# Ischaemic heart disease

## Angina

= clinical syndrome characterised by central chest tightness radiating to the arms and neck, due to myocardial ischaemia

Angina may be
- Stable
  - Infrequent
  - Predictable exercise threshold (other precipitants = emotion, cold weather, heavy meals)
  - Relieved by GTN
- Unstable (part of ACS spectrum)
  - New onset (≥ CCS[1] class III)
  - At rest
  - Increasing: more frequent (esp. crescendo), longer, lower threshold (change by ≥ 1 CCS class to ≥ CCS class III)
- Vasospastic/Prinzmetal's (rare)
  - Due to coronary artery vasospasm
  - Unpredictable in pattern of onset
  - Atypical drug response – CCBs often best
- Decubitus (rare)
  - Due to ↓LVEDP, or associated with cold sheets, dreaming, or coronary spasm during REM sleep

Myocardial oxygen requirements are determined by
- Preload venous return – remember Starling's Law
- Heart rate
- Afterload aortic impedance

Angina can thus be relieved and prevented by:
- Reducing myocardial $O_2$ demand
  - Reduce preload
  - Control heart rate
  - Reduce afterload
- Improving myocardial $O_2$ supply
  - Dilate coronary arteries

Also consider Rx under the headings
- Anti-thrombotics: aspirin, enoxaparin, GP IIb/IIIa antagonists
- Anti-ischaemics: nitrates, β-blockers, CCBs, nicorandil

## ACS

Comprises unstable angina, NSTEMI/NQWMI and STEMI/QWMI

## β-blockers

[1] Canadian Cardiovascular Society
- Grade I: only on strenuous or prolonged exertion
- Grade II: on two flights of stairs
- Grade III: on walking one block on the level (requires intervention)
- Grade IV: at rest (requires urgent intervention)

### *Mechanism*

In heart, $\beta_1$ predominates (sympathetic nerve endings), also some $\beta_2$ (circulating CAs) – thus β-blockers are

- -vely chronotropic
- -vely inotropic

- ↓afterload
- Probably ↓preload by reducing plasma volume through unknown mechanism

### *Cardioselectivity*

Both coronary and peripheral arteries have $\beta_2$ receptors that mediate dilatation and this forms the rationale for using 'cardioselective' $\beta_1$ blockers in IHD and HT.
But: this does not appear to be significant in practice, in that cardioselective agents are no better at reducing blood pressure and no better at preventing angina – why is this?
Even highly $\beta_1$ selective agents (bisoprolol, atenolol) are CI in patients with asthma.

## Calcium channel blockers

### *Mechanism*

- ↓afterload

- Dilatation of coronary arteries
- ↓inotropic
- ↓chronotropic (non-DHPs)

CCBs are the drugs of choice for coronary artery vasospasm where β-blockers are CI (esp. non-selective agents).

## Nitrates

### *Preparations*

**GTN**

- 100% first-pass metabolism – cannot give orally
- $t_{1/2}$ = 2min; rapidly converted to di- and mononitrates

*Routes*

- Spray – short shelf life, but cheap
- Buccal/sublingual tablets – slow dissolution over 2h, akin to IVI
- Patches – convenient/inconvenient, might forget to remove at night, CI in diathermy

**ISMN**

- Longer $t_{1/2}$

*Routes*

- Oral

### *Mechanism*

Act by generating nitric oxide (EDRF)
→ reduce preload by venodilatation
→ dilate coronary arteries

### *Contraindications*

- HOCM
- AS
- Constrictive pericarditis
- Closed-angle glaucoma

### *Adverse effects*

- Thumping headache (tolerates out in about 3 days)
- Flushing
- Postural hypotension

- Requires drug-free period to prevent tachyphylaxis
    - 6h/24h, best at night when resting anyway
    - E.g. Imdur 60mg od and worn off by bed time

- No proven effect on survival (GISSI-3, ISIS-4), but no research impetus either

## Nicorandil

Most recently introduced agent; used as 3rd line instead of nitrate or as 4th line add on.

### *Mechanism*

- Potassium channel activator (arterial dilatation)
- Also has hybrid nitrate activity (mostly venous dilatation)
- May have antiarrhythmic action

**IONA trial**

- Significant reduction in incidence of major coronary events and all cardiovascular events
- In view of almost universal concomitant nitrate use, these benefits are likely to be conferred by nicorandil's unique potassium channel opening and preconditioning properties

### *Adverse effects*

- Headaches (less likely to tolerate out than with nitrates)
- Flushing
- Postural hypotension

## PTCA

### *Indications*

Emergency

- Failed medical Rx, incl. failed thrombolysis (STE not decreased by >50% at 90min post thrombolysis)

Elective

- Not suitable for CABG/previous CABG
- Stenosis of ≤2 vessels

### *Complications*

- Emergency CABG (<3%)
- MI (<2%)
- Death (<0.5%)

- Restenosis (20-30% within 6m, lower with stenting ± brachytherapy)

## CABG

IMA grafts markedly superior to SV ones (long-term patency and amenability to PTCA)

### *Indications*

- Disease
    - Vessels: 3, 2 with severely affected proximal LAD, left main stem
    - Lesions: multiple severe stenoses, distal vessel disease
- Failed PTCA

**CABG vs. PTCA**

- Better Sx control and less further interventions
- Longer recovery time and inpatient stay

## Treatment of stable angina

Aim: relieve symptoms, prevent progression

**General principles**
Full Hx+Ex
- Assess symptoms
- Assess risk factors
- DH of e.g. α-blockers, TCAs

Ix
- Bloods
  - FBC – anaemia?
  - UE – RF?
  - TFT – hyper/hypo?
  - Glu, lipids
- ECG – arrhythmia, ischaemia
- Consider ETT
- Consider angio

Rx
- Treat other contributing causes, e.g. anaemia, arrhythmia
- GTN
- Aspirin 75mg
- Statin and risk factor modification

Aim to prevent or reduce frequency of attacks to a minimum on prophylactic drug therapy; GTN as 'rescue' for 'breakthrough' angina
- Add β-blocker
- Add Ca-channel blocker (DHP; can use NDHP if β-blocker CI)
- Consider nicorandil
- Consider invasive Ix (angio) + Rx (PTCA, CABG)

Indications for referral
- Diagnostic uncertainty
- New angina of sudden onset
- Angina uncontrolled by drugs
- Recurrent angina after PTCA/CABG

## Treatment of NSTE ACS

### *Treatment*
- Constant ECG monitoring for rhythm/ischaemia/infarction
- Bed rest
- MONA incl. IV nitrates + enoxaparin 1mg/kg bd
  - If IV nitrates required for >3d, switch to IV ISDN (Isoket 0.05% 25mg/50ml, 4-20ml/h)

**Addenbrooke's high risk criteria (need 3/5; approximate to ESC high risk criteria)**
- Patient history (age, DM, previous MI/PTCA/CABG)
- Recurrent ischaemia (symptoms)
- Dynamic ΔST
- ↑trop
- Impaired LV function (clinical or echo), major arrhythmia (VT/VF)

Stratify
- If high risk: consider GP IIb/IIIa antagonist (e.g. tirofiban) and in-patient cardiology referral for potential angio ± PTCA/CABG
  - 400ng/kg/min for 30min 'bolus', followed by 100ng/kg/min for a maximum of 108h
  - CIs are similar to those for thrombolysis
  - Monitor Hb and platelets before, after 6h, then daily

- If low risk: await 2nd trop, treat as high risk if elevated

Symptoms settling and low risk:
- ↑oral Rx, wean off GTN infusion when stable on oral Rx
- Stop heparin when pain-free for 24h
- Gradual mobilization
- 1/52 GP review
- Out-patient ETT and cardiology review

## Treatment of STE ACS

Treatment as for NSTE ACS, plus thrombolysis

### *Thrombolysis*

Aim for door-to-needle time of 30min
Boosts recanalisation rate from 15% to 70%

**Indications**
- Typical pain at rest within 12 hours of presentation at any age
- 12-24 hours if pain continues
- Must have
  - ≥1mm STE in ≥2 chest leads
  - ≥2mm STE in ≥2 limb leads
  - New LBBB
  - True post. MI

**Agents**
- Streptokinase
  - 1.5 million U/100ml 0.9% NaCl over 60min
  - First choice
  - Little clot selectivity – little binding to fibrin, has similar affinity for free or bound plasminogen
- tPA
  - 10U twice, separated by 30min (supported by RAPID 1)
  - Indicated if
    - Patient under 75 years with anterior MI and within 6h of onset of chest pain
    - SK more than 5 days or under 1 year
    - Previous anaphylaxis to SK
    - Recent streptococcal infection
    - Cardiogenic shock (SBP<80mmHg with clinical features of low CO – discuss with cardiology SpR)
    - Low risk intracerebral bleed
  - Clot selectivity
    - Binds to fibrin
    - Activates plasminogen bound to fibrin >100-fold faster than circulating plasminogen
    - Levels of tPA during thrombolysis are 30-300x > physiological levels – hence some loss of clot selectivity
  - INJECT trial: at least as effective as streptokinase
  - GUSTO trial: better than streptokinase but effect small (14 vs. 10% ↓ in 30-day mortality)
  - Disadvantages
    - Short-acting, also need 24h IV heparin (5000U bolus followed by infusion 18U/kg/h to maintain APTT ratio 1.5-2.5; APTT ratio at 6h and then daily)
    - Higher risk of intracerebral bleed
    - 5-10 fold more expensive than SK

**Contraindications to thrombolysis**
- Bleeding tendency
  - General
    - Congenital
    - Acquired (INR>2.5)
  - Local
    - STREPT

        - Vasoocclusive CVA <6m, any haemorrhagic CVA
        - Intracranial SOL
        - Pericarditis
- HT >180/110mmHg
- Risk of embolism
    - IE
    - Aortic dissection
    - AAA

**Information given to patients before thrombolysis**
Must discuss risks and benefits with patient, and document this.

- They are having a heart attack, but effective treatment is available
- The heart attack is due to blockage of an artery in the heart by clot, and thrombolysis can usually dissolve that clot
- The most important side-effect is bleeding severe enough to require transfusion (0.3%)
- The increased risk of haemorrhagic stroke is more than offset by the reduced risk of ischaemic stroke (overall risk of stroke with streptokinase and aspirin is 0.6%)

Overall the benefits far outweigh the risks.

**Adverse effects**

- Haemorrhage (more likely with tPA): stop, consider FFP/cryoprecipitate
- CVA: stop, CT
- Reperfusion arrhythmias (more likely with streptokinase): stop, Rx arrhythmia as usual, restart
- Hypotension (more likely with streptokinase): stop until BP recovers, restart slowly; if persistent treat conventionally but try to restart
- Rigors: stop, recommence slowly
- Allergic reaction: stop, Rx as usual, restart if possible

**Other indications for thrombolysis**

- Arterial thrombosis, both peripheral and massive PE (in latter, no evidence to support central over peripheral thrombolysis)
- Vasoocclusive CVA (under trial)

### *β-blockade*

**Indications** as for thrombolysis

- Atenolol 50mg PO after 15min, followed by further 50mg after 12h
- If unable to take PO: atenolol 5-10mg by slow IV injection after 1h

**Contraindications**

- HR<50
- SBP<100
- Usual β-blocker CIs

### *Consider PTCA*

- QMC criteria: persistent symptoms and STE 90min after commencing thrombolysis
- 80% suitable
- 3% occlude acutely, 30% restenose within 3m
- Stenting: esp. in dissection flaps, diabetics, saphenous vein grafts

## Secondary prophylaxis

As under stable angina; always give β-blocker or CCB

Consider ACE-I on day 2
Indications

- Anterior QWMI
- Heart failure
- Impaired LV function on echo (LVEF<40% on MUGA - SAVE study)

Also

- 48h bed rest
- Daily Ex
- DVT/PE prophylaxis; consider warfarinisation in large anterior MIs (risk of mural thrombus)
- ETT
    - Inpatient if thrombolysed but no significant ↑trop
    - Outpatient otherwise unless CI
- Cardiac rehabilitation
    - 1m off driving and sex
    - 2m off work
- Review at 5w for Sx

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## Inotropes

### *Dobutamine*

- $\beta_1 > \beta_2$; less $\alpha$ activity than dopamine; no renal vasodilator effect
- At higher doses $\beta_2$ action predominates causing hypotension

- First line in cardiogenic shock: 5-20μg/kg/min

- Renal clearance
- Adverse effects: tachyarrhythmias, hypokalaemia

### *Dopamine*

- Natural precursor of NorAdr

- <5μg/kg/min: 'renal dose', acts on $D_1$ and $D_2$ receptors, ↑renal/splanchnic/cerebral/coronary blood flow, not necessarily ↑UO, controversial as no impact on outcome in ARF, may cause arrhythmias and GI ischaemia
- 5-20μg/kg/min: $\alpha + \beta_1$ stimulation
- >20μg/kg/min: increasing $\alpha$ stimulation – starts to resemble NorAdr (increase in afterload – probably undesirable)

- Renal clearance
- Adverse effects: tachyarrhythmias, hypokalaemia

### *Adrenaline*

- Second line in cardiogenic shock (more potent than dobutamine): 0.1-1μg/kg/min
- Bradycardia unresponsive to atropine: 2-10μg/min

- Predominant β-agonist at low dose, α-agonism at high dose

### *Noradrenaline*

- Vasodilatory shock in the absence of hypovolaemia
- Alternative to epinephrine for cardiogenic shock
- Start at 0.1μg/kg/min

- Risk of excessive vasoconstriction and organ hypoperfusion/↑afterload

### *Isoprenaline*

- Reduces peripheral resistance, diverting blood away from vital organs, e.g. kidneys
- Limited value

| | $\beta_1$ | $\beta_2$ | $\alpha_1$ | $\alpha_2$ | $D_1$ | $D_2$ |
|---|---|---|---|---|---|---|
| Adr | | | | | | |
| Low dose | ++ | + | + | ± | - | - |
| Moderate dose | ++ | + | ++ | + | - | - |
| High dose | ++ | +(+) | ++++ | +++ | - | - |
| NorAdr | ++ | - | +++ | +++ | - | - |
| Isoprenaline | +++ | +++ | - | - | - | - |
| Dopamine | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Low dose | ± | - | ± | + | ++ | + |
| Moderate dose | ++ | + | ++ | + | ++(+) | + |
| High dose | +++ | ++ | +++ | + | ++(+) | + |
| Dobutamine | ++ | + | ± | ? | - | - |