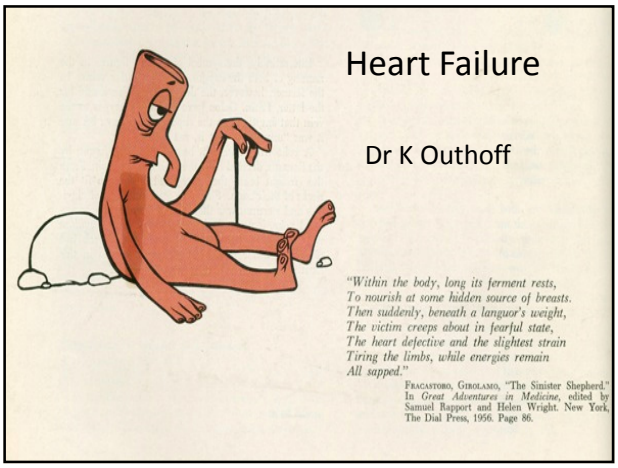
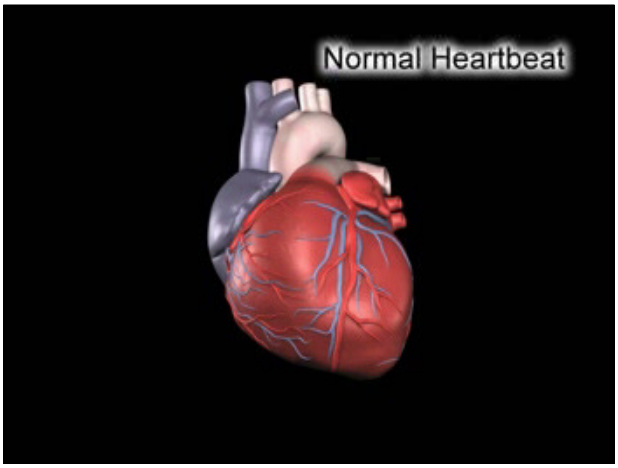
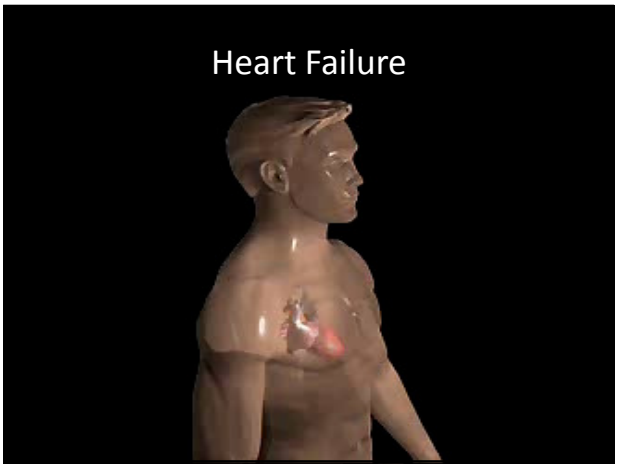


Heart failure

- Heart fails to deliver adequate amounts of oxygenated blood to tissues
- Failure of pump action
  - Chronic: fatigue, ankle oedema, dyspnoea, orthopnoea
  - Acute: sudden onset pulmonary oedema with S.O.B
- Reduction in life expectancy
- Causes several patho-physiological changes that are counterproductive.
- Treatment directed at reversing these counter-regulatory changes.

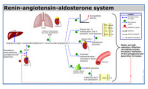




Counter-regulatory changes

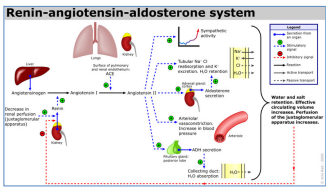
<u>Activation of renin-angiotensin-aldosterone system</u>

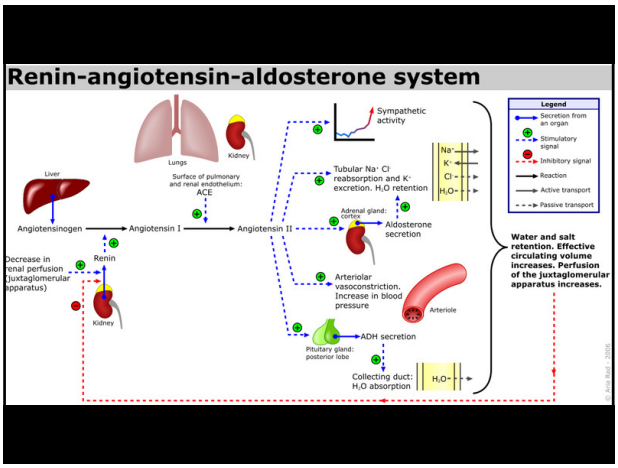
- Release of renin
- Increases production of angiotensin II
  - Direct vasoconstriction
  - Indirect synergy with sympathetic NS
- Also increases production of aldosterone
  - Salt and water retention



Counter regulatory changes

- Activation of sympathetic NS reflexes
  - Increase in sympathetic tone
  - Tachycardia
  - Vasoconstriction





Cardiac Performance determined by:

- Preload (how much the ventricles are stretched by filling pressure))
  - Blood volume due to Na / water retention
  - Increased capacitance vessel tone due to sympathetic NS
- Afterload (impedence to ventricular emptying)
  - Systemic vascular resistance
  - V. High in heart failure due to activation of RAAS, sympathetic NS
- Myocardial contractility
  - Intrinsic contractility of heart
  - Positive inotropes (digoxin) can improve contractility temporarily (at the expense of increasing work and oxygen demand
- Heart rate
  - Increase heart rate, increase cardiac output
  - Digoxin = negative chronotrope

Aims of Heart Failure Management

To achieve improvement in symptoms:

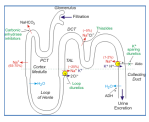
- Diuretics [mainstay]
- ACE inhibitors [mainstay]
- Digoxin

To achieve improvement in survival:

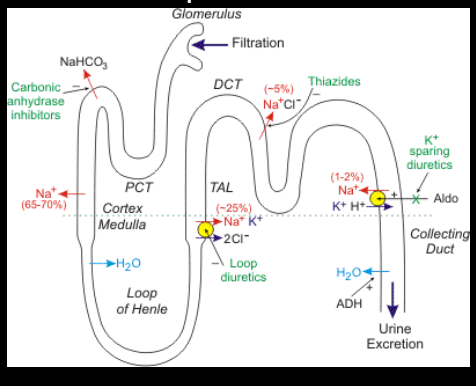
- ACE inhibitors
- Beta blockers (carvedilol, bisoprolol, metoprolol)
- Oral nitrates + Hydralazine
- Spironolactone

Diuretics

- Effective in providing symptomatic relief
- First line treatment, esp. if oedema present
- No evidence though of prognostic benefit
- Should be introduced at low dose; dose titration according to clinical response
- Regular review necessary (over / under treating)
  - Loop diuretics
  - Thiazide and thiazide-like diuretics
  - K sparing diuretics



Loop diuretics



Loop diuretics
furosemide and bumetanide

- Powerful diuretic action
- Increase the excretion of sodium and water at the ascending loop of Henle by inhibiting Na / K / 2Cl co-transport
  - Decrease cardiac preload
  - Reduce oedema
  - Indirect vasodilator effect
- Rapid onset of action iv 5 min,
- Oral 4-6hrs, absorption delayed by CCF (oedema of GIT)
- Steep dose-response curve
- Eliminated in urine
- Secreted by proximal tubule, becomes progressively more concentrated, to exert its effect selectively in kidney

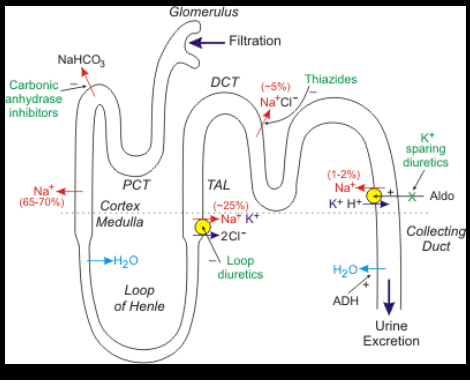
Furosemide

- Adverse effects:
- Patients receiving high doses should be monitored for renal and electrolyte abnormalities
- Hypokalaemia (precipitates arrhythmias) to be avoided with K supplements or concomitant K sparing agent
- Acute gout relatively common

Furosemide

- Adverse effects:
  - Hypok
  - HypoNa
  - HypoMg (cardiac excitability)
  - Gout
- Idiosyncratic
  - Rashes
  - Bone marrow depression
    - Neutropeania
    - Thrombocytopaenia
  - Acute renal failure
- Rapid high dose / excessive peak concentrations:
  - Ototoxicity (deafness, tinnitus) because endolymph in inner ear requires an Na / K / 2Cl co-transporter!

Thiazide diuretics



Thiazide diuretics benzofluazide, hydrochlorothiazide

- Act on cortical segment of nephron
- Inhibit reabsorption of Na and Cl in early distal convoluted tubule resulting in natriuresis
- Also have direct vasodilatory effects on resistance vessels
- Often ineffective in elderly
  - Age related heart failure and low GFR
- Hyponatraemia and Hypokalaemia associated with high doses
- K supplements / K sparing agents

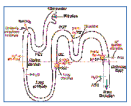
Thiazide diuretics adverse effects

- Impotence
  - Increased plasma renin due to contraction of plasma volume
- Electrolyte changes
  - hypoNa
  - hypoK (increased Na delivery to distal nephron, Na and K ions exchanged
  - hypoMg
- Metabolic changes
  - Hyperuricaemia (↓urate clearance)
  - Hyperglycaemia in NIDDM (reduced glucose tolerance)
  - Hypercalcaemia (↓calcium clearance)
  - Hypercholesterolaemia (transient, insignificant)

Thiazide diuretics

<u>DDI</u>

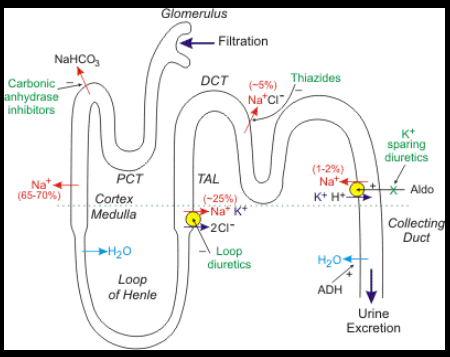
1. NSAIDs reduce efficacy of diuretics by inhibiting PGE and prostacyclin synthesis (Na, water retention)
2. Lithium (Increased absorption from PCT)
3. Digoxin toxicity
4. Ca channel blocker (↓ efficacy)



Loop and thiazide combined

- In some patients with severe heart failure (esp. In presence of chronic renal impairment), oedema may persist despite conventional doses of loop diuretics.
- In these cases a thiazide diuretic may be combined with a loop diuretic
- Blocks reabsorption of Na at different sites (double nephron blockade)
- Synergistic action leads to
  - Greater diuretic effect
  - Greater metabolic abnormalities
- Therefore to be done under close supervision only.

Potassium sparing diuretics

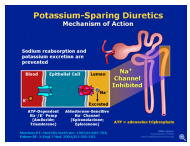


Potassium sparing diuretics Amiloride and spironolactone

- Weak diuretic action when used alone
- Amiloride most commonly used in fixed dose combinations with a loop diuretic (Co-amilofruse)
- Traditionally avoided in patients on ACE inhibitors.
  - Potential risk of hyperkalaemia
    - Spironolactone dose >50mg / day
    - High doses of ACE inhibitor
    - Evidence of renal impairment
  - But hyperkalaemia uncommon when dose of spironolactone is low < 25mg daily
  - Recommended monitoring of serum creatinine and [K]

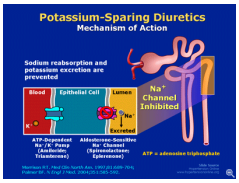
Spironolactone

- Competitive aldosterone antagonist
- Competes for aldosterone receptors in distal tubule
- Aldosterone promotes Na retention, K loss
- Therefore spironolactone promotes Na, water loss and conserves K
- Particularly in hyperaldosteronism
  - Conn's
  - Cirrhosis
  - Heart failure



Spironolactone

- Structure related to oestrogen
- Onset of action 2-3 days
- Main metabolite: canrenone has half life 16hrs
- Interferes with tubular secretion of digoxin
- Adverse effects:
  - Gynaecomastia
  - Menstrual irregularities



Aims of Heart Failure Management

<u>To achieve improvement in symptoms:</u>

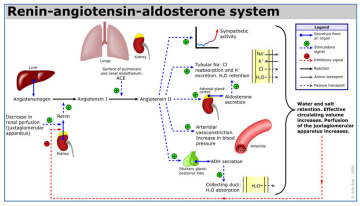
- Diuretics [mainstay]
- ACE inhibitors [mainstay]
- Digoxin

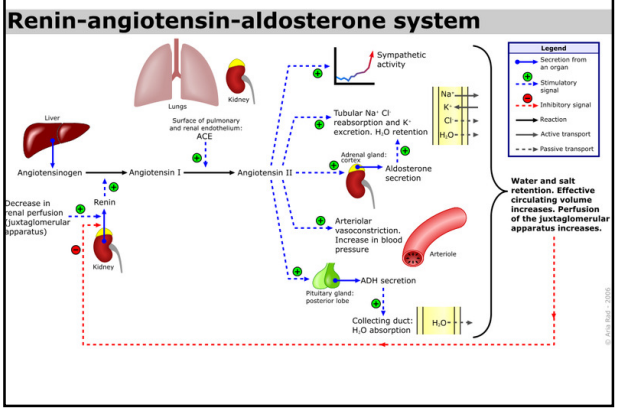
<u>To achieve improvement in survival:</u>

- ACE inhibitors
- Beta blockers (carvedilol, bisoprolol, metoprolol)
- Oral nitrates + Hydralazine
- Spironolactone

ACE inhibitors

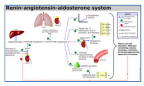
- Captopril
- Enalopril
- Lisinopril
- Quinapril
- Perindopril
- Ramipril
- Trandolapril





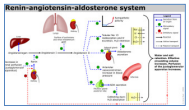
ACE inhibitors

- Have consistently shown beneficial effects on mortality, morbidity, and quality of life
- Indicated in all stages of symptomatic heart failure resulting from impaired left ventricular systolic function
- Start low dose, gradual titration to **highest** tolerated maintenance dose associated with significant decrease of morbidity and hospital admissions



ACE inhibitors mechanism of action

- Inhibit production of Angiotensin II (a potent vasoconstrictor and growth promoter)
- Increase the levels of the vasodilator bradykinin by inhibiting its degradation
- Bradykinin associated with release of
  - NO
  - Prostacyclin
- Bradykinin also responsible for some adverse effects:
  - Dry cough from stimulating cough afferents
  - Hypotension
  - Angio-oedema

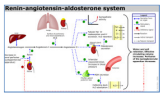


ACE inhibitors

- Reduce the activity of the sympathetic nervous system as angiotensin II promotes
  - Release of noradrenaline
  - Inhibits its re-uptake
- Improve:
  - beta receptor density (causing up-regulation)
  - Variation in heart rate
  - Baroreceptor function
  - Autonomic function (incl. Vagal tone)

ACE inhibitors clinical effects

- Symptomatic left ventricular dysfunction:
  - When added to diuretics, improve symptoms, exercise tolerance, survival in chronic heart failure
- Asymptomatic left ventricular dysfunction:
  - Enalapril has been shown to reduce the development of heart failure
- Left ventricular dysfunction after myocardial infarction:
  - Lower mortality in patients with impaired systolic function, irrespective of symptoms
- Slowing disease progression:
  - From mild to severe heart failure

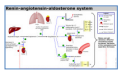


ACE inhibitors Adverse Effects

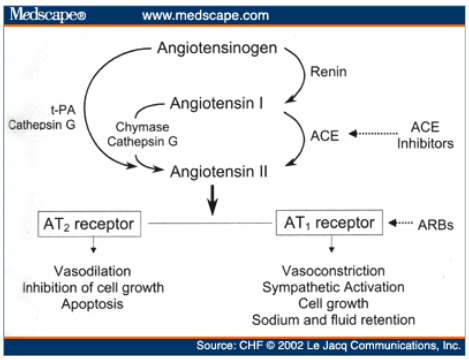
- Cough, urticarial reactions, angio-oedema
- Dizziness (first dose hypotension)
- Deterioration in renal function
- Renal failure in foetus, oligohydramnios and birth defects
- Modest increase in K (reduced aldosterone secretion) – monitor in renal failure and diuretics

Drug interactions

- Useful interaction with loop and thiazide diuretics
  - Diuretics increase renin which limits their efficacy
  - ACE-inhibitors interrupt this loop and confer greater diuretic efficacy
- Life-threatening hyperkalaemia
  - K sparing diuretics
  - K supplements
  - Renal failure
  - NSAIDs contra-indicated in heart failure and may cause severe hyperkalaemia and fluid retention in patients receiving ACE-I

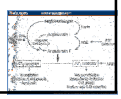


Angiotensin Receptor Blockers (ARBs)



ARBs - angiotensin receptor (AT-1) blockers
LOSARTAN, valsartan, olmesartan, candesartan

- Newer class of agents
- Orally active angiotensin II type 1 receptor antagonist
- Alternative for blocking renin-angiotensin system
- Improved tolerability – no bradykinin, no cough
- Some develop angioedema
- Acceptable alternative in patients who develop intolerable side effects from ACE-inhibitors
- Should not be used in combination with ACE-inhibitors



Aims of Heart Failure Management

<u>To achieve improvement in symptoms:</u>

- Diuretics [mainstay]
- ACE inhibitors [mainstay]
- Digoxin

<u>To achieve improvement in survival:</u>

- ACE inhibitors
- Beta blockers (carvedilol, bisoprolol)
- Oral nitrates + Hydralazine
- Spironolactone

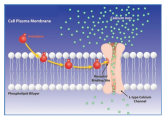
Oral nitrates and hydralazine (combined treatment)

- Survival benefit in symptomatic heart failure
- Modest improvement in exercise tolerability
- Survival rates higher with ACE-inhibitors
- Do not confer an additive effect to ACE-inhibitors

- Consider oral nitrates in patients with:
  - angina and impaired left ventricular systolic function
  - Severe renal impairment where ACE inhibitors contra-indicated

Other vasodilators

- Calcium channel blockers that exacerbate heart failure due to negative chronotropic and inotropic properties:
  - Diltiazem
  - Verapamil
- Newer CCBs safer in congestive heart failure and used to treat hypertension and angina:
  - Amlodipine
  - Felodipine



Aims of Heart Failure Management

To achieve improvement in symptoms:
- Diuretics [mainstay]
- ACE inhibitors [mainstay]
- Digoxin

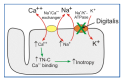
To achieve improvement in survival:
- ACE inhibitors
- Beta blockers (carvedilol, bisoprolol, metoprolol)
- Oral nitrates + Hydralazine
- Spironolactone

Digoxin indications

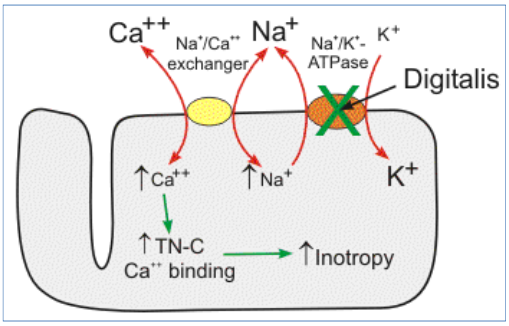
- Use of Digoxin varies across countries
- Potentially invaluable in patients with atrial fibrillation with co-existent heart failure
  - Improves control of ventricular rate and allows more effective filling of the left ventricle
- Chronic heart failure secondary to left ventricular systolic impairment who remain symptomatic despite diuretics and ACE-inhibitors
  - it acts as an inotrope.
- Severe left ventricular systolic dysfunction with cardiac dilatation
- Recurrent admissions for heart failure

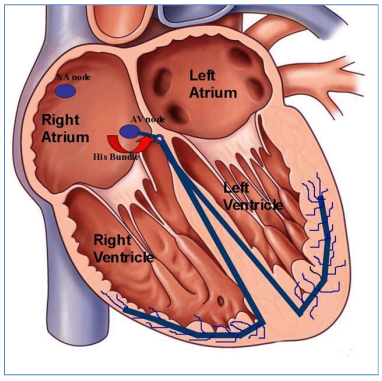
Digoxin mechanism of action

- Digoxin inhibits membrane Na^+/K^+ ATPase which actively extrudes Na^+ from myocardial (and other) cells
- Causes accumulation of intracellular Na^+
- Which indirectly increase intracellular Ca^{++} content:
  - Reduced Na^+/Ca^{++} exchange
  - Increased Ca^+ storage
- Positive inotropic effect
- Negative chronotropic effects from ventricular slowing
  - Increased vagal activity at AV node
- Leads to improved filling of ventricle during diastole
- Improved cardiac output



Digoxin mechanism of action

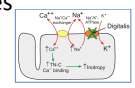




Digoxin pharmacokinetics

- Oral / iv administration
- Half life 1-2 days
- Small amt metabolised, and excreted in bile
- Majority is excreted unchanged in the urine
- Eliminated by glomerular filtration
- Small amt tubular secretion, reabsorption

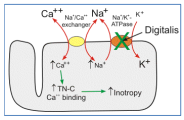
- Low therapeutic index
- Measure trough levels for toxicity studies



Digoxin toxicity hypokalaemia

- Adverse symptoms:
  - Nausea
  - Vomiting
  - Headache
  - Confusion
  - Visual symptoms

- Fatal Cardiac Arrhythmias:
  - AV junctional rhythms
  - Atrial tachycardia
  - AV block
  - Ventricular tachycardia



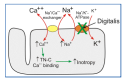
Digoxin drug interactions

Pharmacokinetic

- Reduced digoxin absorption: antacids, tetracyclines, cholestyramine
- Reduced renal elimination of digoxin: spironolactone, quinidine, verapamil, amiodarone

Pharmacodynamic:

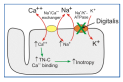
- Drugs causing hypokalaemia predispose to dig. tox
  - Diuretics
  - Beta agonists,
  - glucocorticoids
- Drugs causing hypomagnasaemia predispose to dig.tox
  - Diuretics
  - Alcohol
- Beta blockers: start slowly



Other inotropes

- Improve symptoms, but INCREASE MORTALITY:
  - Xamoterol: beta blocker
  - Dobutamine: dopamine, alpha and beta agonist
  - Milrinone: phosphodiesterase inhibitor

- Digoxin remains the only positive inotrope that is valuable in the management of cardiac failure



Anti-arrhythmic treatment

- Class I anti-arrhythmics in patients with atrial fibrillation and chronic heart failure increase the risk of mortality

- Address precipitating factors;
  - Electrolyte disturbances (K, Mg)
  - Digoxin toxicity
  - Drugs causing electrical instability (antidepressants)
  - Continued myocardial ischaemia

Anti-arrhythmics

Vaughn-Williams/Singh classification

Class I	Class II
• a. Quinidine • a. Procainamide • a. Disopyramide • b. Lidocaine • b. Mexiletine • c. Flecanide • c. Propafenone	• Atenolol Class III • Amiodarone • Sotalol • Dofetilide • Ibutilide Class IV • Verapamil • Diltiazem

Drug	MOA	Indications / Comments
Lidocaine	Blocks Na+ channels (prolongs refractory period)	Ventricular tachycardia; Ventricular fibrillation
B-blockers (Atenolol, Esmolol)	β-1 selective; Negative chronotrope / inotrope	Post MI; SVT (exercise / emotion); thyrotoxicosis
Amiodarone	Prolongs cardiac action potential (prolongs QT interval on ECG)	Supra- and ventricular dysrhythmias; many SE's
Sotalol	Prolongs cardiac action potential	Supra- and ventricular dysrhythmias;
Verapamil	Blocks L-Type voltage dependent Ca++ channels; negative inotrope	SVT
Adenosine	Adenosine 1 receptor	Used to terminate SVT
Atropine	Anti-muscarinic; positive inotrope	Sinus bradycardia
Adrenaline	α and β agonist	Cardiac arrest

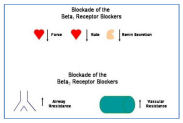
Aims of Heart Failure Management

To achieve improvement in symptoms:
- Diuretics [mainstay]
- ACE inhibitors [mainstay]
- Digoxin

To achieve improvement in survival:
- ACE inhibitors
- Beta blockers (carvedilol, bisoprolol, metoprolol)
- Oral nitrates + Hydralazine
- Spironolactone

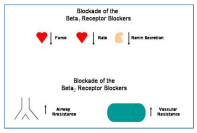
Beta blockers

- Traditionally avoided in heart failure due to negative inotropic effects
- However, sufficient evidence to support their use in patients with chronic stable heart failure resulting from left ventricular systolic dysfunction
- Combining beta blockers with ACE inhibitors and diuretics supplements the benefits and shows improvements in
  - Left ventricular function,
  - Symptoms,
  - Survival
  - And reduction in admissions to hospital



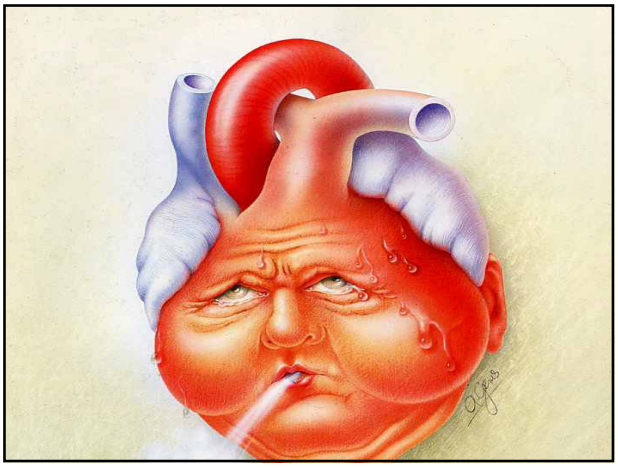
Beta blockers proven benefit in heart failure

- Carvedilol
- Bisoprolol
- Metoprolol



- Start low dose
- Slow increase under expert supervision
- Short term may show deterioration of symptoms, which may improve with alteration of the diuretics

Aims of Heart Failure Management

To achieve improvement in symptoms:
- Diuretics [mainstay]
- ACE inhibitors [mainstay]
- Digoxin

To achieve improvement in survival:
- ACE inhibitors
- Beta blockers (carvedilol, bisoprolol)
- Oral nitrates + Hydralazine
- Spironolactone