**Pharmacological Management:**

<table>
<thead>
<tr>
<th>&lt;55 years (young Caucasians are more likely to have high renin HTN)</th>
<th>&gt;55yo or black patients of any age (older patients and black patients usually have low renin HTN)</th>
<th>A: ACE inhibitor (or AT2 receptor antagonist if ACE intolerant)</th>
<th>C or D: calcium-channel blocker or thiazide-type diuretic</th>
<th>STEP 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+C or A+D</td>
<td>STEP 2</td>
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<tr>
<td>A+C+D</td>
<td>STEP 3</td>
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<tr>
<td>Add: Further diuretic therapy Or Alpha-blocker Or Beta-blocker</td>
<td>STEP 4</td>
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**Drug**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Adverse Effects</th>
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</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>&gt;55yo, black patients, stroke secondary prevention or &gt; 65yo, renal dysfunction or Primary hyper-aldosteronism</td>
<td>Gout, diabetes, hypokalaemia. Can increase serum cholesterol and impair glucose tolerance. Hypokalaemia</td>
</tr>
</tbody>
</table>

| Beta-adrenoceptor blockers | HTN + coronary heart disease e.g. post-MI or angina. Heart failure (bisoprolol and carvedilol) Not initial therapy, but can be useful in young people or in those with intolerance to ACE inhibitors | Bradycardia, bronchospasm, cold extremities, fatigue, bad dreams, hallucinations. CI in diabetes, peripheral vascular disease, asthma/COPD, heart block, unstable HF |

| ACE Inhibitors | <55yo, Caucasians, heart failure | Cls: renal failure, peripheral |

**Drug Indications**

- **Diuretics**
  - Bendroflumethiazide 2.5mg daily
  - Chlortalidone 25mg daily
  - Furosemide 40-80mg daily
  - Spironolactone 50-400mg daily

**Drug Indications**

- **Beta-adrenoceptor blockers**
  - Atenolol 25-100mg daily
  - Bisoprolol 1.25-20mg daily
  - Carvedilol 12.5-50mg daily

  Work by attenuating the effects of the SNS and renin-angio systems

- **ACE Inhibitors**
  - Enalapril 50-100mg daily

- **Labetalol 100-200mg BD (max 2.4g/day)**

- **HTN in pregnancy**
Lisinopril 2.5-40mg daily  
Perindopril 2.0-8.0mg daily  
Ramipril 1.25-10mg daily

Work by blocking the conversion of angiotensin 1 to angiotensin 2 (a potent vasoconstrictor). They also block degradation of bradykinin, a potent vasodilator.

<table>
<thead>
<tr>
<th>Angiotensin 2 receptor antagonists</th>
<th>ACE inhibitor intolerant.</th>
<th>Renal failure</th>
</tr>
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<tbody>
<tr>
<td>Losartan 50-100mg/day</td>
<td>&lt;55yo, Caucasian, HTN with LVH, HF, LV dysfunction, MI, diabetic nephropathy, chronic renal disease</td>
<td>Peripheral vascular disease</td>
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<tr>
<td>Candesartan 2.0-32mg/day</td>
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<td>Pregnancy</td>
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<tr>
<td>Valsartan 40-320mg/day</td>
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<tr>
<td>Olmesartan 10-40mg/day</td>
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<tr>
<td>Telmisartan 40mg/day</td>
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</table>

Share many of actions of ACE inhibitors, but do not have any effect on bradykinin, so do not produce the dry cough.

<table>
<thead>
<tr>
<th>Calcium-channel blockers</th>
<th>Useful in patients with ischaemic heart disease</th>
<th>SEs seen more so with the short acting agents: headaches, sweating, ankle oedema, palpitations, flushing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine 5.0-10mg/day</td>
<td>&gt;55yo, black patients, angina.</td>
<td>Bradycardia, heart block, heart failure, CI with beta-blockers</td>
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<tr>
<td>Nifedipine (long acting) 20-90mg/day</td>
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<tr>
<td>Diltiazem (long acting) 90-180mg/BD</td>
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<tr>
<td>Verapamil 120-240mg/BD</td>
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Cause arteriolar dilatation, some also reduce force of cardiac contraction.

<table>
<thead>
<tr>
<th>Alpha-adrenoceptor blockers</th>
<th>Benign prostatic hypertrophy</th>
<th>Posturoal hypotension, urinary incontinence, Profound hypotension</th>
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<tbody>
<tr>
<td>Doxazosin 1.0-16mg/day</td>
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<tr>
<td>Indoramin 25-100mg/BD</td>
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<tr>
<td>Phenoxybenzamine 1mg/kg IV over &gt;2h</td>
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Phaeochromocytoma crisis
• Initial infarct – expansion of the infarct (hours to days) – global remodelling (days to months)
  • E.g. remodelling in diastolic failure – heart becomes hypertrophied
  • E.g. remodelling in systolic failure – heart becomes dilated

Myocardial Gene Expression:
  • Haemodynamic overload of the ventricle stimulates changes in cardiac contractile protein gene expression – overall it increases protein synthesis, but many proteins also switch to fetal and neonatal isoforms.
  • Human myosin is composed of 2 heavy chains and 2 light chains
    o MHC come in alpha and beta forms – they have different contractile properties and different ATPase activity
    o Alpha, alpha-MHC predominates in the atria
    o Beta, beta-MHC in the ventricles
      ▪ In animal models, pressure overload results in a shift from alpha, alpha to beta, beta in the atria = results in reduced atrial contractility but reduced energy demands.
      ▪ This shift also occurs in the ventricle, but is less significant as beta-beta isoform already predominates.
    o Other genes affected: Na/K-ATPase, Ca-ATPase, beta1-adrenoceptors
  • Abnormal calcium homeostasis
    o In heart failure, there is prolongation of the calcium current = prolongs contraction and relaxation
  • Apoptosis
    o Associated with irreversible congestive heart failure
    o Demonstrated in animal models of ischaemic-reperfusion injury, rapid ventricular pacing, mechanical stretch and pressure overload
    o Though to result from cytokines, free radicals as well as other triggers.
  • Natriuretic peptides
    o Atrial natriuretic peptide (ANP)
      ▪ Released from atrial myocytes in response to stretch
      ▪ Induces: diuresis, natriuresis, vasodilatation, suppression of renin-angiotensin system (essentially tries to decrease pressure and stretch by off loading water and salt, while vasodilating the vessels)
        • Levels of ANP are increased in congestive HF
        • However, in HF the renal response to ANP is attenuated. This is likely secondary to:
          o Reduced renal perfusion
          o Receptor downregulation
          o Increased peptide breakdown
          o Renal sympathetic activation
          o Excessive renin-angiotensin activity
    o Brain natriuretic peptide (BNP) (named as it was first discovered in the brain)
      ▪ Predominantly secreted by the ventricles
      ▪ Has similar action to ANP
      ▪ Has greater diagnostic and prognostic value than ANP
    o C-type peptide
      ▪ Limited to vascular endothelium and CNS
      ▪ Has similar effects to ANP and BNP.
  • Endothelial function in heart failure
Investigating heart failure:

- **Bloods** – FBC, LFTs, Us&Es, cardiac enzymes in acute heart failure, BNP, thyroid function
- **CXR** – cardiomegaly, pulmonary congestion with upper lobe diversion, fluid in the fissures, Kerley B lines, oedema
- **ECG**
- **Echo** – chamber dimensions, systolic and diastolic function, wall motion, valvular disease, cardiomyopathies
- **Stress echo** – assess viability in a dysfunctional myocardium – dobutamine can identify contractile reserve in stunned or hibernating myocardium
- **Nuclear cardiology** – quantify ejection fraction, ischaemia, viability.
- **Cardiac MRI** – assess viability of myocardium
- **Cardiac catheterization** – diagnose ischaemic heart failure and suitability for revascularization, manage pulmonary artery pressure, left atrial wedge pressure, LV end-diastolic pressure
- **Cardiac biopsy** – cardiomyopathies
- **Cardiopulmonary exercise testing** – VO2 max is predictive of hospital admission and death in heart failure.
- **Ambulatory 24h ECG (Holter)** – in patients with suspect arrhythmias

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<th>Signs</th>
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<td>Exertional SOB</td>
<td>Cardiomegaly</td>
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<td>Orthopnoea</td>
<td>3rd and 4th heart sounds</td>
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<tr>
<td>Paroxysmal nocturnal</td>
<td>Elevated JVP</td>
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<tr>
<td>dyspnoea</td>
<td>Tachycardia</td>
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<tr>
<td>Fatigue</td>
<td>HTN</td>
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<td>Bi-basal crackles</td>
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<td>Pleural effusion</td>
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<td>Peripheral ankle oedema</td>
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**Symptoms**
- Exertional SOB
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Fatigue

**Signs**
- Cardiomegaly
- 3rd and 4th heart sounds
- Elevated JVP
- Tachycardia
- HTN
- Bi-basal crackles
- Pleural effusion
- Peripheral ankle oedema
- Ascites
- Tender hepatomegaly

**Treatment of Heart Failure:**

**Lifestyle advice**
- Education – counselling, weight management
- Obesity control
- Dietary modification – salt restriction, weight reduction if needed, in severe HF fluid restriction is necessary. Alcohol has negative inotropic effect, moderate consumption.
  - Omega-3 polyunsaturated fatty acids reduce mortality and admission to hospital.
- Smoking cessation
- Physical activity/training/rehab – for exacerbations, bed rest can be useful for a few days as it reduces the demands on the heart. Low level endurance exercise e.g. 20-30 min walking three to five times per week, can help reverse ‘deconditioning’ of peripheral muscle metabolism. Avoid strenuous isometric activity.
- Sexual activity – patients on nitrate should not take phosphodiesterase type-5 inhibitors (e.g. sildenafil) as it can induce profound hypotension.