Reducing the load; the ACE way

Angiotensin-converting enzyme inhibitors

What are ACE inhibitors?

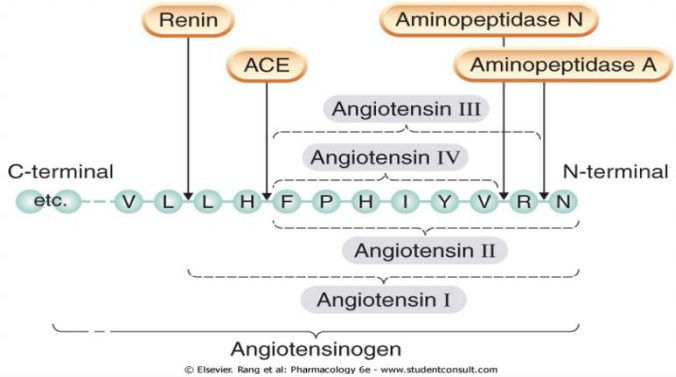
- ACE-I are indirect Vasodilator drugs that leads to reducing load on the vasculature
- They work by:
  - ACE-I occupy the enzyme as false substrates.
  - They inhibit the conversion of angiotensin I to angiotensin II.
- They have many uses and are generally well tolerated.

Some Physiology basics

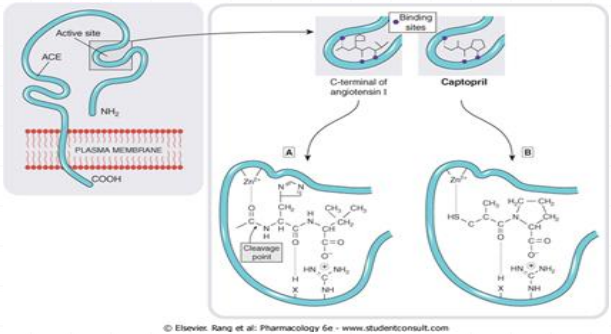
- To reduce the load on the heart:
  - Reduce TPR
    - Vasodilation
    - Decrease viscosity

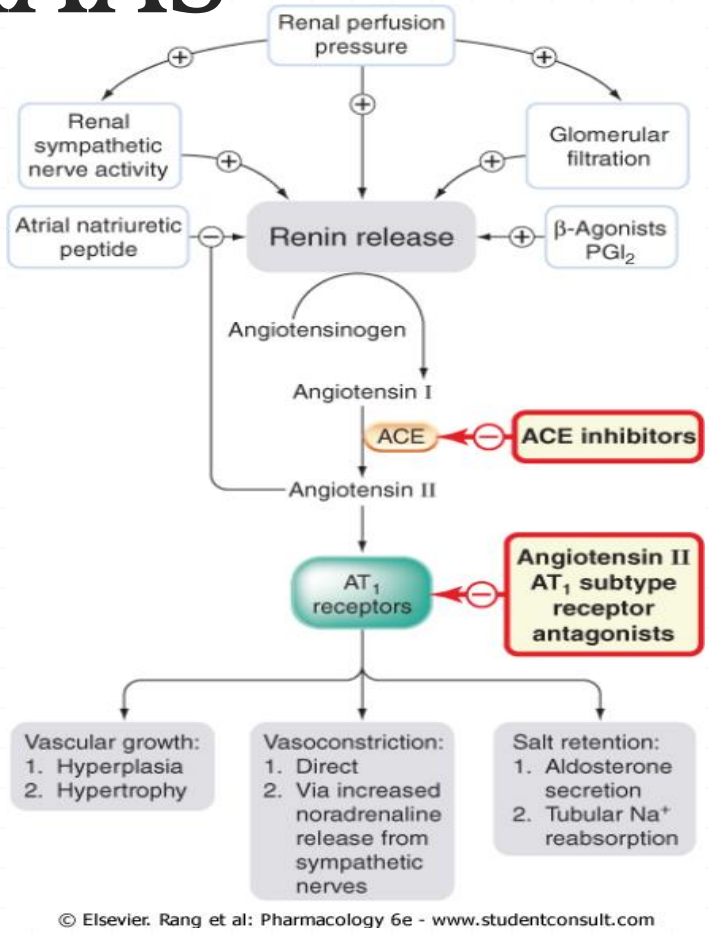
- A major control of vasotone is modulated by the RAAS system and its end product Angiotensin II (40x more potent than adrenaline)

ACE on RAAS



ACE-I





Reasons to use ACE-I

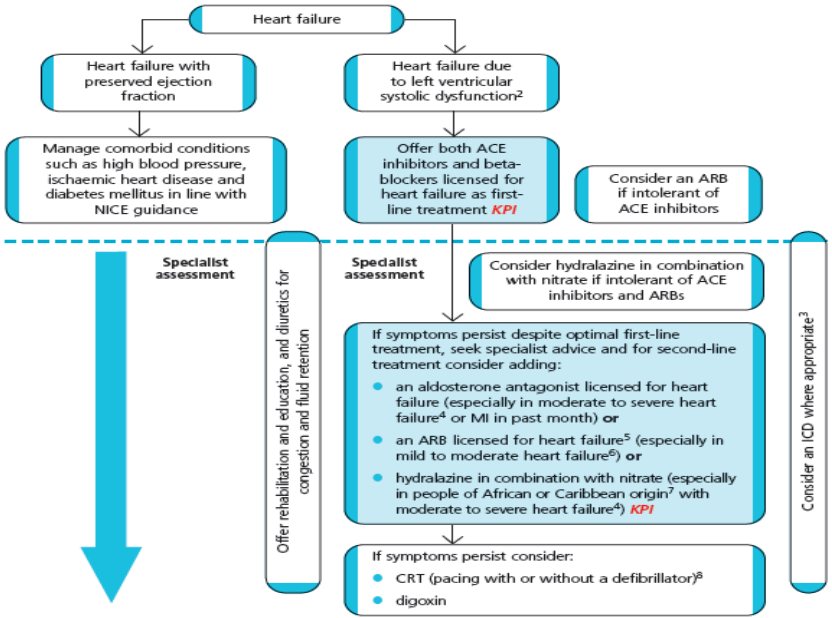
- Reduce heart load for
  - Heart failure
  - Hypertension

- Other
  - Diabetic nephropathy

Indications- Heart failure

- Used in all grades of heart failure (usually combined with a beta-blocker).
- Risk of hyperkalemia- discontinue potassium supplements and re-consider potassium sparing diuretics.
- Profound first-dose hypotension may occur when ACE inhibitors are introduced to patients with heart failure who are already taking a high dose of a loop diuretic (initiate under specialist supervision).

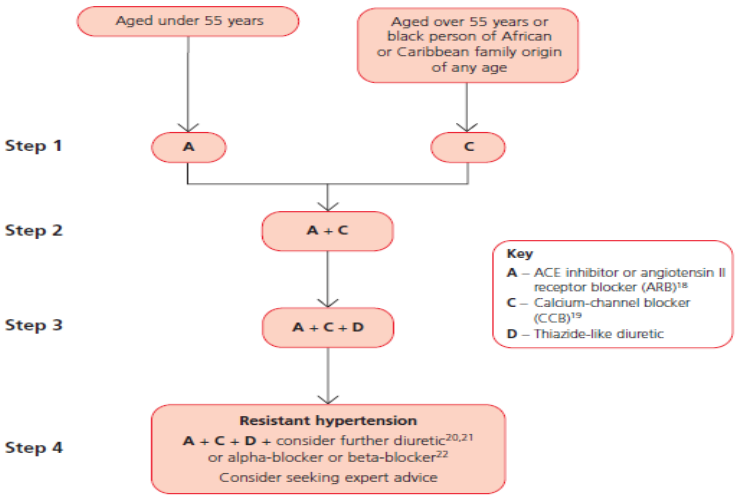
NICE Guidelines- CHF



Hypertension

- An ACE inhibitor may be the most appropriate initial drug for HTN in younger Caucasian patients.
- Afro-Caribbean patients, those aged over 55 years, and those with primary aldosteronism respond less well.
- ACE inhibitors are particularly indicated for HTN in patients with type 1 DM with nephropathy.
- May reduce blood pressure very rapidly, particularly in those receiving diuretics; the first dose should preferably be given at bedtime.

NICE Guidelines- HTN



Indications- other

- Diabetic nephropathy.
- Prophylaxis of cardiovascular events- Used in the early and long-term management of patients who have had a MI. May also have a role in preventing CV events. NICE guidelines-

ACE inhibitors

- Offer ACE inhibitors early after presentation and titrate upwards to the maximum tolerated or target dose.
- Do not routinely prescribe ARBs unless the patient is intolerant or allergic to an ACE inhibitor.
- Continue ACE inhibitors indefinitely in patients with preserved LV function or LVSD, whether or not they have heart failure symptoms.
- Early after an acute MI, do not routinely use the combination of ACE inhibitor/ARB for patients with heart failure and/or LVSD.

Assessment/monitoring

- Assess LV function in all patients who have had an MI.
- Measure renal function, serum electrolytes and BP before starting an ACE inhibitor or ARB and again within 1 or 2 weeks.
- Monitor patients as the dose is titrated and more frequently for patients at increased risk of deterioration in renal function.
- Monitor patients with chronic heart failure in line with NICE clinical guideline 5.

The good, the bad and the dreadful

Drug	Dose	Conditions favouring use	Cautions/contraindications
Angiotensin-converting enzyme inhibitors			
Enalapril Lisinopril Perindopril Ramipril	5.0–40 mg daily 2.5–40 mg daily 2.0–8.0 mg daily 1.25–10 mg daily	<55 years old, Caucasian, heart failure or left ventricular dysfunction, myocardial infarction or cardiovascular disease, diabetic nephropathy, chronic renal disease, stroke secondary prevention	Renal failure (monitor electrolytes), peripheral vascular disease (if renovascular disease), pregnancy

Drug Class	Major Contraindications	Side Effects
ACE inhibitors	Pregnancy Bilateral renal artery stenosis Hyperkalemia	Cough Hyperkalemia Angioedema Leukopenia Fetal toxicity Cholestatic jaundice (rare fulminant hepatic necrosis if the drug is not discontinued)

Caution

Impaired renal function and renovascular disease.

- For ALL patients check before initiating, increasing dose, and monitor throughout treatment-
  - Renal function
  - Electrolytes (hyperkalemia)

- ACE inhibitors may have a role in some forms of renal disease.
- ACE inhibitors might cause impairment of renal function which may progress and become severe.

- Concomitant treatment with NSAIDs increases the risk of renal damage.

- Contraindicated in patients with **severe bilateral renal artery stenosis**- reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure.
- Contraindicated In patients with severe unilateral renal artery stenosis (long term consequences are unknown) unless BP cannot be controlled by other drugs.
- Caution in patients who may have undiagnosed and clinically silent renovascular disease (patients with peripheral vascular disease or those with severe generalised atherosclerosis).

Caution

Concomitant diuretics

- ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients (Patients receiving diuretics, on a low-sodium diet, on dialysis, dehydrated, or with heart failure).
- Treatment should therefore be initiated with very low doses.

Caution

- Collagen vascular disease- The risk of agranulocytosis is possibly increased (blood counts recommended).
- Patients with severe or symptomatic aortic stenosis (risk of hypotension).
- Hypertrophic cardiomyopathy.
- A history of idiopathic or hereditary angioedema.
- If jaundice or marked elevations of hepatic enzymes occur during treatment, then the ACE inhibitor should be discontinued (risk of hepatic necrosis).

Contraindications

- Patients with hypersensitivity to ACE inhibitors (including angioedema).
- Hepatic impairment- Use of prodrugs (cilazapril, enalapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, and trandolapril) requires close monitoring.
- Renal impairment- close monitoring and dose reduction.
- Pregnancy- Avoided unless essential (may adversely affect fetal and neonatal blood pressure control and renal function; cause skull defects and oligohydramnios).
- Breast-feeding- (information is limited). Risk of profound neonatal hypotension.

Side effects

- Profound hypotension.
- Renal impairment.
- Persistent dry cough.

- Angioedema (onset may be delayed; higher incidence reported in Afro-Caribbean patients).
- Rash (may be associated with pruritus and urticaria).
- Pancreatitis.
- URTI symptoms- sinusitis, rhinitis, and sore throat.
- GI effects- nausea, vomiting, dyspepsia, diarrhoea, constipation, and abdominal pain.

- Altered liver function tests, cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure.
- Hyperkalaemia.
- Hypoglycaemia.
- Blood disorders- thrombocytopenia, leucopenia, neutropenia, and haemolytic anaemia.
- Headache, dizziness, fatigue, malaise, taste disturbance, paraesthesia, bronchospasm, fever, serositis, vasculitis, myalgia, arthralgia, photosensitivity.
- Positive ANA, raised ESR, eosinophilia, leucocytosis.

100 drugs list - Ramipril

Indications

- HTN
- Symptomatic heart failure (adjunct).
- Prophylaxis after MI (start >48 hrs after infarction).
- Following MI in patients with clinical evidence of heart failure.
- Prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or with DM and at least one additional risk factor for cardiovascular disease.
- Nephropathy.

100 drugs list - Ramipril

Caution

- Impaired renal function, Renovascular disease.
- Concomittent diuretic therapy, volume depletion.
- Collagen vascular disease.
- Severe or symptomatic aortic stenosis .
- Hypertrophic cardiomyopathy.
- History of angioedema.
- If jaundice or marked elevations of hepatic enzymes occur during treatment, then the ACE inhibitor should be discontinued (risk of hepatic necrosis).

Contra-indications

- Hypersensitivity to ACE inhibitors (including angioedema).
- Hepatic impairment- close monitoring.
- Renal impairment- close monitoring and dose reduction.
- Pregnancy- Avoided unless essential.
- Breast-feeding- Not recommended.

100 drugs list - Ramipril

Side-effects-

- Arrhythmias, angina, chest pain, syncope, cerebrovascular accident, MI.
- Loss of appetite, stomatitis, dry mouth.
- Skin reactions including erythema multiforme and pemphigoid exanthema.
- Precipitation or exacerbation of Raynaud's syndrome.
- Conjunctivitis, onycholysis.
- Confusion, nervousness, depression, anxiety.
- Impotence, decreased libido.
- Alopecia.
- Bronchitis.
- Muscle cramps.