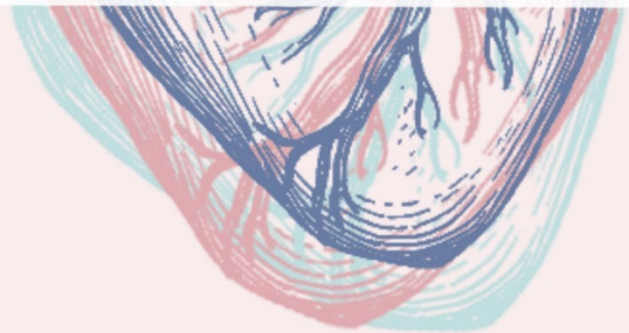
# Cardio-Vascular System

2

# Pharmacology

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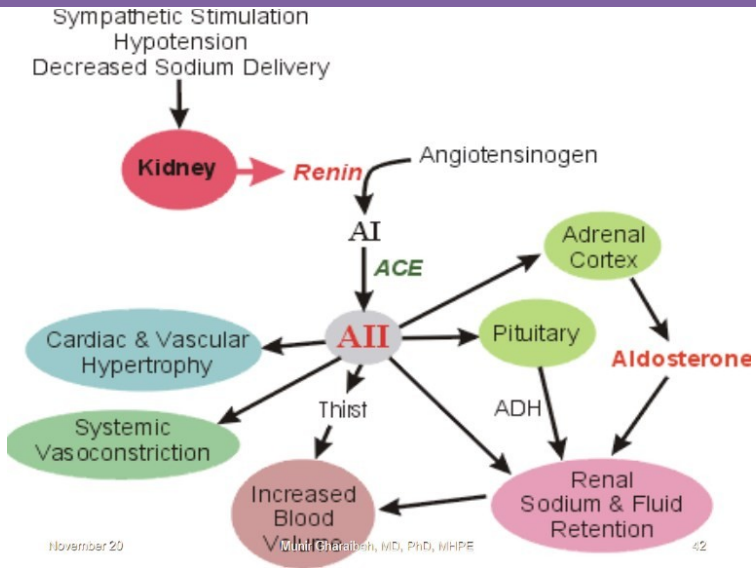
# Renin-Angiotensin-Aldosterone System




There are receptors in the afferent arteriole of the kidney that can sense the salt concentration as well as the blood pressure, so if BP drops, this triggers the release of renin from the afferent arteriole.

Now, renin converts angiotensinogen (which is produced from the liver) into angiotensin I.

Angiotensin I goes to the lungs and there it meets the enzyme angiotensin-converting
enzyme (ACE) which converts it into angiotensin II.

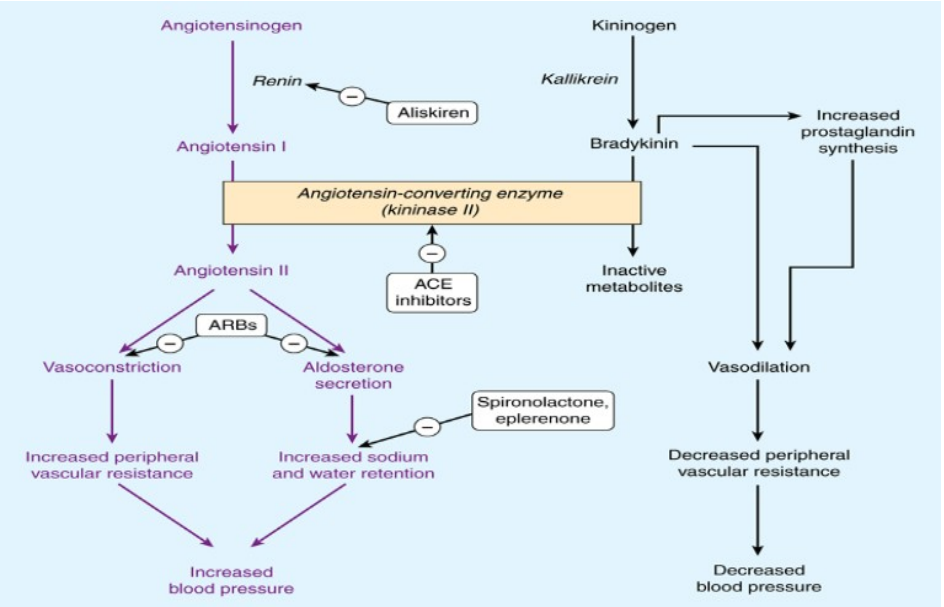
Angiotensin II = Kininokinase II

Note that : ACEIs are in the heart of the diagram which means that they play a major role in the renin-angiotensin system and produce very wide effects, while if we need limited effects we can use angiotensin II receptor blockers, and if we are targeting sodium and water retention we have other drugs like spironolactone
If we want to target more proximal point (more wide spread activity) it will be the renin enzyme

As mentioned in the figure above, angiotensin II has many effects. Please read them!

There many drugs which target this system, Aliskiren (inhibits renin), ACEI (angiotensin- converting enzyme inhibitors), ARBs (angiotensin receptor blockers).

Spironolactone, eplerenone these inhibit aldosterone secretion as well as aldosterone receptors.




ACE also metabolizes bradykinin, bradykinin increases prostaglandin synthesis causing vasodilation. Therefore, inhibiting ACE would not only decrease angiotensin II levels but also stopping bradykinin from being metabolized, resulting in increased levels of bradykinin, which ultimately causes vasodilation, decreased PVR and decreased blood pressure.

## Angiotensin II:

Angiotensin II, as a part of the renin-angiotensin-aldosterone system, its major function is to regulate the blood pressure as well as body fluids.

- Potent vasoconstrictor by itself. (More than NE)
- Facilitates release of NE. (acting as neuro-mediator for the sympathetic nervous system, which also increases the blood pressure)
- Central actions to increase BP.
- Promotes release of aldosterone, aldosterone increases the BP by increasing salt and water retention.
- Regulates tubular function in the kidney.
- Regulates intra-renal blood flow.

# Angiotensin converting enzyme inhibitors (ACEIs)

These drugs inhibit the enzyme angiotensin-converting enzyme (ACE) which is responsible for converting angiotensin I into angiotensin II.

- Have many applications nowadays, for hypertension and other diseases.
- Inhibit ACE in the lungs.
- Also inhibit kinin metabolism

## Cardiorenal Effects of ACE Inhibitors:

- Vasodilation (arterial & venous):
  - Reduces arterial & venous pressure.
  - Reduce ventricular afterload and preload.
- Decreases blood volume (through inhibiting aldosterone), therefore having a natriuretic (induces sodium excretion) and diuretic activity.
- Depresses sympathetic activity.
- Inhibits cardiac and vascular hypertrophy.
- All of them have similar efficacy (produce same maximal effects) .. But differ in toxicity.

## Examples of ACEI:

- Captopril is the prototype. It was discovered in 1970s, newer drugs with less side effects are now discovered
- Enalapril, Quinapril, Lisinopril, Benazepril, Fosonopril.

## Therapeutic Benefits of ACEI:

- Effective in high-rennin hypertension (which makes 20% of all hypertension cases), heart failure (HF) and ischemic heart disease (IHD).
- Do not increase HR; they don't work directly on the heart. (No stimulation of baroreflex effect)
- Useful in diabetic nephropathy by dilating efferent arterioles thus reducing intraglomerular pressure and consequently protects against progressive glomerulosclerosis (glomerulosclerosis is a nephropathy that commonly occur in diabetics). It's now used as a prophylactic agent in diabetic patients even if the blood pressure isn't very high
- No need for a diuretic but a diuretic can be added (because they cause sodium-water retention). In contrast to vasodilators and CCBs where resistance can develop if not given along with diuretics.
- Can be combined with CCBs.
- Should not be combined with Beta blockers.
- No metabolic side effects, in contrast to Beta blockers and diuretics that can cause diabetes and hyperlipidemia.
- Contraindicated in pregnancy (teratogenic) and bilateral renal artery stenosis

## Side Effects of ACEI:

They are relatively safe drugs except for captopril.

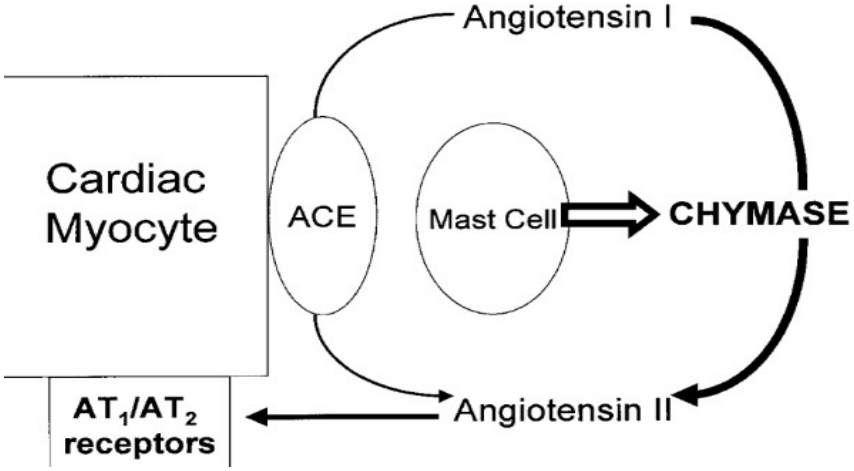
- Captopril is SH containing drug, so very toxic (bone marrow suppression, dysgeusia (change in taste sensation), proteinuria, allergic skin rash, fever). In general sulfhydryl containing drugs are toxic as they can bind many different enzymes and disrupt their actions.
- Hypotension (first dose phenomena) especially with renovascular hypertension. So these drugs are contraindicated in patients with this condition. (May cause syncope)
- K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs.
- Cough, in 10% of patients, you might consider to change the preparation or even the whole class.
- Angioedema.

# Chymase

Long-term treatment with ACE inhibitors is often associated with so-called "angiotensin escape" (resistance) characterized by the return of plasma angiotensin II concentration to pretreatment levels.

If ACE is inhibited then we shouldn't have high levels of angiotensin II? But we still find high levels of angiotensin II, so there must be some other site producing it. This place is the heart tissue.

This rebound generation of angiotensin II occurs through the action of the serine proteases such as chymase and cathepsin G. Chymase is an enzyme found in the heart. It can convert angiotensin I to angiotensin II.




- Vascular chymase has been implicated in the ACE-independent mechanism for local angiotensin II formation in human arteries.
- ACE-independent generation of angiotensin II plays a central role in the regulation of renal hemodynamics during the progression of diabetic nephropathy.

The physiologic importance of chymase is uncertain, because of the presence of natural protease inhibitors in the interstitial fluid which inhibit chymase-induced angiotensin II production. Therefore, the beneficial effects of ACE inhibitors on blood pressure usually persists.

## Angiotensin II Receptor Blockers (AT-1)

AT-1 or ARBs (same thing different name) work directly on angiotensin receptors found on cell surfaces, resulting in more complete inhibition of angiotensin actions, with NO effects on bradykinins. In contrast to ACE inhibitors.

- May be only indicated when ACEI are intolerable. Simply because they very expensive.
- Most expensive, but fastest growing class of antihypertensive drugs.
- Free of side effects, especially cough, since they work inside the lungs, but ARBs work outside.
- May be better than ACEI in protection against stroke (due to activation of AT-2 receptor which facilitates collateral vessels and neuronal resistance).

### Examples of ARBs:

- Losartan, Valsartan, Candesartan, Irbesartan, Eprosartan.
- Telmisartan (it has additional peroxisome proliferator-activated receptor PPR-γ agonist activity).

## Renin Enzyme Inhibitors

### Aliskiren:

- The first in this group.
- Not widely used, other better studied medications are typically recommended due to concerns of higher side effects and less evidence of benefit.

# Centrally Acting Antihypertensive Drugs

These drugs work directly on the brain specifically in the vasomotor center, there, we have both alpha and beta receptors but their effect is reversed; meaning that alpha receptors activation decreases BP while Beta receptor activation increases BP.

The vasomotor center constitutes of the following nuclei:

1. Nucleus Tractus Solitarius
2. Nucleus Ambiguss
3. Rostral Ventral Medulla.

The vasomotor center controls both the sympathetic and parasympathetic systems.

## Common Properties of these drugs:

- Cross BBB.
- Reduce preganglionic sympathetic activity.
- Orthostasis is unusual, due to preservation of peripheral sympathetic activity.
- CNS side effects.

## Examples of these drugs include:

- Propranolol (Beta blocker).
- Reserpine (acts on sympathetic nerve terminals). With sever side effects
- a-Methyl Dopa.

## a-Methyl Dopa:

- An old drug, that's thought to act as a pseudo-transmitter (by being converted into a-methyl-norepinephrine), which works peripherally. Now, it's proved to have central alpha agonist activity.
- a-MD (alpha methyl-dopa) is converted into a-MDA (alpha methyl-dopamine) which is then converted to a-MNE (alpha methyl-norepinephrine).
- It lowers BP but doesn't affect CO or renal blood flow.
- It can cause lactation and positive Coomb's test. **As side effects**
- Safe in pregnancy (drug of choice for treatment of eclampsia or preeclampsia- a pregnancy complication characterized by high blood pressure and signs of damage to another organ system- and for treatment of hypertension in pregnancy).

## Clonidine:

- Imidazoline derivative, tried initially as a nasal decongestant (local effect).
- Central alpha agonist (lowering blood pressure).
- I.V administration of clonidine would have biphasic effect; initially, it acts peripherally causing vasoconstriction of blood vessels which further raises the blood pressure (that's why clonidine I.V. administration is contraindicated), then central actions begin (lowering BP).
- Given orally, so that the initial vasoconstrictive effect would be reduced, by slower absorption from the GI.
- Also available as transdermal patch (extended activity for about 7 days).

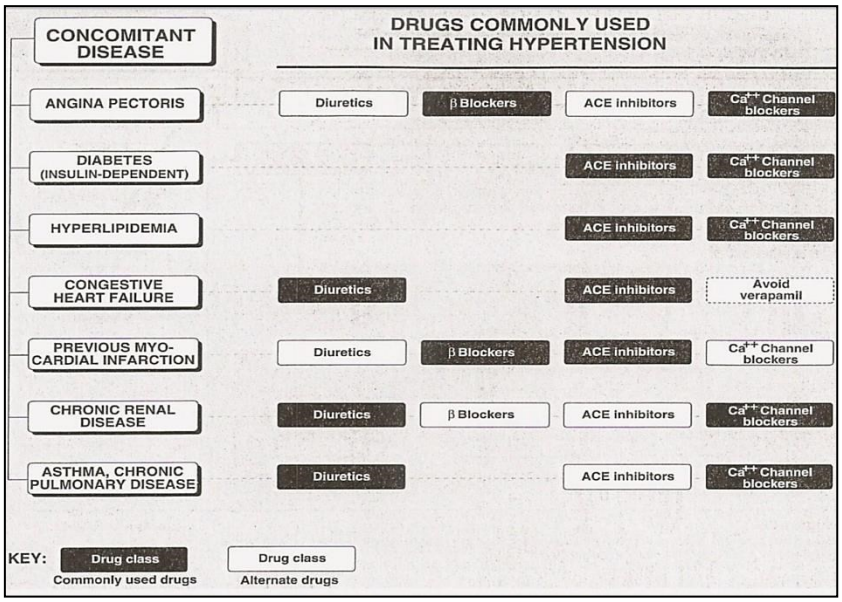
# Causes of Resistant Hypertension

Resistant hypertension means that it doesn't respond to drugs. The causes include:

- Improper BP measurement
- "White coat hypertension" (we don't measure BP in clinic directly; rather, we wait a little bit to avoid it).
- Non-compliance to the prescribed drugs
- Psychological stresses
- Secondary hypertension (to a tumor like pheochromocytoma)
- Sleep disorders
- Volume overload
- Pseudo-tolerance to drugs
- Excess sodium intake
- Volume retention from kidney disease
- Inadequate diuretic therapy
- Inadequate doses
- Inappropriate combinations
- NSAID, cyclooxygenase 2 inhibitors (e.g. Aspirin, Ibuprofen, and Voltaren)
- Cocaine, amphetamines, anorectics, and other illicit drugs
- Sympathomimetic drugs
- Oral contraceptives
- Corticosteroids
- Cyclosporine
- Erythropoietin
- Licorice عرق السوس (including some chewing tobacco).
- Excess alcohol intake

→ A summary for some drugs and their other indications besides treating hypertension.

- The drugs in black are commonlyused drugs.
- The drugs in white are alternative drugs.




# Good luck