Cardio-Vascular Pharmacology

Dr. Shadi HOMSI

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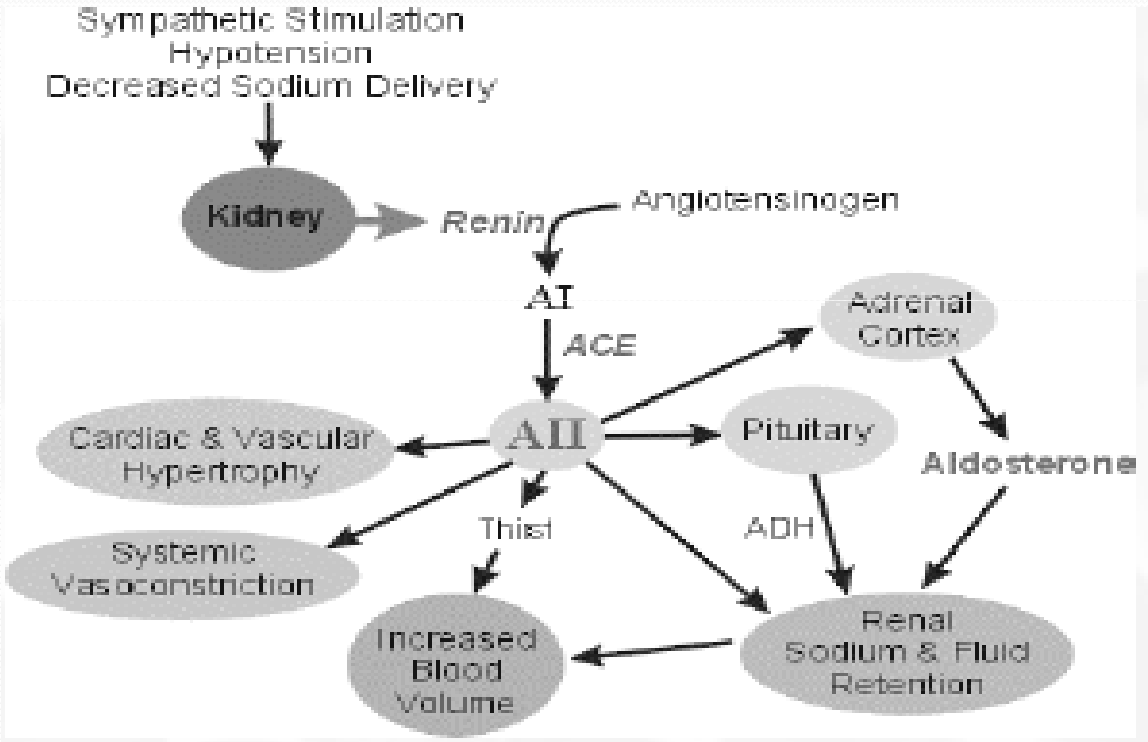
The Renin-Angiotensin System



A- Inhibitors of the Renin-Angiotensin System

- **<u>HF leads to activation of the RAAS via two mechanisms</u>**:

1) increased renin release by juxtaglomerular cells in renal afferent arterioles due to diminished renal perfusion pressure produced by the failing heart and

2) renin release by juxtaglomerular cells promoted by sympathetic stimulation and activation of β receptors.

- The production of angiotensin II, a potent vasoconstrictor, and the subsequent stimulation of aldosterone release that causes salt and water retention lead to increases in both preload and afterload that are characteristic of the failing heart.

- In addition, high levels of angiotensin II and of aldosterone have direct detrimental effects on the cardiac muscle, favoring remodeling, fibrosis, and inflammatory changes.

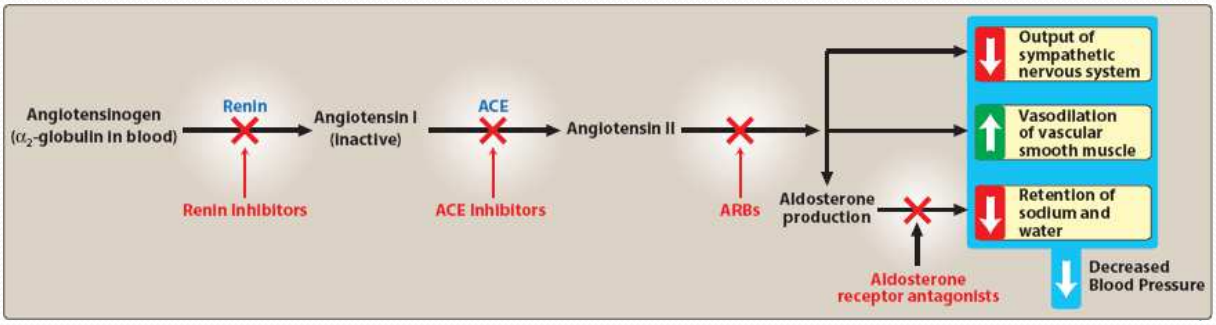
A- Inhibitors of the Renin-Angiotensin System

1- Angiotensin-converting enzyme inhibitors

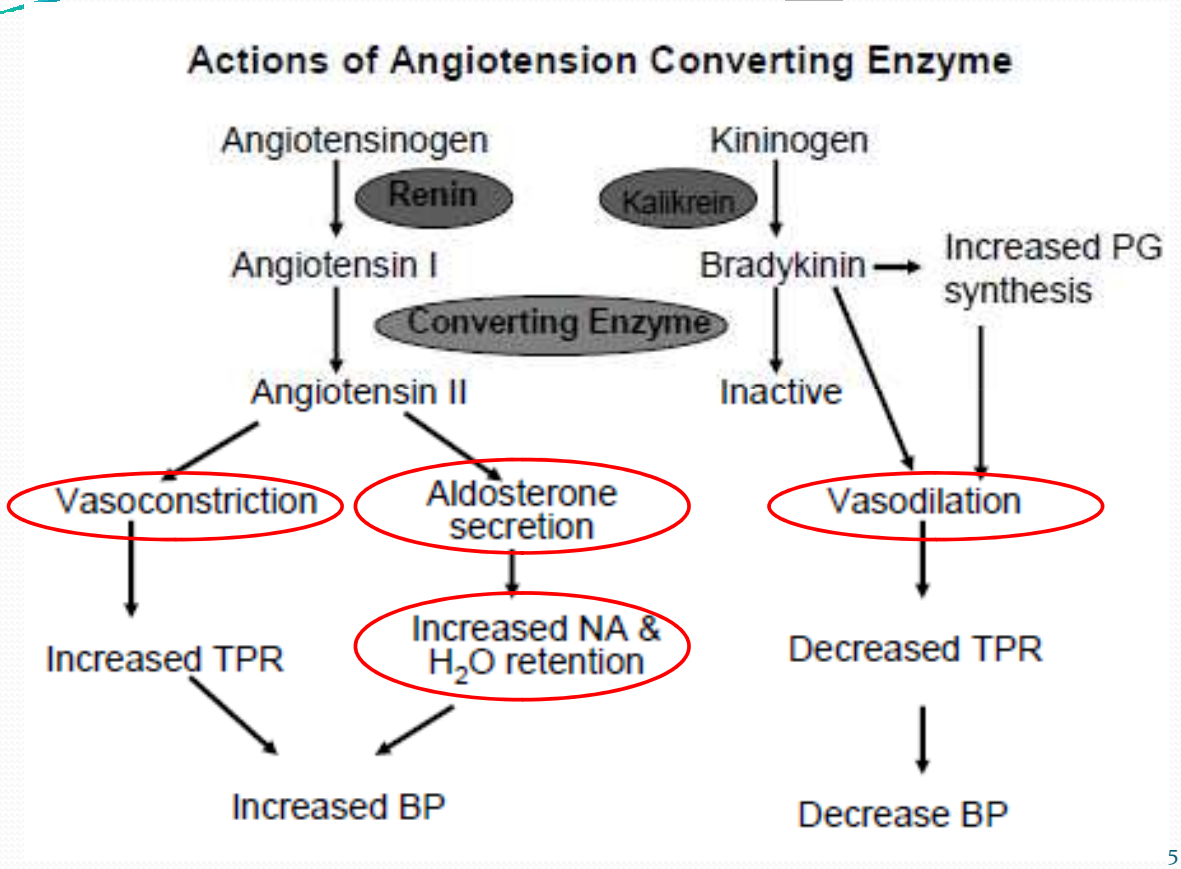
2- Angiotensin-receptor blockers

3- Renin Inhibitor

4- Aldosterone antagonists



1-Angiotensin-converting enzyme inhibitors



1- Angiotensin-converting enzyme inhibitors

- The ACE inhibitors, such as *enalapril and lisinopril* , are recommended as **first-line treatment** of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

- ACE inhibitors are a part of standard pharmacotherapy in HF.
These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II.

- They also diminish the inactivation of bradykinin.

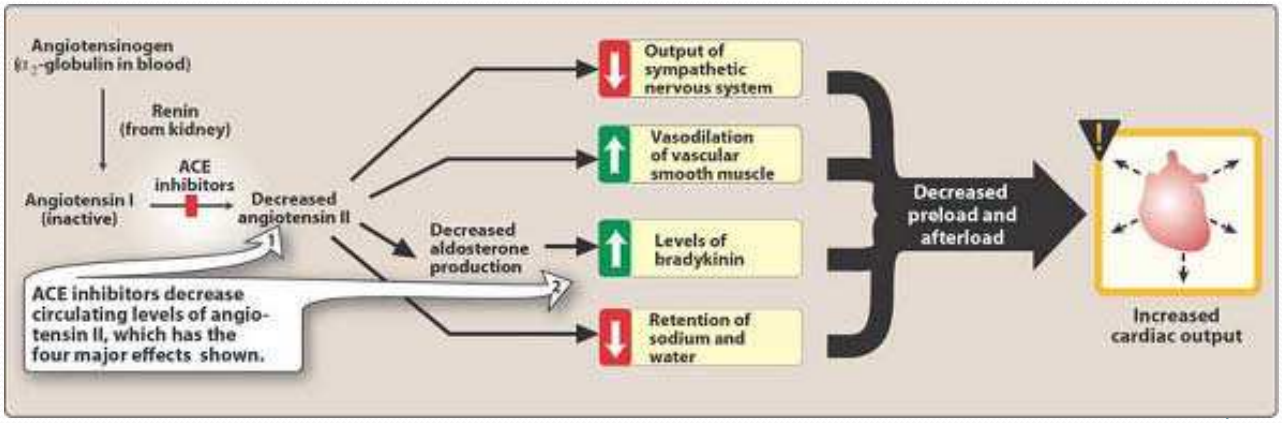
- Vasodilation occurs as a result of decreased levels of the vasoconstrictor angiotensin II and increased levels of bradykinin (a potent vasodilator).

- By reducing angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone.

1- Angiotensin-converting enzyme inhibitors

A. Actions on the heart:

- The ACE inhibitors lower BP by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility.
- ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output.
- ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF.



1- Angiotensin-converting enzyme inhibitors

B. Therapeutic uses

- Slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy.
- ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction.
- ACE inhibitors are first-line drugs for treating heart failure (asymptomatic and symptomatic HF), hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease.
- Depending on the severity of HF, ACE inhibitors may be used in combination with diuretics, β-blockers, *digoxin, aldosterone antagonists, and hydralazine/isosorbide dinitrate fixed-dose combination.*

1- Angiotensin-converting enzyme inhibitors

C. Pharmacokinetics:

- ACE inhibitors are adequately absorbed following oral administration.
- Food may decrease the absorption of *captopril, so it should be taken on an empty stomach.*
- Except for *captopril, ACE inhibitors are prodrugs that require* activation by hydrolysis via hepatic enzymes.
- Renal elimination of the active moiety is important for most ACE inhibitors except *fosinopril.*
- *Plasma half-lives of active compounds* vary from 2 to 12 hours.
- *Enalaprilat* is the only drug in this class available intravenously.

1- Angiotensin-converting enzyme inhibitors

D. Adverse effects

- Common side effects: dry cough, rash, fever, altered taste, postural hypotension and hyperkalemia.
- Angioedema is a rare but potentially life-threatening reaction.
- ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

2- Angiotensin-receptor blockers

- The ARBs, such as *losartan and irbesartan:* alternatives to the ACE inhibitors in patients with severe cough or angioedema.
- Block the AT2 receptors, ⬇ ⬇ the activation of AT2 receptors by angiotensin II.
- Their pharmacologic effects are similar to those of ACE inhibitors.
- They may be used as first-line agents for the treatment of HT (hypertension), especially in patients with diabetes, heart failure, or chronic kidney disease.
- Adverse effects **and drug interaction** profile are similar to those of ACE inhibitors with decreased risks of cough and angioedema (ARBs do not increase bradykinin levels).
- **ARBs should not be combined with an ACE inhibitor**.
- These agents are also teratogenic and should not be used by pregnant women.

2- Angiotensin-receptor blockers

Pharmacokinetics:

- Orally active drugs and require only once-a-day dosing
- *Losartan* undergoes extensive first-pass hepatic metabolism, including conversion to its active metabolite. The other drugs have inactive metabolites.
- Elimination of metabolites and parent compounds occurs in the urine and feces

3- RENIN INHIBITOR

- *Aliskiren (*selective renin inhibitor) *directly inhibits renin and, thus, acts* earlier in the RAAS than ACE inhibitors or ARBs.
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- *Aliskiren should not be* combined with an ACE inhibitor or ARB.
- *Aliskiren can cause diarrhea,* especially at higher doses, and can also cause cough and angioedema, but probably less often than ACE inhibitors.
- *Aliskiren is contraindicated during pregnancy.*
- *Aliskiren is metabolized* by CYP 3A4.

4- Aldosterone antagonists

- *Spironolactone is a direct antagonist* of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia
- *Eplerenone is a* competitive antagonist of aldosterone at mineralocorticoid receptors.
- Aldosterone antagonists are indicated in patients with more severe stages of HF and recent myocardial infarction.