TREATMENT OF CARDIOVASCULAR DISEASES
The need to reduce risk factors is common to all stages of treatment of CHD. For every individual, there is a need to act against the causative factors of CHD. Thus, attempts should be made to control hypertension, heart failure, arrhythmias, hyperlipidemia, obesity, diabetes mellitus, thyroid disease, anemia and cardiac valve disorders. Apart from medications, these will require careful attention to ① DIET and ② EXERCISE and will necessitate ③ STOPPING SMOKING.

Antithrombotics, most commonly with aspirin, is of proven benefit in patients with angina or MI. Gastrointestinal hemorrhage, stroke and poor compliance tend to offset any reduction in CHD. Postmenopausal estrogen replacement therapy is of benefit in preventing coronary events in women without known coronary artery disease. Replacement therapy is known to promote arterial vasodilatation by several mechanisms and have beneficial effects on serum lipid profiles. Use of HRT as secondary prevention CANNOT be recommended at present (used only for primary prevention).

TREATMENT OF STABLE ANGINA

ABCD:


Changing lifestyle to ↓ the demand on the heart and slow disease progression is of utmost importance. Drug treatment is directed towards ↓ the workload of the heart & to a lesser extent improving the coronary blood supply, this should provide symptomatic relief and improve prognosis. Unless otherwise contraindicated, β-blockers are first-line agents for angina. Nitrates, calcium channel blockers, or both, may be added. Verapamil should be AVOIDED with β-blockers or can be indicated as an alternative for β-blockers. Treatment of acute attacks is by small doses of sublingual nitrates, which may be used prior to an activity that would be expected to cause an attack.

Aspirin

Aspirin as a prophylaxis of infarction at 75-300 mg/day, is of proven benefit in all forms of CHD.

CONT. CORONARY HEART DISEASE
MODIFICATIONS OF RISK FACTORS
They are useful for preventing angina in exercise because they:

1. Decrease the rise in blood pressure.
2. Reduce the resting heart rate.
3. Decrease the force of ejection in systole.

The decreased heart rate not only reduces the energy demand but also permits better perfusion of the subendocardium by the coronary circulation.

A β-blocker may also reduce energy demanding supraventricular or atrial arrhythmias (antiarrhythmics).

While β-blockers are widely used, their tendency to cause bronchospasm and peripheral vascular spasm makes them CONTRAINDICATED in asthma, COPD and peripheral vascular disease as well as in acute heart failure and bradycardia.

They are used with caution in insulin-dependent diabetics, where the signs of hypoglycaemic attack may be masked, and in patients with a history of heart block.

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CARDIOSELECTIVE agents (e.g. atenolol, metoprolol, bisoprolol) are preferred because of their reduced tendency to cause bronchoconstriction.

Agents with low lipophilicity (e.g. atenolol) penetrate the CNS to a lesser extent than others (e.g. propranolol) and don't cause the CNS SEs (nightmares, hallucinations & depression) that are sometimes found with lipophilic agents.

CNS-mediated fatigue or lethargy is found in some patients with all β-blockers although it must be distinguished from that of myocardial suppression.

β-blockers shouldn't be stopped abruptly for fear of precipitating angina through rebound receptor hypersensitivity.

All β-blockers tend to reduce renal blood flow, but this is only important in renal impairment.

Nitrates

Nitrates are valuable in angina because they:

1. Dilate veins (decreasing preload).
2. Dilate arteries to a much lesser extent (decreasing afterload).

The production of nitric oxide from nitrates is mediated by intracellular thiols.

TOLERANCE is one of the main limitations to the use of nitrates, which remain the most useful class of agents in all forms of angina.

While it was formerly thought that it was important to have high blood levels of nitrate at all times, it is now recognized that tolerance develops rapidly, and a NITRATE FREE PERIOD of a few hours in each 24-hour period is beneficial in maintaining the effectiveness.

Nitrates should coincide with the period of lowest risk, and this is usually night time, but not early morning, which is a high risk period for infarction.

Patients receiving short-acting nitrates 2-3 times/day would do well to have their doses between 7 a.m. and 6 p.m.

All nitrates may induce tachycardia.

3 main nitrates are used: glyceryl trinitrate [GTN] (sublingual, buccal, transdermal and IV), isosorbide dinitrate [ISDN] and isosorbide mononitrate [ISMN].

All are effective if given in appropriate doses at suitable dose intervals.

Drug interactions: Heparin, Sildenafil.
Nitrates Preparations:

- Include intravenous infusions, conventional or slow release tablets and capsules, transdermal patches and ointments, sublingual tablets and sprays and adhesive buccal tablets.
- Stable angina patients should be controlled by CONVENTIONAL TABLETS/CAPSULES.

<table>
<thead>
<tr>
<th>PREPARATION</th>
<th>✔ advantages</th>
<th>✗ disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONVENTIONAL TABLETS/CAPSULES</td>
<td>1 cheap, 2 can be administered 2-3 times daily (which permit a nitrate free period at night),</td>
<td>-</td>
</tr>
<tr>
<td>SLOW RELEASE PREPARATIONS &amp; TRANSDERMAL PATCHES</td>
<td>-</td>
<td>1 expensive, 2 do not offer flexible dosing rates (may not permit a nitrate free period).</td>
</tr>
<tr>
<td>OINTMENTS</td>
<td>-</td>
<td>messy</td>
</tr>
<tr>
<td>BUCCAL TABLETS</td>
<td>Like sublingual sprays and tablets: 1 rapid onset of action and 2 bypasses the liver, which has an extensive first-pass effect on oral nitrates, 1 expensive and 2 offer no real therapeutic advantage in regular therapy.</td>
<td>-</td>
</tr>
</tbody>
</table>

- There is **NO advantage** in using more than one preparation.
- The sublingual preparations (sprays, suckable or chewable tablets) are used for the prevention or relief of acute attacks but may elicit the two principal side-effects of nitrates, hypotension (with dizziness & fainting) and a throbbing headache.
- To minimize these effects, patients should be advised to sit down, and to spit out (or swallow) the tablet once the angina is relieved.
- **Sublingual GTN** tablets have a very short shelf life on exposure to air and should be stored carefully and replaced frequently.

NicoRandal

Exhibits the properties of a nitrate but which also activates ATP-dependent potassium channels.

Calcium Channel blockers

- CCBs act on a variety of smooth muscle and cardiac tissues and there are a large number of agents; which have differing specificities for different body tissues.
- Those of importance in angina are arterial vasodilators, but some also possess antiarrhythmic activity, and most are myodepressants.
- Nifedipine and nicardipine (and other DHPs) have no effect on the conducting tissues and are very effective ARTERIAL DILATORS, decreasing afterload and improving coronary perfusion but causing flushing, headaches and reflex tachycardia.
- The tachycardia is overcome by use of a β-blocker.
- They have a particular role in the management of Prinzmetal’s (variant) angina, which is thought to be due to coronary artery spasm.
- CAUTION should be exercised in considering their use with *β*-blockers because of the additive effects on bradycardia and myodepression.
- Verapamil is suitable for patients in whom *β*-blockers are contraindicated due to respiratory or peripheral vascular disease; the most important non-cardiovascular side-effect is marked constipation.

**Ivabradine:**
- Acts by blocking If current. This regulates the pace maker activity in SA node & controls HR.
- Used in patients whom *β*-blockers are contraindicated.
- Their side effects include dose dependent transient visual symptoms.

**Ranolazine:**
- A selective inhibitor of late sodium influx.
- It increases exercise tolerance, reduces angina episodes & reduce the use of GTN.
- Safe addition in advanced multi-drug treatment for uncontrolled patients.
- Side effects include dizziness, nausea, constipation & prolongation of QT interval.

**ACS**

**UA**
- Stenosed artery by thrombus → ischemic symptoms without myocardial damage.
- Troponin-ve.

**NON-STEMI**
- Brief block, or vessel remain open but thrombus shed → tiny areas of infarction.
- Troponin+ve.

**STEMI**
- The most severe.
- Complete block of the vessels.
- Troponin +ve.

**TREATMENT OF UNSTABLE ANGINA AND NSTEMI**

- Should be treated in HOSPITAL with complete bed rest and vigorous management.
- The death or infarction rate at 1 month is 15-20% in some series and about 8% in unstable angina alone.
- Several agents are given SIMULTANEOUSLY, rather than by stepwise addition, including oxygen, nitrate infusions and possibly a sedative, such as diazepam.
- A 2-5 day course of either UFH or LMWH confers additional benefit over aspirin in UA.
- There is little evidence to support the subsequent use of oral warfarin because of the risk of bleeding.
- THROMBOLYSIS with, for example, alteplase decreases mortality.
- The antiplatelet agents ticlopidine or clopidogrel are expensive but effective alternatives to aspirin and clopidogrel showed a small advantage over aspirin in one study “first line” aspirin followed by clopidogrel.
- A greater adv. was observed in the CURE study when clopidogrel was given with aspirin for 3-12 months.
- LMWH have the advantage over UFH of greater predictability of effect, reduced monitoring, and possibly enhanced survival.
- Coronary ANGIOGRAPHY or ANGIOPLASTY may be performed once the acute episode has settled or when medical management has failed.
Treatment of infarction may be divided into three categories:

1. **Immediate care**: that is designed to remove pain, prevent deterioration and improve cardiac function.
2. **Management of complications**: notably heart failure and arrhythmias.
3. **Prevention of a further infarction or death (secondary prevention)**.

The management of HF and arrhythmias are covered in other sections. The remaining therapeutic aims are pain relief, thrombolysis, ↓ of infarct size, prophylaxis of arrhythmias & 2ry prevention.

The **TIMING** of treatment is **vital**, since myocardial damage after onset of acute ischemic episode is **progressive** and there are data to suggest that it is **irreversible at 6 hours**.

Clinical data from large studies of thrombolysis have shown that the **sooner treatment is started** after the onset of pain, the **better**, although there is still some benefit **up to 12 hours** after infarction.

60% of **post-infarction deaths occur within 1 hour**, but while treatment within 1 hour has been found to be advantageous it’s **extremely difficult to achieve** for logistic reasons in anyone who has an infarct outside hospital.

**Pain relief** should be administered rapidly with **intravenous diamorphine** or morphine together with an antiemetic such as prochlorperazine or cyclizine, and **oxygen**.

The rhythm and **blood pressure** should be stabilized and **diagnostic tests** performed.

Several studies have shown the benefit of an **aspirin tablet** (usually 162 mg) chewed **as soon after the infarct** as possible and followed by a **daily enteric-coated dose** for at least **1 month**.

Follow-up of those studies shows **additional benefit in continuing to take daily aspirin**, probably **for life**.

**Enteric-coated preparations are not proven to reduce the risk of GIT bleeding** which is increased in patients taking even small doses of aspirin.

Doses tend to be in the range **75-150 mg daily** after an **initial 300 mg**.

The reduction in mortality with aspirin is additional to that obtained from thrombolytic therapy.

**Thrombolysis**

There is a great benefit from thrombolitics **given soon after the onset of pain**.

There is a **lack of difference** between **streptokinase** (fibrin non specific) and the more expensive **tissue plasminogen activator** (rt-PA, duteplase, alteplase) and **anistreplase** (anisoylated plasminogen streptokinase activated complex, APSAC, now discontinued) **in reducing mortality**.

The patency studies suggest that **tissue plasminogen activator produces earlier and more frequent arteries recanalization**, especially if **intravenous heparin** is administered.

**Heparin ↓ incidence of re-occlusion** after tissue plasminogen activator but has no effect on **streptokinase**.

Further benefit is obtained if **trained and appropriately equipped paramedics** or general practitioners administer thrombolytics **before the patient goes to hospital**, especially if the journey time is great.
• Tenecteplase &reteplase has been marketed more recently with the advantage that it can be administered by bolus injection.
• All agents cause HAEMORRHAGE, which may present as a stroke or a GIT bleed, and there is an increased risk with regimens that use intravenous heparin.
• Hirudin has greater specificity for thrombus but the increased risk of bleeding counteracts the benefits of increased vessel patency.
• Recent strokes, bleeds, pregnancy and surgery are CONTRAINDICATIONS to thrombolysis.
• Old age is no longer considered to be a contraindication to thrombolysis.
• Streptokinase induces cross-reacting antibodies that ↓ its potency & may cause an anaphylactoid response.
• Patients with exposure to streptokinase, or with a history of rheumatic fever or recent streptococcal infection, should NOT receive the drug.
• The use of hydrocortisone, to reduce allergic response, has fallen out of favor, and patients should be carefully observed for hypotension during the streptokinase administration.
• The use of glycoprotein IIb-Ilia inhibitors (e.g., abciximab) as an adjunct to thrombolytics results in increased early blood flow in blocked coronary arteries, which may translate into increased survival, but also increases the incidence of major bleeding.

ACE Inhibitors

• ACEIs have been tried in various doses & durations → proved beneficial in ↓ the incidence of HF & mortality.
• Current practice would be to give all patients an ACEI for 4-6 weeks and then assess patients, continue treatment in patients with signs or symptoms of HF or LVD.
• CONTRAINDICATIONS include hypotension or intractable cough.
• Angiotensin II blockade alone (ARBS) maybe suitable for patients who cannot tolerate an ACEI but does not cause the accumulation of bradykinins that may be part of the benefit of ACEIs.

ACEI + Aspirin + Statins + β-blocker

Lipid lowering agents

• Decreasing cholesterol intake and using lipid lowering agents reduces morbidity in patients with established CAD. The goal is to ensure LDL-C < 2 mmol/L & total cholesterol < 4 mmol/L

Insulin

• Patients with MIs have high serum and urinary glucose levels, described as a stress response, while diabetics are known to do poorly after infarction.
• Further work is required on defining the criteria for treatment, especially in patients who have a glucose stress response but no known diabetic history, since the presence of a stress response in a broader group of intensive care patients is associated with poor outcome, which improves, by intensive insulin therapy.
• Current guidelines DON’T support use of insulin in NON-DIABETIC STEMI patients.
• For diabetics, it’s reasonable to control blood glucose levels within the normal range immediately post-infarct.

Antidepressants and rehabilitation

• A quarter of patients with infarctions experience marked depression and this is associated with poor medication compliance, a lower quality-of-life score, and quadrupled mortality.
• Antidepressants have not been subjected to formal trials but it seems reasonable to try to prevent such a risk. SSRI are preferred since they are less prone to cause arrhythmia.
• Rehabilitation programs, which include social interaction and education, are of proven benefit.
Patient Care

- All patients need **counseling** on preventive measures including **diet**, **smoking** and **exercise**.
- **Prophylactic medication** is important and for most patients will include **aspirin** and **statins**.
- **Doses of some statins** need to be **titrated against effect**.
- Patients need advice on how to **reduce the risk of GI bleeding** by **taking aspirin with food** and **dissolved in water** when the soluble preparation is prescribed.
- Patients should be encouraged to adopt a **lifestyle** that makes the most of their abilities without undue **hazard to their health**.
- A **diary of anginal attacks** is very useful as a **record of progress** and may be used to adjust treatment.
- The use of **sublingual GTN** should be recorded as well as details of the activities or circumstances that provoke angina.
- Patients should **avoid OTC preparations containing sympathomimetic drugs** (e.g. cold cures) but occasional aspirin for analgesia does not affect the anti-platelet action of low dose aspirin.
- Many patients will find the lifestyle changes **burdensome** or contrary to their wishes and it is **essential they have support from their doctors of pharmacists**. This is particularly when drugs are prescribed that may further diminish QOL:
  - **Nitrates** may cause **headaches** and **hypotensive** episodes and **β-blockers** can be associated with **bad dreams**, **difficulty sleeping**, **cold extremities**, **fatigue**, etc.