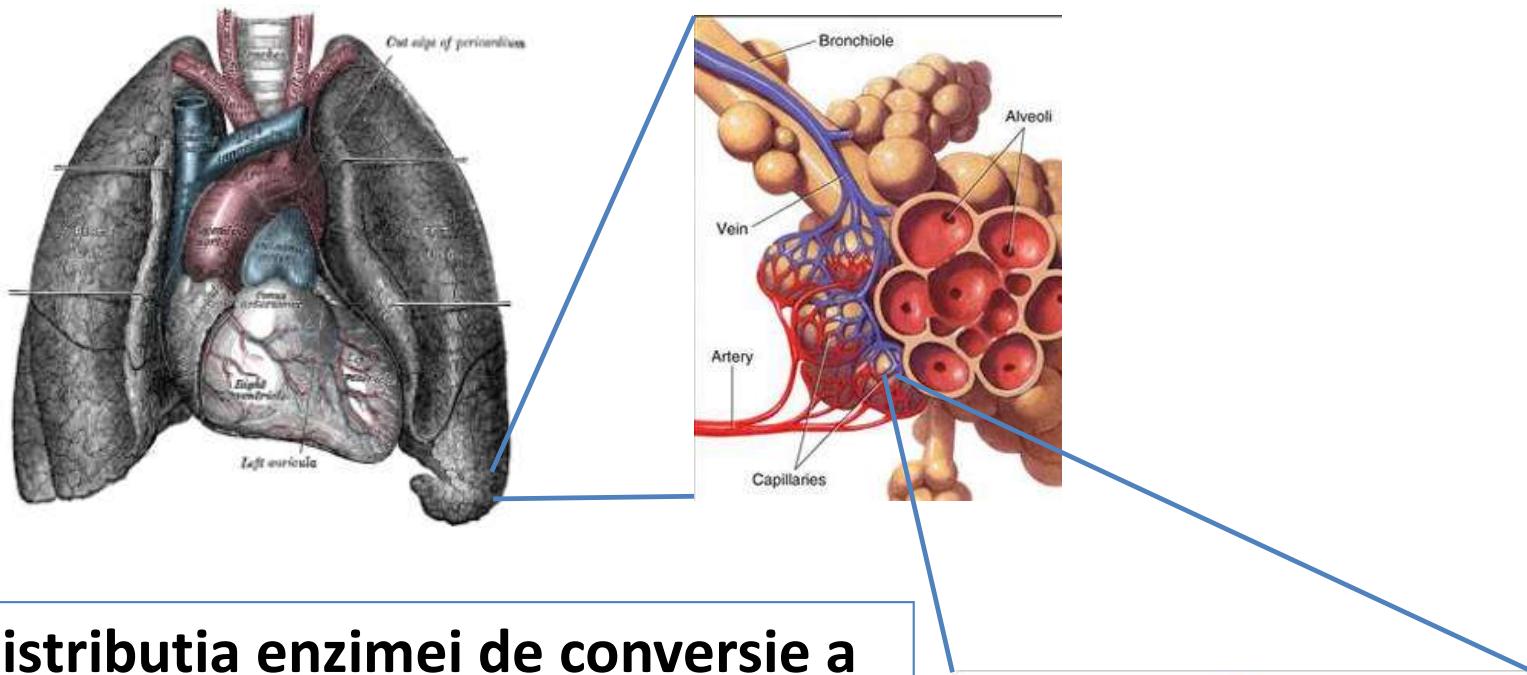
Molecular Weight

551.758g/mol

(2*S*,4*S*,5*S*,7*S*)-5-amino-N-(2-carbamoyl-2-methylpropyl)-4-hydroxy-7-{{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-8-methyl-2-propan-2-yl-nonanamide

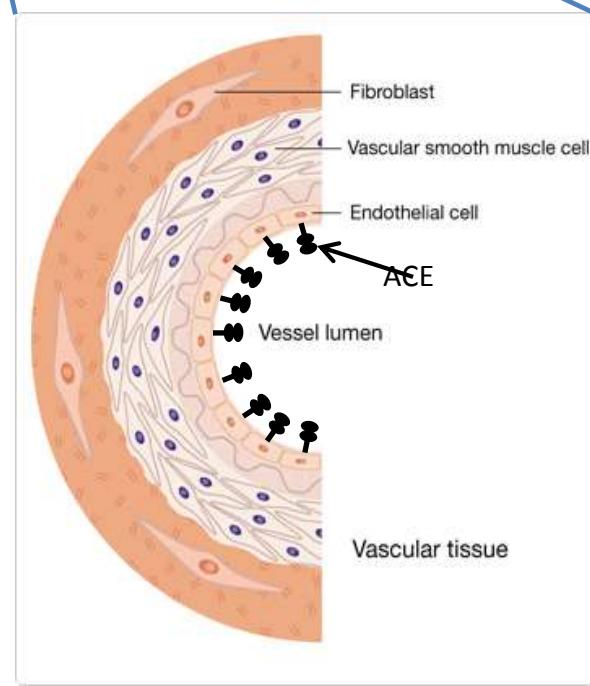


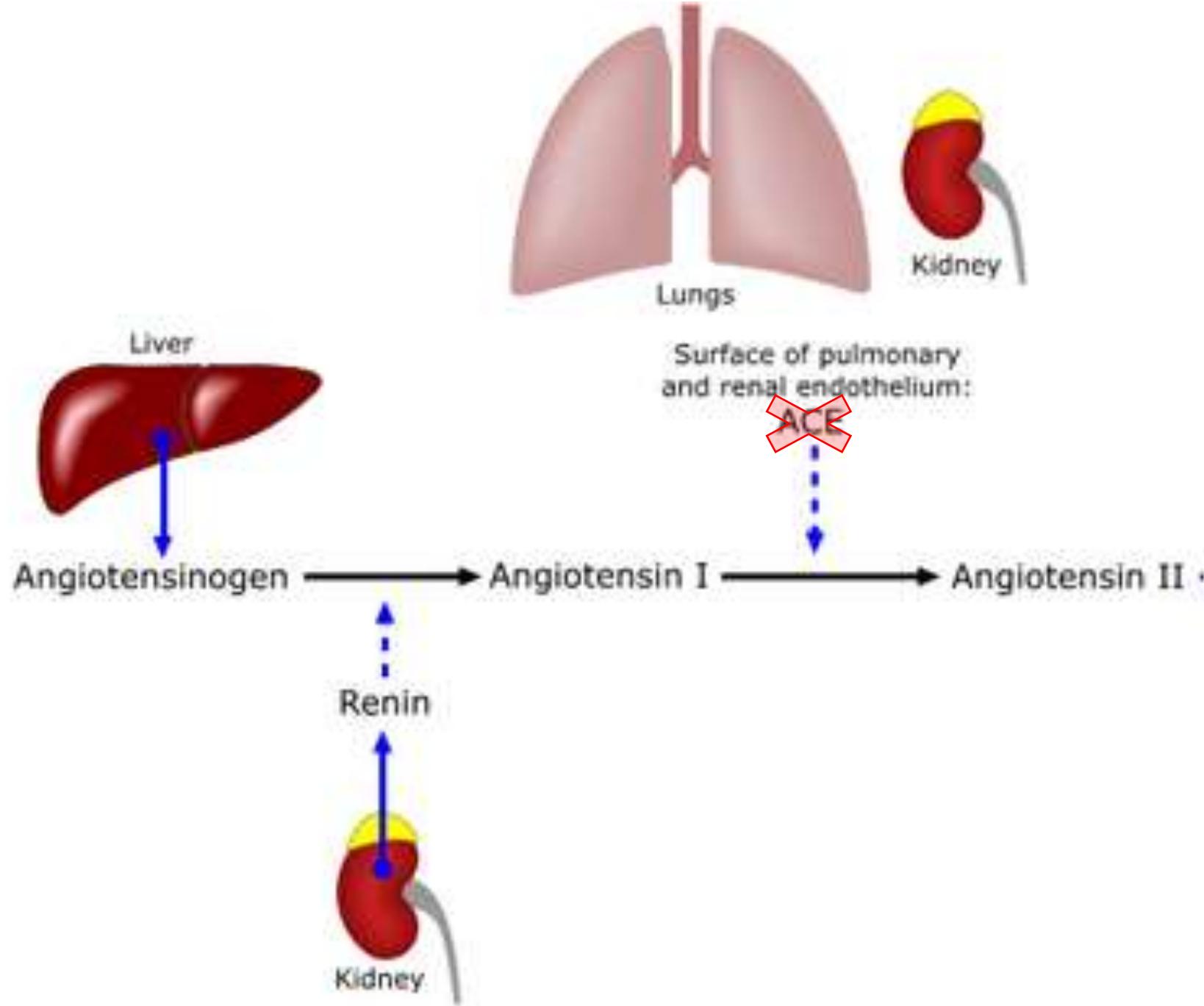


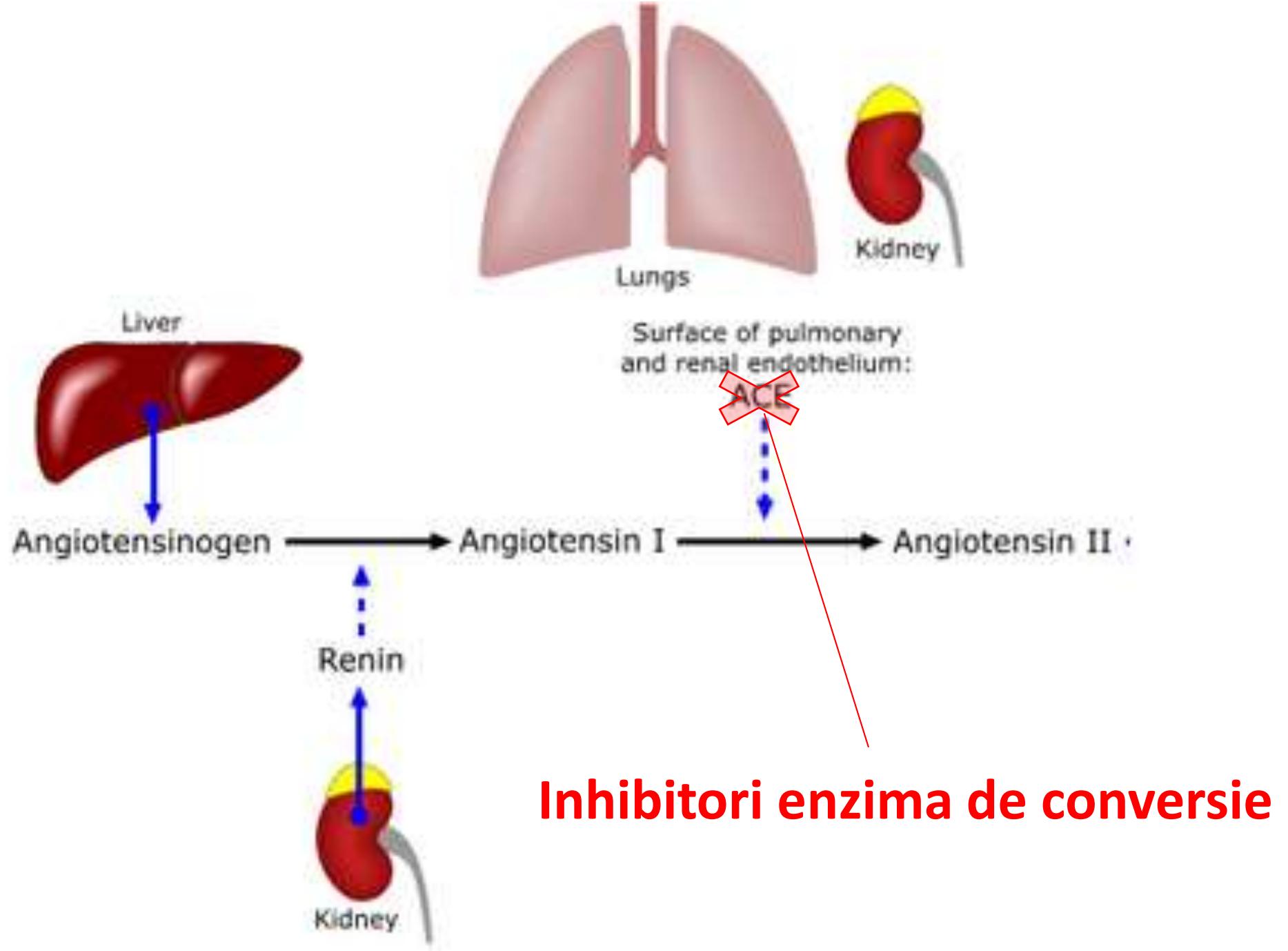


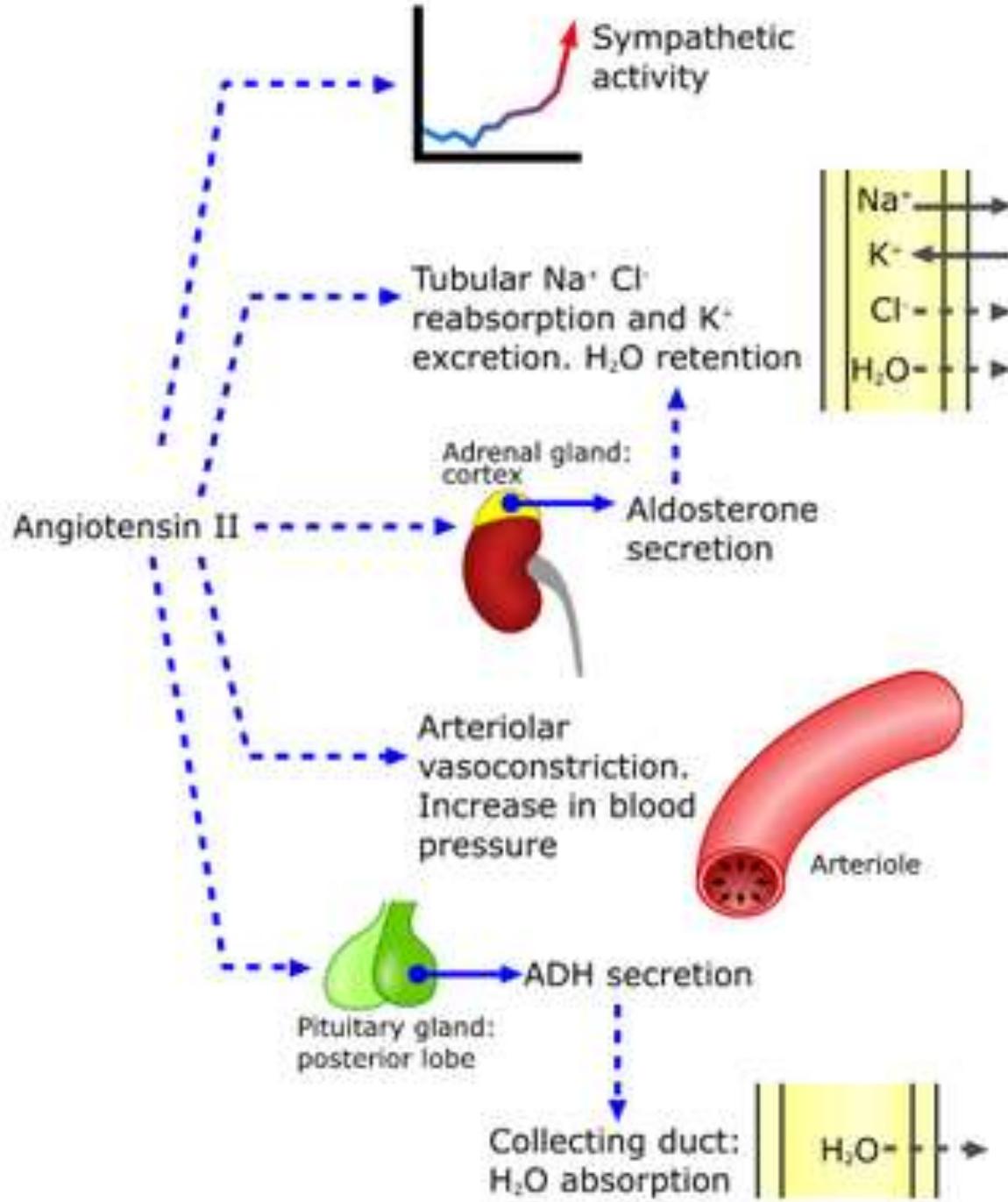
Distributia enzimei de conversie a angiotensinei I:

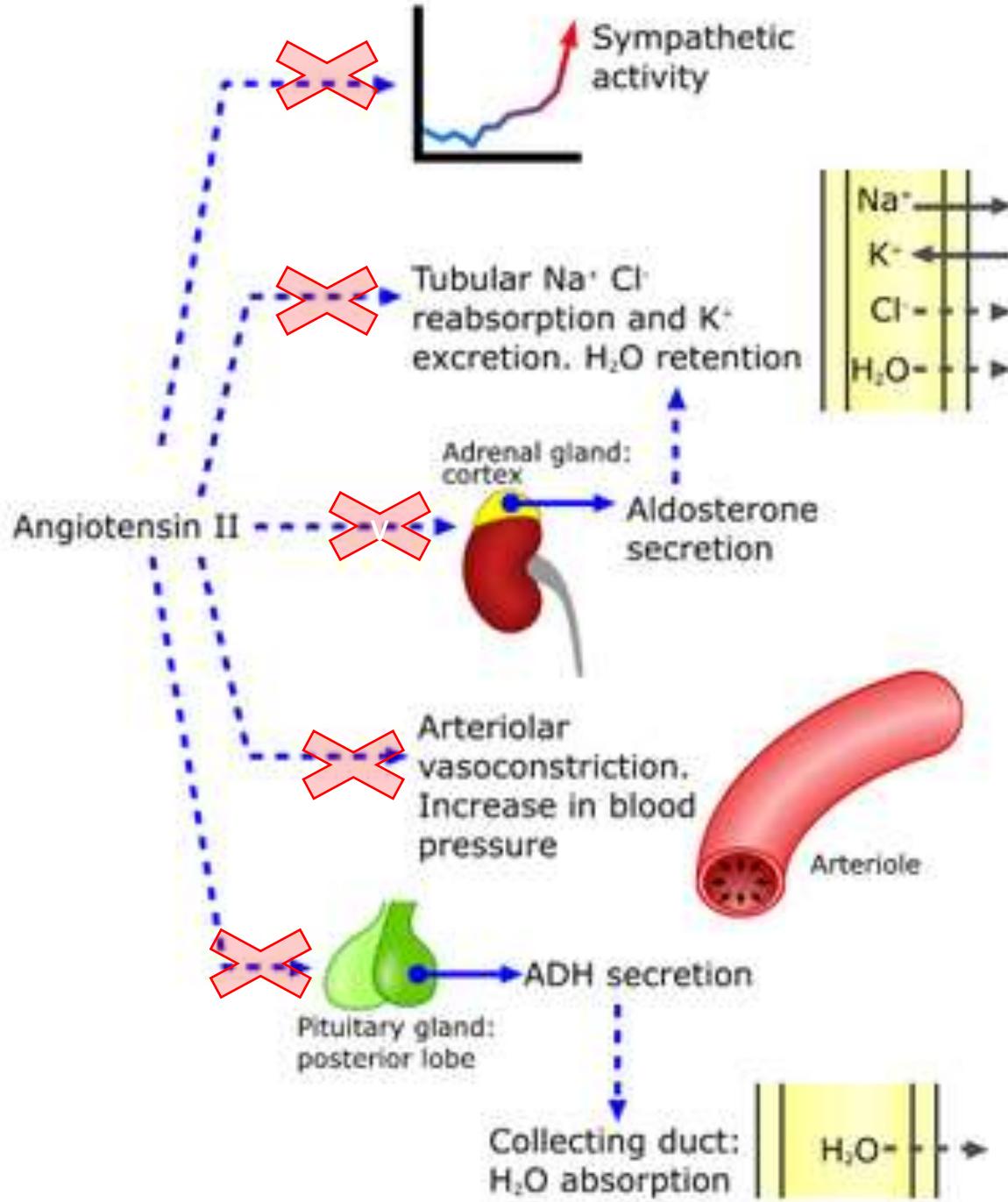
- endoteliul vascular pulmonar
- celulele epiteliale din:
 - tubii proximali renali
 - intestin subtire
 - placenta
 - plexuri coroide

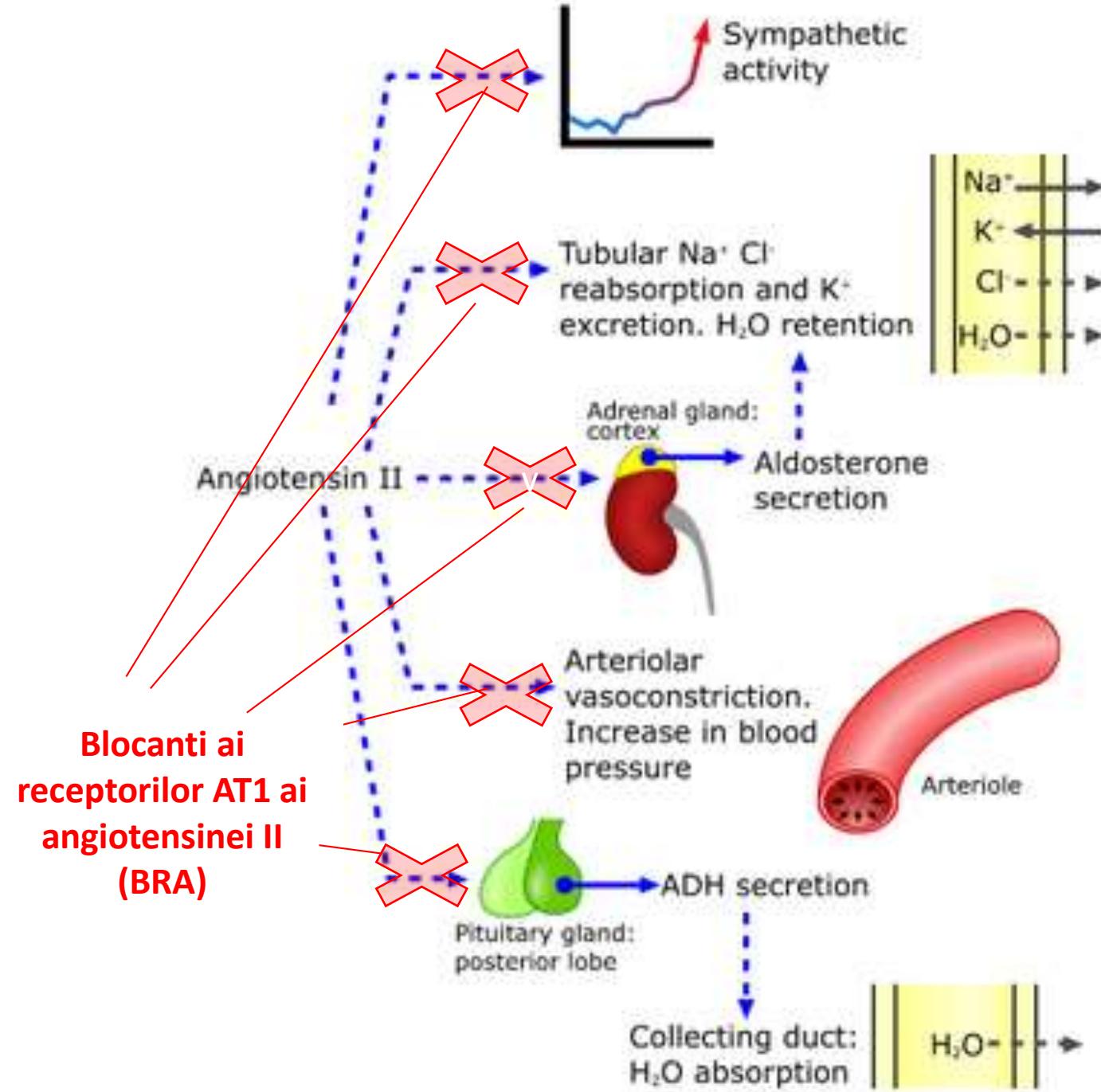






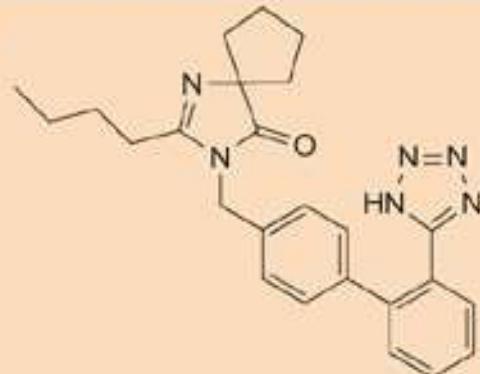






Blocantii receptorilor AT₁ ai Angiotensinei II

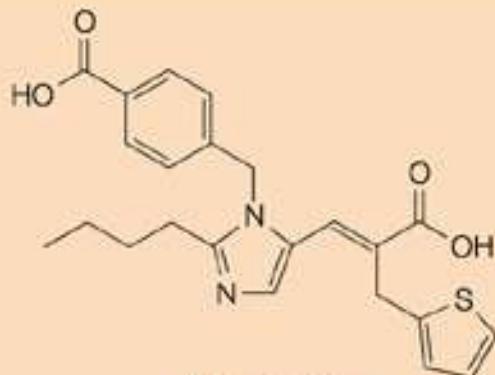
b



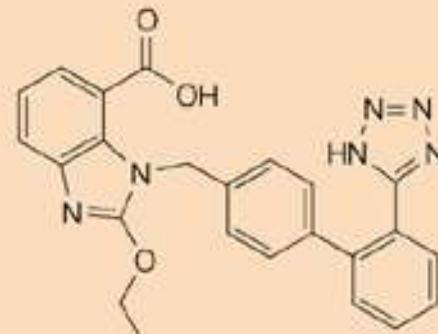
Irbesartan



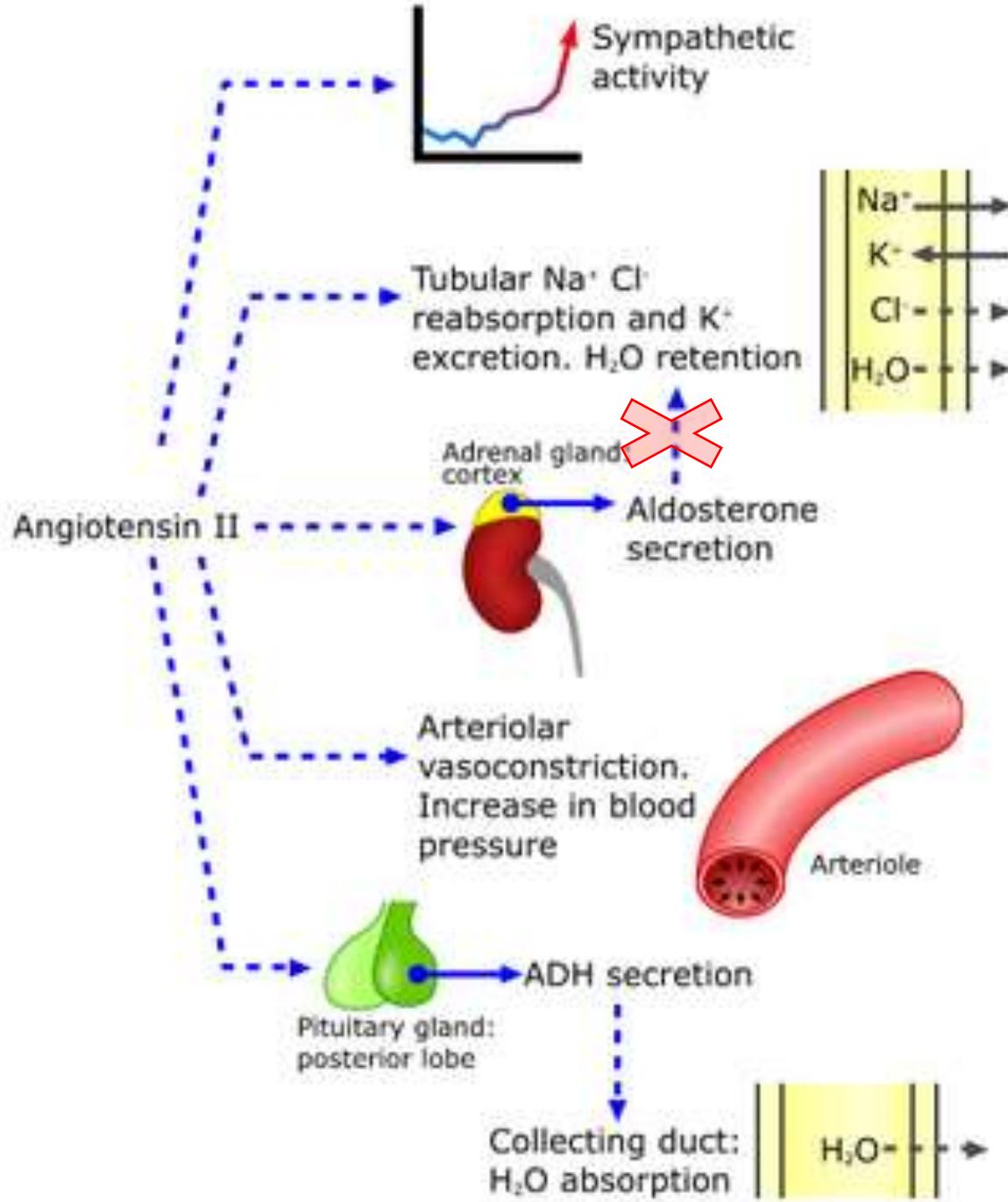
Losartan

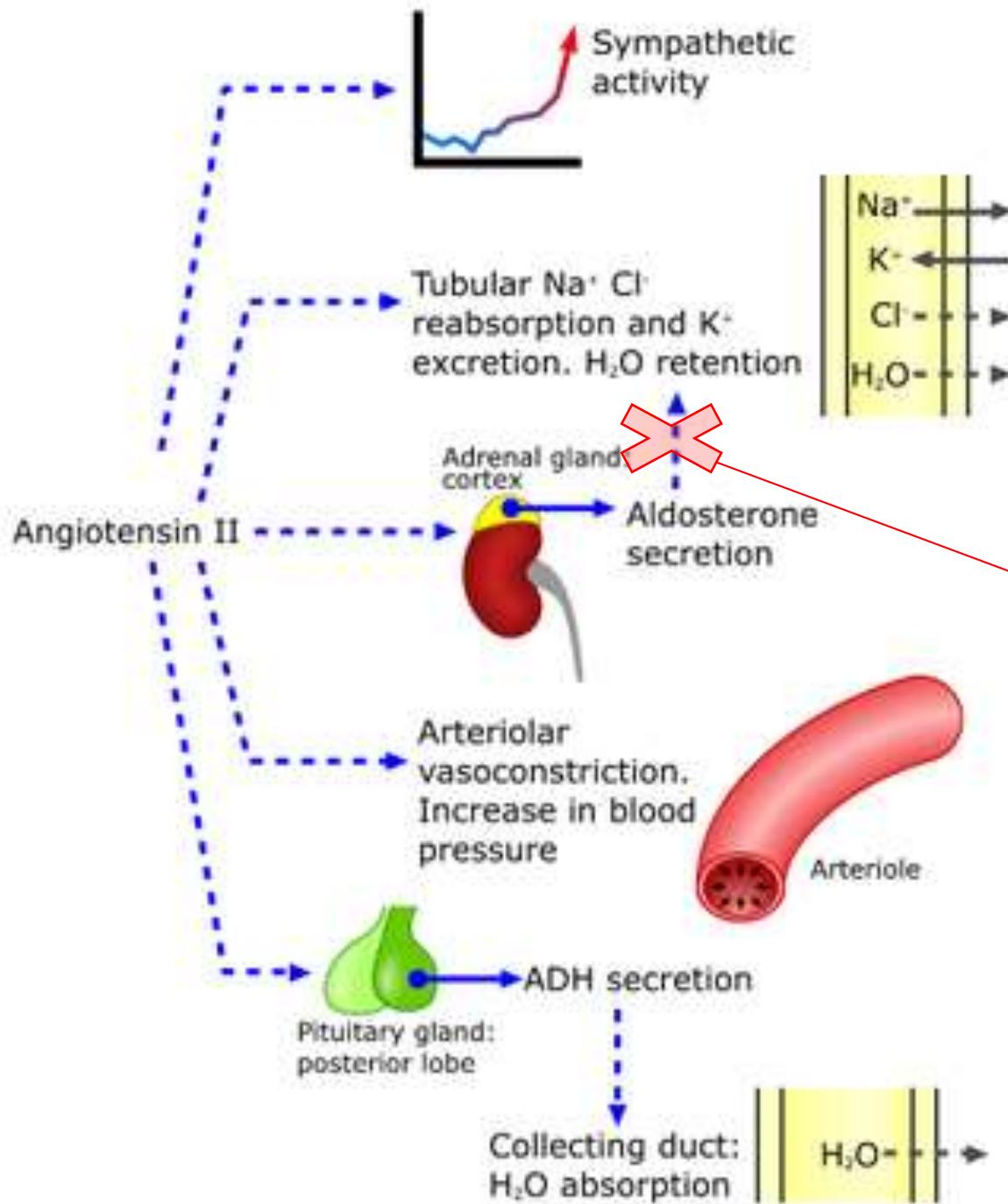


Eprosartan



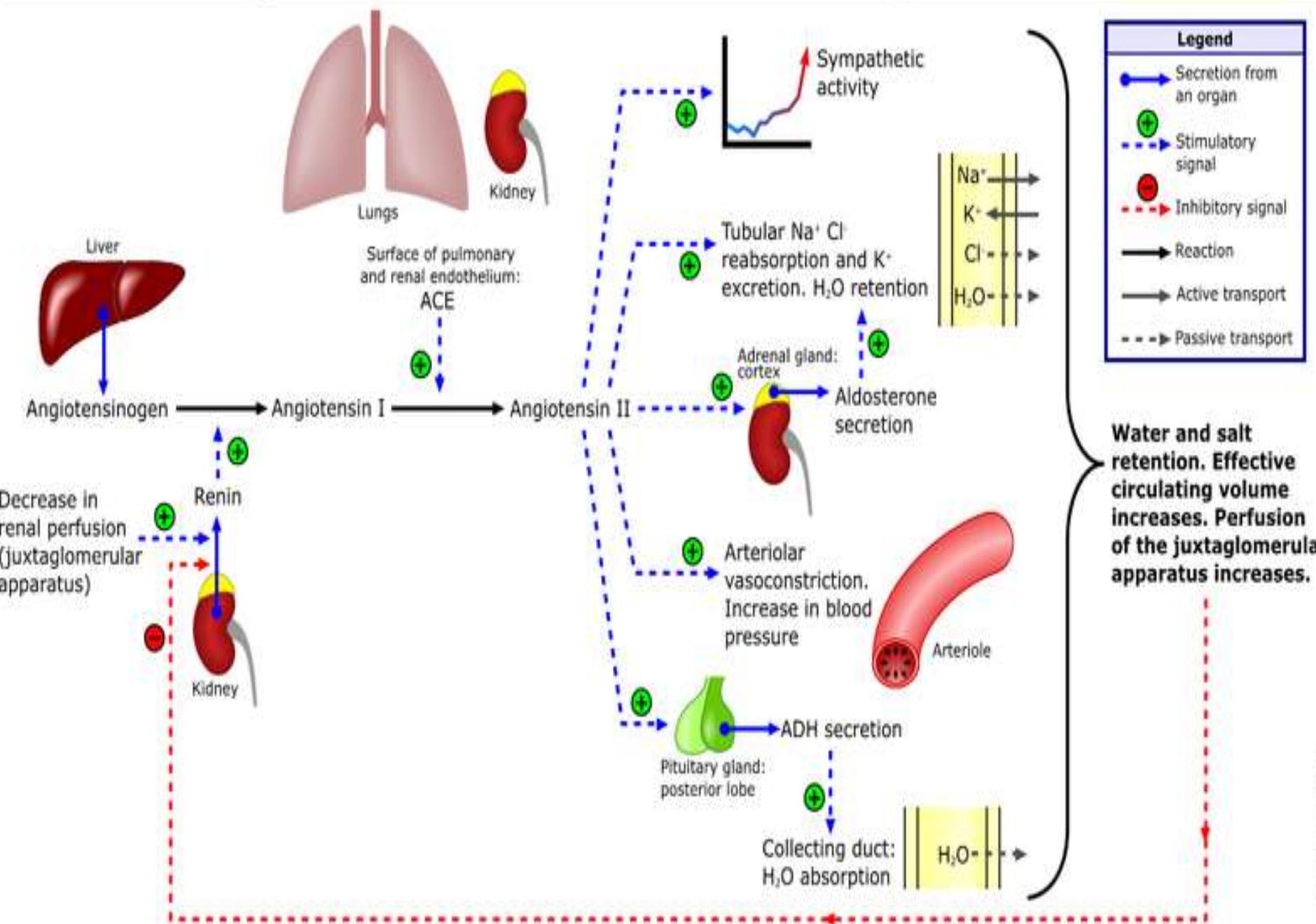
Candesartan



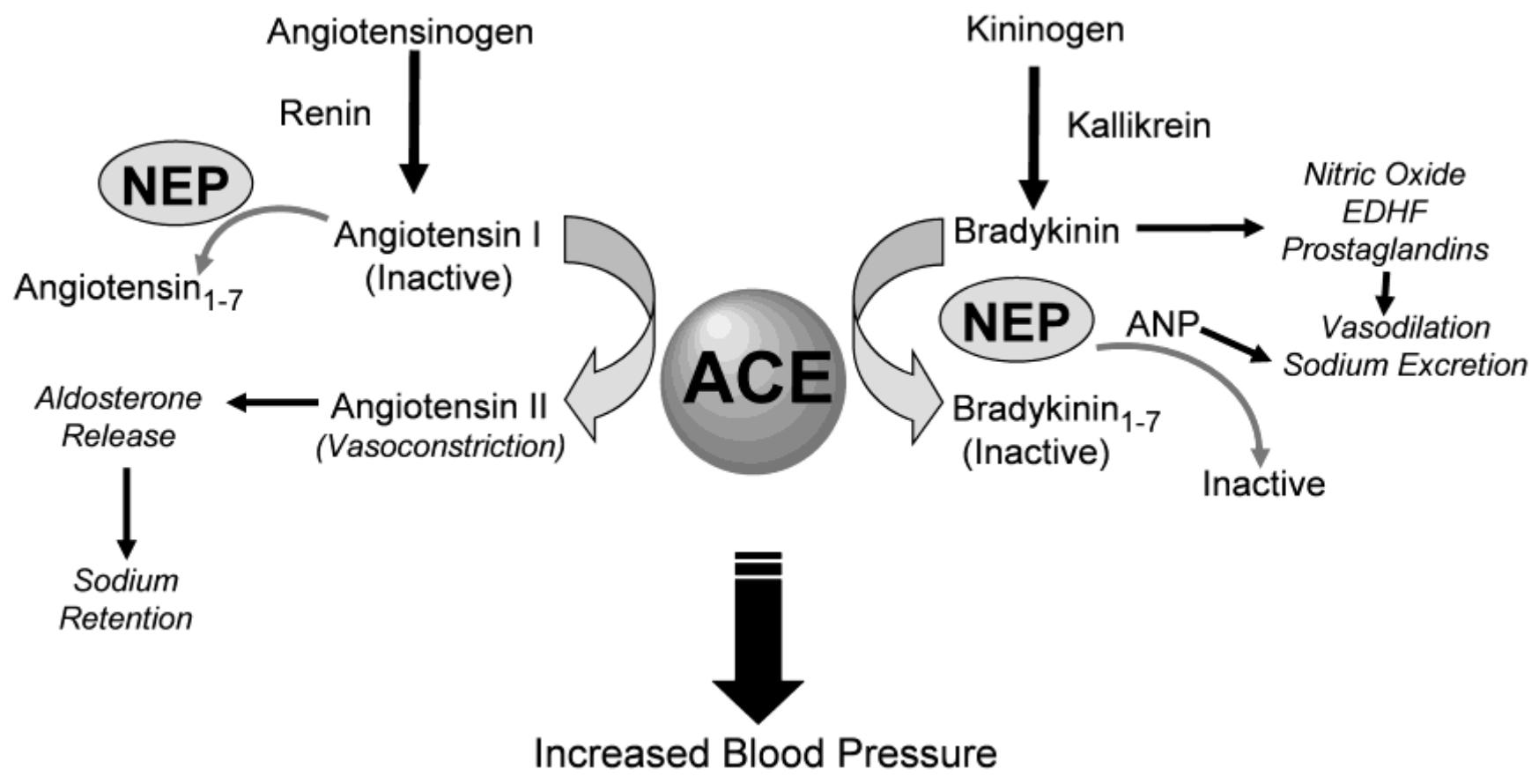


Inhibitori receptorii mineralocorticoizi (antialdosteronice) (ex.: spironolactona, eplerenona)

Renin-angiotensin-aldosterone system



Sistemul Renina-Angiotensina si Kalikrein-Kinina



Importanta Inhibitorilor Enzimei de Conversie a Angiotensinei I (IECA)

- IECA – pe locul 4 in topul celor mai prescrise medicamente in SUA (159.8 milioane Rp in 2008).
- Lisinopril – pe locul 2 in topul celor mai prescrise medicamente in SUA (75.5 milioane Rp in 2008).

Indicatii IECA

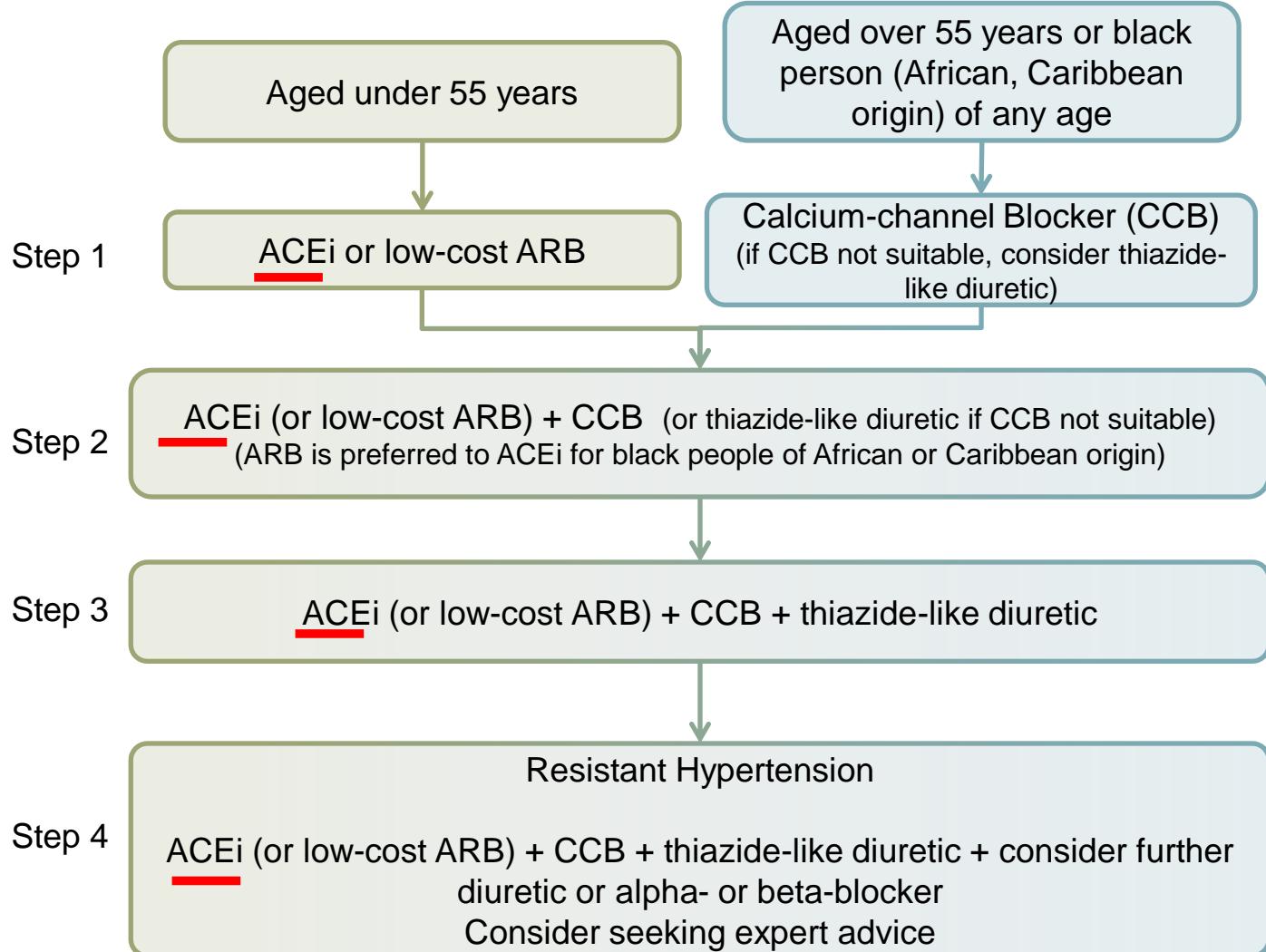
NICE: Treating Hypertension (CG127)²



National Institute for
Health and Clinical Excellence

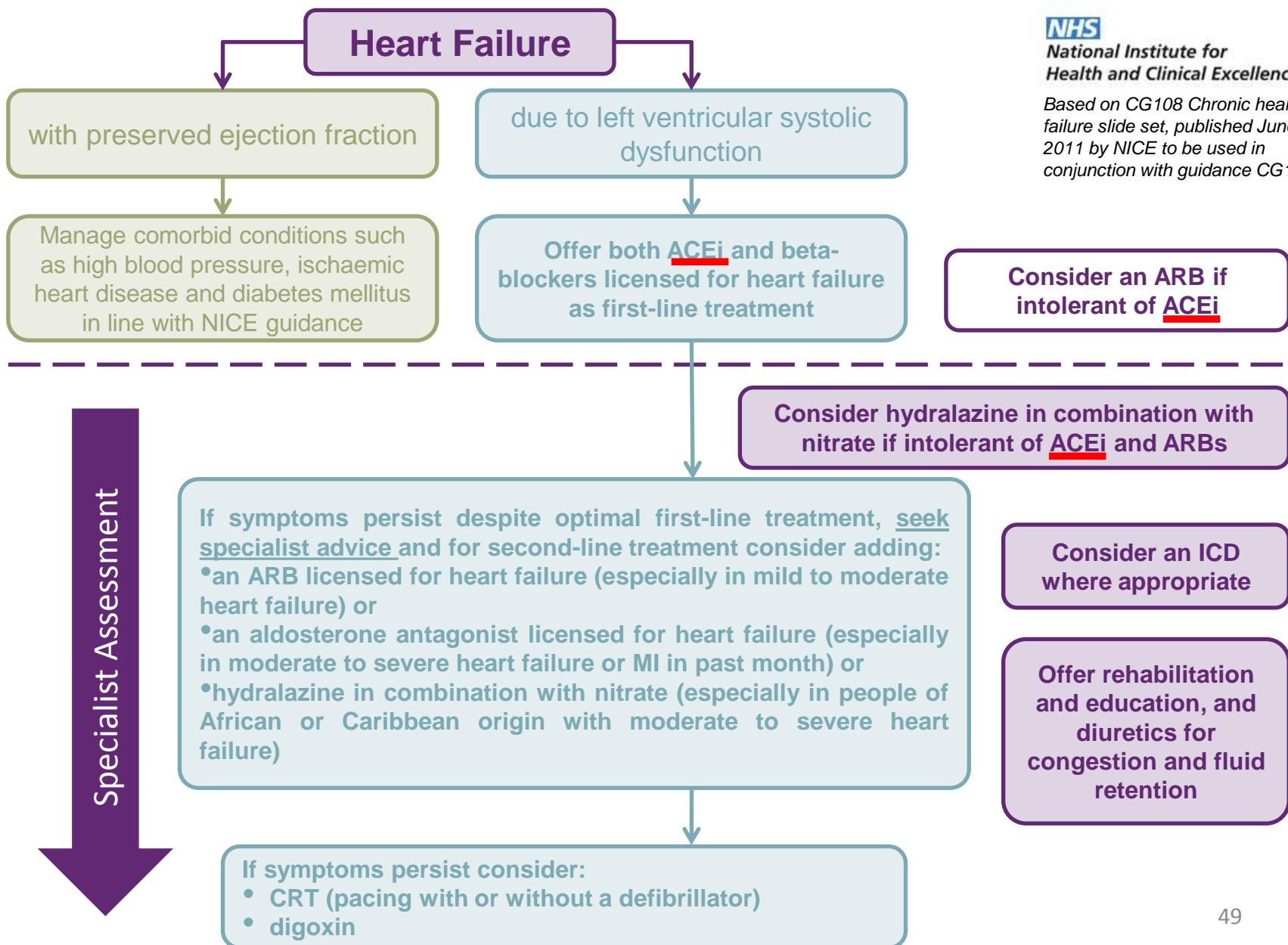
Based on CG127 Hypertension
slide set, published August 2011
by NICE to be used in conjunction
with guidance CG127

**ACEi and ARBs
contraindicated
in pregnancy**



The GDG considered ACEi and ARBs to have equivalent effects on clinical outcomes in hypertension.
Over the lifetime of this guideline, the costs of ACEi and ARBs will probably become similar.
No evidence to support use of ACE + ARB combination.

NICE: Treating heart failure (CG108)³



NHS
National Institute for
Health and Clinical Excellence

Based on CG108 Chronic heart failure slide set, published June 2011 by NICE to be used in conjunction with guidance CG108

Avantaje IECA

- Ofera protectie cardiovasculara pe termen lung si reduc incidenta **accidentelor ischemice**
- Cresc supravietuirea si imbunatatesc performanta cardiaca la pacientii cu **infarct miocardic acut**
- Eficiente in tratamentul **HTA** si al **insuficientei cardiace**
- Incetinesc evolutia **nefropatiei diabetice**

Efectele IECA

- **Hipertensiunea arterială**
 - ↓ Rezistența Vasculară Sistemica
 - ↓ Stimularea simpatica reflexă sau indusă de stress
 - → frecvența cardiacă
 - ↑ excreția de Sodiu, ↓ volumul circulant
- **Insuficiența cardiacă congestivă**
 - ↓ Rezistența Vasculară Sistemica, volumul circulant
 - ↑ debitul cardiac (nu schimba consumul miocardic de O₂)
- **Nefropatia diabetica**
 - Dilată arteriolele aferente și eferente renale
 - ↓ presiunea capilară glomerulară
 - ↓ (inhibă) creșterea celulelor mezangiale (?)

TABLE C136.1**U.S. FOOD AND DRUG ADMINISTRATION-APPROVED INDICATIONS
FOR ANGIOTENSIN-CONVERTING ENZYME INHIBITORS**

Drug	Hypertension	Heart failure	Diabetic nephropathy	High-risk cardiovascular disease
Captopril	•	• (Post-MI) ^a	•	
Benazepril	•			
Enalapril	•	• ^b		
Fosinopril	•	•		
Lisinopril	•	• (Post-MI) ^a		
Moexipril	•			
Perindopril	•			• ^c
Quinapril	•	•		
Ramipril	•	• (Post-MI)		• ^c
Trandolapril	•	• (Post-MI)		

MI, myocardial infarction.

^aCaptopril and lisinopril are indicated for heart failure treatment post-myocardial infarction and as adjunctive therapy for heart failure.

^bEnalapril is indicated for high-risk individuals and for asymptomatic and symptomatic patients.

^cOn the basis of results of the Heart Outcomes Prevention Evaluation (HOPE) study and The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA).

Reactii adverse.

Tusea

- Tusea indusa de IECA este seaca, uscata, iritativa, persistenta, predominant nocturna
- Este cel mai comun efect advers (5-20%) la cei cu tratament de lunga durata cu IECA, mai crescuta la pacientii cu IC congestiva si două ori mai frecventa la femei
- Este si cei mai frecvent motiv pentru oprirea tratamentului.
- Se atribuie excesului de bradikinina, prostaglandine si stimularii vagale.
- Inlocuirea IECA cu un antagonist al receptorului AT1 (losartan).

Reactii adverse.

Hipotensiunea

- Scaderea marcata a tensiunii arteriale la inceputul tratamentului, mai ales dupa prima doza.
- Frecventa de 0,5-5% (cifrele mai mari sunt valabile pentru captopril)
- Favorizata de:
 - tratamentul diuretic si dieta hiposodata
 - de hiperreninemie
 - de IR (indeosebi la batrini)
 - hipertensiunea maligna.

Reactii adverse.

Insuficienta renala

- Apare foarte rar sub tratamentul cu *IECA*
- Factori de risc:
 - asocierea IECA + AINS + diuretice
 - IC severa
 - hipovolemiil severe
 - pacientii cu stenoza de artera renala uni- sau bilaterală

Reactii adverse.

Hiperpotasemia

- Mecanism - scaderea secretiei de aldosteron
- Incidența < 1 % din pacientii tratati
- Factori favorizanti:
 - restrictia marcata de sodiu
 - insuficienta cardiaca
 - diabet
 - asocierea inadecvata de diuretice care economisesc potasiu si AINS
 - asocierea furosemidului reduce riscul de hiperkaliemie

Reactii adverse.

Angioedemul

- Apare rar, incidenta sub 0,1%
- Mecanismul se bazeaza pe formarea de bradikinina
- Tratament: adrenalina.
- Pacientii cu istoric de angioedem nelegat de *I*ECA pot prezenta un risc crescut
- Poate pune in pericol viata
- Se impune oprirea imediata a tratamentului cu *I*ECA

Reactii adverse

Efecte secundare in sarcina

- Toti *IECA* sunt contraindicați în sarcina deoarece produc embriopatii și chiar moartea fetusului mai ales în trimestrul al II-lea și al III-lea.

Alte reactii adverse

- Tulburarile de gust
- Reactii cutanate
- Reactii adverse hematologice survin foarte rar, dar pot fi extrem de grave (leucopenie etc.)
Insuficienta renala, collagenozele (lupus eritematos diseminat, sclerodermie), bolile hematologice si medicatia imunodepresiva sunt factori favorizanti.
- Insuficienta hepatica este foarte rar asociata cu *IECA*

Contraindicatii

- Hipersensibilitate la *IECA*
 - Antecedente de angioedem
 - Afectiuni cardiace:
 - stenoza aortica, stenoza mitrala severa
 - hipertrofie miocardica,cardiomiotatie hipertrofica obstructiva
 - pericardita obstructiva
 - HT pulmonara (cord pulmonar cronic si cardiopatii congenitale)
- In aceste conditii *IECA* nu au eficienta si pot produce hTA severe.

Contraindicatii

- Stenoza bilaterală de artera renala (doze mici de *IECA* produc hTA severă și insuficiență renală).
- Insuficiență renală cronică în stadiul predialitic (pot scădea filtrarea glomerulară și agrava gradul retentiei azotate)
- Insuficiență renală cu o creatininemie > 3mg % (contraindicație relativă).
- Boli autoimune.
- Sarcina

Mod de administrare

- Oral - toti reprezentanti clasei
- Sublingual - captopril
- Intravenos - enalapril

TABLE C136.2

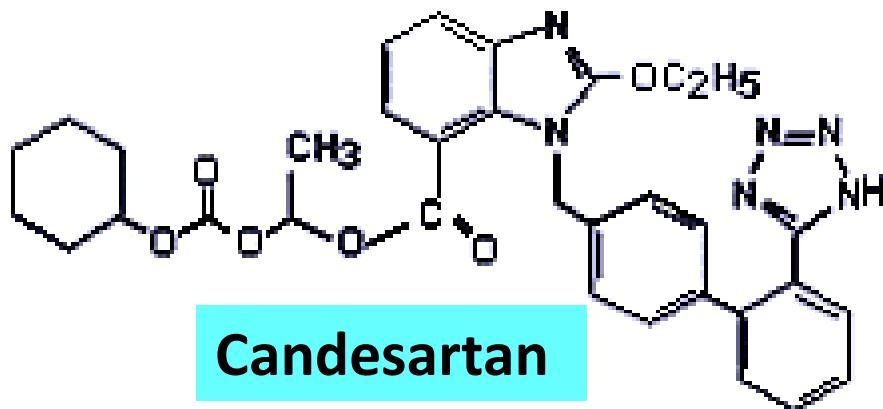
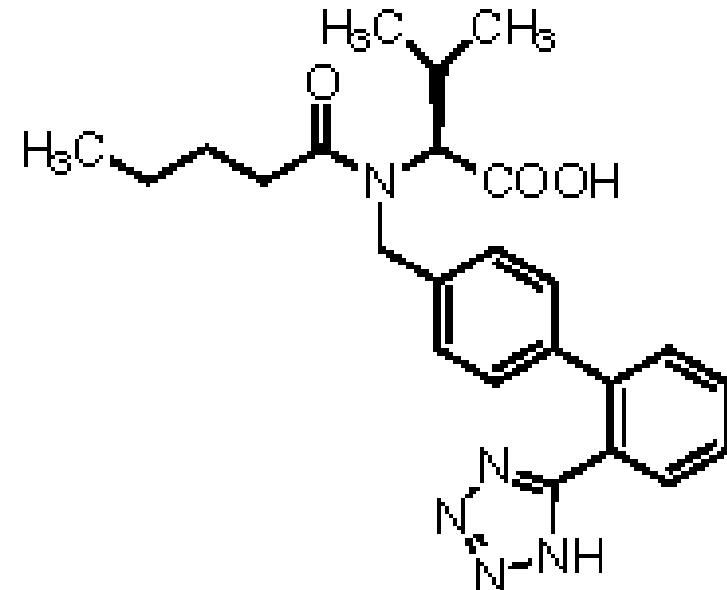
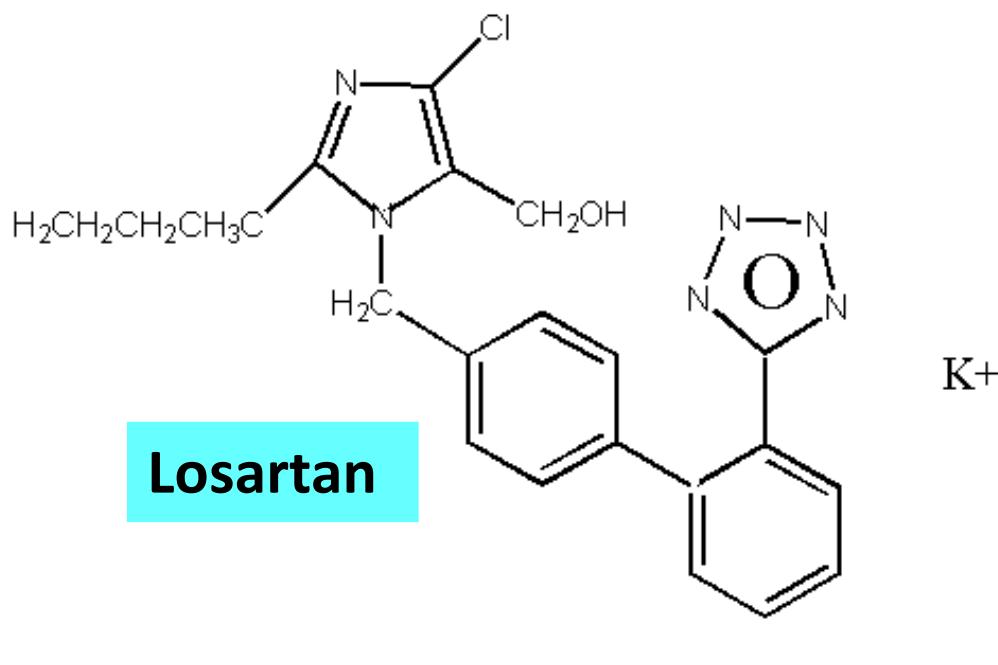
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS: DOSAGE STRENGTHS AND TREATMENT GUIDELINES

Drug	Trade name	Usual total daily dose in hypertension (mg) (frequency/d) ^a	Usual total daily dose in heart failure (mg) (frequency/d) ^a	Comment	Fixed-dose combinations ^b
Benazepril	Lotensin	20–40 (1)	Not FDA approved for heart failure		Benazepril and hydrochlorothiazide (Lotensin HCT)
Captopril	Capoten	75–300 (2–3)	18.75–150.00 (3)	Generically available	Captopril and hydrochlorothiazide (Capozide ^c)
Enalapril	Vasotec	5–40 (1–2)	5–40 (2)	Generic and intravenous	Enalapril and hydrochlorothiazide (Vaseretic)
Fosinopril	Monopril	10–40 (1)	10–40 (1)	Renal and hepatic elimination	Fosinopril and hydrochlorothiazide (Monopril-HCT)
Lisinopril	Prinivil, Zestril	10–40 (1)	5–20 (1)	Generically available	Lisinopril and hydrochlorothiazide (Prinzide, Zestoretic)
Moexipril	Univasc	7.5–30.0 (1)	Not FDA approved for heart failure		Moexipril and hydrochlorothiazide (Uniretic)
Perindopril	Aceon	4–16 (1)	Not FDA approved for heart failure	Indicated in high-risk vascular patients	
Quinapril	Accupril	20–80 (1)	10–40 (1–2)		Quinapril and hydrochlorothiazide (Accuretic)
Ramipril	Altace	5–20 (1)	10 (2)	Indicated in high-risk vascular patients	
Trandolapril	Mavik	2–8 (1)	2–4 (1)	Renal and hepatic elimination	

FDA, U.S. Food and Drug Administration; HCT, hydrochlorothiazide.

^aLower doses are often recommended to initiate therapy. Higher doses are recommended for chronic therapy to provide full 24-hour coverage.^bFixed-dose combinations in this class all contain a thiazide-type diuretic.^cCapozide is indicated for first-step treatment of hypertension.

Blocantii receptorilor de Angiotensina II (BRA)



Hipertrofie
Cardiaca si Vasculara

Vasoconstrictie

Retentie renala
de sodiu

↑ Contractilitatea
Cardiaca

Angiotensina II

Secretie
Aldosteron

Stimulare
Simpatica:
Centrala
Terminatii
nervoase

Eliberare ADH

↑ Sete

Toate efectele fiziologice cunoscute sunt mediate
de receptorii AT1 ai Angiotensinei II

Blocantii receptorilor de Angiotensina II (BRA)

- Blocheaza doar receptorii AT1
- Blocheaza toate efectele Angiotensinei II
- Au efecte comparabile cu IECA majoritatea situatiilor.
- Scade mai putin rata filtrarii glomerulare la pacientii cu hipovolemie
- Nu blocheaza sistemul kininei – nu se acumuleaza bradikinina
- Lipsa efectelor secundare de tipul: tuse, angioedem, rash cutanat

IMPLICATII ANESTEZICE

- Cele mai importante intrebari:
 1. Continuarea IECA perioperator (inclusiv in dimineata interventiei) sau oprirea lor?
 2. Continuarea BRA perioperator (inclusiv in dimineata interventiei) sau oprirea lor?



- În cazul în care se decide intreruperea IECA / BRA:
 3. Cu cat timp înainte de intervenție trebuie să fie interrupțe?

- În cazul în care se decide intreruperea IECA / BRA:
 3. Cu cat timp înainte de intervenție trebuie să fie interrupțe?
 - a. 12 ore

- În cazul în care se decide intreruperea IECA / BRA:
 3. Cu cat timp înainte de intervenție trebuie să fie interrupte?
 - a. 12 ore
 - b. 1 zi

- În cazul în care se decide intreruperea IECA / BRA:
 3. Cu cat timp înainte de intervenție trebuie să fie interrupte?
 - a. 12 ore
 - b. 1 zi
 - c. 7 zile

Implicatii anestezice

- PRO CONTINUARE

Implicatii anestezice

- PRO CONTINUARE

EFFECTE PROTECTOARE CARDIOVASCULARE

Implicatii anestezice

- CONTRA CONTINUARE

Implicatii anestezice

- CONTRA CONTINUARE
 - risc de hipotensiune la inductie si intraoperator
 - in special:
 - la pacienti cu hipovolemie
 - in caz de pierderi sanguine
 - daca exista bloc simpanic (anestezii locoregionale)

Premize

Oprirea preoperatorie a

- beta blocantelor
- statinelor

RISC CRESCUT DE ACCIDENTE ISCHEMICE!!!

Daumerie G, Fleisher LA. *Perioperative β -blocker and statin therapy*. Current Opinion in Anaesthesiology 2008; 1 (21): 60–65.

CONTRA Continuarii IECA

“The use of these agents before surgery has been associated with a variable incidence of hypotension during the initial 30 min after induction of anaesthesia;

However, these hypotensive episodes have not been conclusively linked to any significant postoperative complications...”

Auron M, Harte B, Kumar A, Michota F. *Renin–angiotensin system antagonists in the perioperative setting: clinical consequences and recommendations for practice.* Postgrad Med J 2011. doi:10.1136/pgmj.2010.112987

PRO Continuare IECA

- Studiu prospectiv observational - 4224 pacienti supusi unui bypass coronarian.
- 1838 pacienti – sub tratament anterior cu IECA
- 2386 – fara expunere anteroara la IECA.
- Postoperator - 4 grupuri:
 - continuare IECA - 915 (21.7%);
 - oprire IECA - 923 (21.8%);
 - adaugare IECA - 343 (8.1%);
 - fara IECA - 2043 (48.4%).

PRO Continuare IECA

- Rezultate:
 - continuare IECA / fara IECA - reducerea semnificativa a evenimentelor nonfatale (adjusted odds ratio for the composite outcome, 0.69; 95% confidence interval, 0.52–0.91; P=0.009) si a incidentelor cardiovasculare (odds ratio, 0.64; 95% confidence interval, 0.46–0.88; P=0.006).
 - adaugare IECA / fara IECA – reducerea semnificativa a evenimentelor nonfatale (odds ratio, 0.56; 95% confidence interval, 0.38–0.84; P=0.004) si a riscurilor cardiovasculare (odds ratio, 0.63; 95% confidence interval, 0.40–0.97; P=0.04).
 - continuare IECA / intrerupere IECA – reducerea evenimentelor cardiace si renale (P<0.001 and P=0.005).

PRO Continuare IECA

- “Preoperative use appears to be associated with fewer major adverse events after cardiac surgery”
- “...is associated with lower 30 day mortality.”

Bandeali S, et al. *Outcomes of Preoperative Angiotensin-Converting Enzyme Inhibitor Therapy in Patients Undergoing Isolated Coronary Artery Bypass Grafting*. American Journal of Cardiology 2012; 7 (110): 919-923.

PRO Continuare IECA

- “...and even when no benefit has been demonstrated the agents appear to be safe.”

Ouzounian M, et al. *Impact of Preoperative Angiotensin-Converting Enzyme Inhibitor Use on Clinical Outcomes After Cardiac Surgery.* The Annals of Thoracic Surgery 2012; 2 (93): 559-564.



IECA = BRA ?

Blocantii receptorilor de Angiotensina II (BRA)

- Au aceleasi beneficii clinice cu IECA
- Prezinta acelasi risc de hipotensiune la inductia anesteziei **DAR**
- hTA nu raspunde la vasopresoarele uzuale (efedrina sau fenylefrina); un raspuns bun este obtinut cu **VASOPRESINA**
- Tinand cont de T_{1/2} se recomanda intreruperea BRA cu 24 ore anterior interventiei.

Brabant S, et al. *The Hemodynamic Effects of Anesthetic Induction in Vascular Surgical Patients Chronically Treated with Angiotensin II Receptor Antagonists*. Anesthesia & Analgesia 1999; 6 (89): 1388.

CONCLUZII

- Recomandari:
 - IECA – pot fi administrati inclusiv in ziua interventiei
 - BRA – se intrerup cu 24 ore anterior interventiei
 - IECA / BRA se reiau cat mai curand posibil
- Precautii:
 - bloc simpanic
 - risc sangerare
 - Hipovolemie
- Hipotensiunea intraanestezica se trateaza cu:
 - efedrina, fenilefrina - sub IECA
 - vasopresina, adrenalina – sub BRA



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Terapie Intensiva si Medicina de Urgenta

Timisoara, 7-9 noiembrie 2013 www.atitimisoara.ro