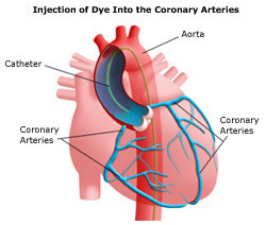
Ischaemic Heart Disease (IHD)

Dr K Outhoff

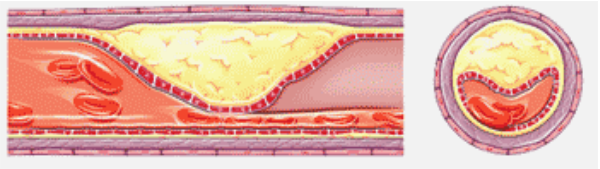


Angina
- Nitrates (s/l or oral)
- Aspirin
- Beta blockers

Unstable angina
- Nitrates (iv)
- Aspirin
- Beta blockers
- Heparin

M.I
- Nitrates (iv) + opioids
- Aspirin
- Beta blockers
- Heparin
- Streptokinase
- +/- ACE- inhibitors

I. Stable angina
Atheroma formation



Pathophysiology of stable angina: Atheromatous obstruction

- Atheroma in one / more coronary arteries
- When plaque exceeds critical value (>50% diameter), myocardial O_2 demand during exertion exceeds supply by stenosed vessel
  - Chest pain on exertion
  - Relieved by rest

Rx of IHD prolongs life

- <u>Directed at</u>

1. Atheroma
2. Haemodynamics (spasm)
3. Thrombosis (platelets)

Management of stable angina

1. Modifiable risk factors
2. Pain relief
3. Prophylaxis
4. Consideration of surgery / angioplasty

Angina
- Nitrates (s/l or oral)
- Aspirin
- Beta blockers

Mx Stable angina
1. Modifiable risk factors and relative risk of morbidity / mortality

- 50%: smoking cessation
- 15-25%: reducing BP in hypertension
- 30-50%: reducing cholesterol with diet and statins (atheroma)
- 50%: regular physical activity
- 25%: anti-platelet therapy with medium dose aspirin (thrombus)
- (20-30%: beta blockers or ACE-I post MI)

Mx of Stable angina
2. Pain relief

- Short acting nitrate:
  - Glyceryltrinitrate (GTN)

Mx of Stable Angina
3. Prophylaxis

Acute prophylaxis:

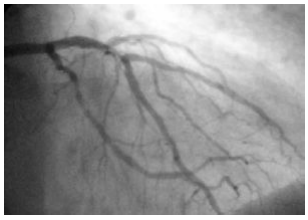
1. **GTN** immediately prior to undertaking pain inducing activity

Long term prophylaxis: (3 drugs)

1. Antithrombotic Rx: **Aspirin**
2. Long acting nitrates: **isosorbide mononitrate (ISM)**
3. Nicorandil if ISM intolerant (K channel opener)
4. **Beta blockers** or
5. Ca- channel blockers if above contra-indicated

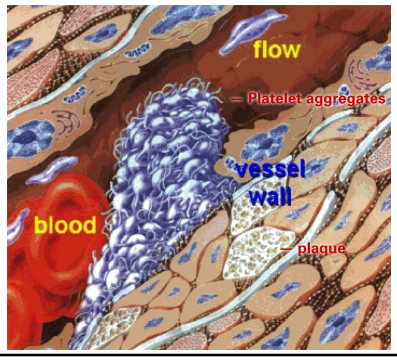
Mx of Stable Angina
4. Consideration of surgery / angioplasty

1. CABG
2. Angioplasty +/- antiplatelet drugs:
   - Ticlopidine
   - Clopidogrel
   - Tirofiban



- L. Main coronary artery
- Severe triple disease

Unstable Angina and MI: thrombus formation



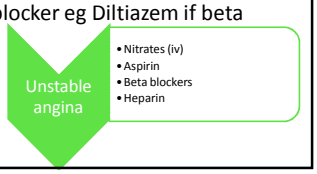
Pathophysiology Unstable Angina (mechanical obstruction)

- Prelude to MI: thrombus formation following disruption of plaque:

i. Fissuring of atheromatous plaque in coronary vessel
ii. Platelets adhere to underlying subendothelium
iii. White thrombus aggregates and extends into lumen
   i. Platelet
   ii. Fibrinogen
   iii. Fibrin aggregates

Management of unstable angina

1. Stop acute pro-thrombotic effects of smoking
2. URGENT (halves likelihood of MI):
   1. Antiplatelet (**Aspirin)**
   2. **Nitroglycerin iv**
   3. Antithrombotic Rx **(Heparin iv**)
3. **Beta blocker**
4. Long acting Ca channel blocker eg Diltiazem if beta blocker contra-indicated
5. Emergency angiography
6. Surgery



Pathophysiology of MI (mechanical obstruction +/- spasm)

- MI results when thrombus occludes the coronary vessel
- Spasm

a. **Vasoconstrictors** released from
   a. formed elements of blood (platelets, RBCs) and
   b. Nerve terminals:
      i. Pro-aggregatory
         5HT
         Thromboxane A2
      ii. Various neuropeptides
      iii. Endothelium derived peptides
         Angiotensin II
         Endothelin

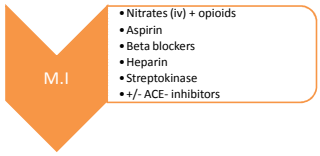
b. Relative **deficiency of endothelium derived vasodilators**
   i. Anti-aggregatory
      NO (nitrous oxide)
      prostacyclin

Myocardial Infarction Acute Management

1. O_2: [highest]
2. Pain relief
   1. Sublingual nitroglycerin (0.4mg - rpt every 5 min)
   2. iv opiate (morphine, diamorphine)(2-4mg every 5-10min)
3. Infarct limitation
   1. Antiplatelet - Aspirin (160-325mg/day)
   2. Anticoagulant - Heparin (continuous infusion)
   3. Fibrinolytic - Streptokinase
4. Treat complications (cardiogenic shock, tachy/brady-arrhythmias

Myocardial Infarction: medium and long term measures

1. Haemodynamic Rx after 5/7 to prevent sudden death or recurrence
   i. ACE-I (only if LV dysfunction)
      i. Ramipril
      ii. Captopril
      iii. Lisinopril
      iv. Trandolopril
      v. NOT enalapril
   ii. Beta blockers
   iii. Continue Aspirin



1. Address risk factors
2. Consideration of angioplasty / surgery
3. Psycho-social factors (cardiac rehab)

Drugs used in IHD

A. Drugs for Atherosclerosis including statins
B. Drugs that influence Haemodynamics
   1. Organic nitrates (angina, MI)
   2. Beta blockers (angina, MI)
   3. Ca-channel blockers (angina)
   4. ACE-I (MI)
C. Drugs that influence thrombosis
   1. Aspirin (angina, MI)
   2. Heparin
   3. Fibrinolytic drugs (MI)

Organic nitrates

- Short acting:
  - Nitroglycerin
  - Isosorbide dinitrate
  - **Glyceryl trinitrate**
- Long acting:
  - **Isosorbide mononitrate**
  - Pentaerythritol tetranitrate
  - Erythrityl tetranitrate

Angina: Acute prophylaxis: short acting nitrate

- GTN
- Sublingual tabs / spray
- Avoids pre systemic metabolism
- Rapid absorption
- Volatile
- 6/52 shelf life
- Store in cool dark container
- AE's minimised by swallowing tab.

Angina: Long term prophylaxis: nitrates

- GTN patch
- Longer acting nitrate:
- Isosorbide mononitrate
  - Reduces frequency of attacks
  - Oral tabs
    - Taken am, lunch time, 6-8 hour respite to avoid tolerance
  - Controlled release taken o.d.

Unstable Angina: IV nitrates

- IV infusion of GTN /nitroglycerin

Organic Nitrates biochemical mechanism of action

- RELAXATION OF VASCULAR SMOOTH MUSCLE
  - Nitrates metabolised by smooth muscle cells
  - Produce NO
  - NO activates guanylyl cyclase
  - ↑cGMP (second messenger)
  - Dephosphorylation of myosin light chain and
  - Sequestration of Ca in SR
  - Thereby relaxing smooth muscle

Organic Nitrates: haemodynamic mechanism of action

- GTN relatively selective for venous smooth muscle
- Venodilation reduces cardiac preload
  - ↓venous return
  - ↓ventricular filling
  - ↓ventricular chamber diameter
  - ↓ventricular wall tension
  - ↓ cardiac work
  - ↓ O_2 demand

Organic Nitrates haemodynamic mechanism of action

↓ LVEDP
- ↑ coronary blood flow

Mild reduction in arterial tone
- ↓ afterload
- ↓ myocardial O_2 demand

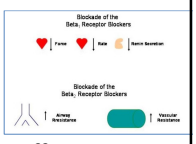
Relaxation of non-vascular smooth muscle
- Oesophageal spasm
- Renal and biliary colic

Organic nitrates adverse effects

- Headaches (vasodilation of meningeal vessels)
- Flushing
- Hypotension and reflex tachycardia, angina
- Tolerance

Beta blockers

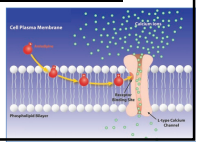
- Prophylaxis of exertional angina
- Reducing sudden death / re-infarction post MI (secondary prevention)
- Reduction of ventricular fibrillation
- Particularly useful in anxiety
- Hypertension



- Negative chronotropic and inotropic effects, reduce myocardial oxygen demand

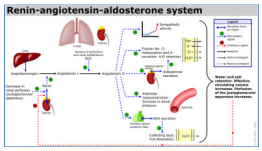
Calcium channel blockers

- Prophylaxis of angina
- Where beta blockers are contra-indicated (where spasm is prominent)
  - Diltiazem or
  - Long acting dihydropyridines (amlodipine) or
  - controlled release preparations of nifedipine (most potent vasodilator) to prevent reflex tachycardia
- Systemic vasodilation with afterload reduction and reduced O_2 demand
- Avoid in heart failure



ACE-I

- Hypertension
- Heart failure
- Early stages of MI if abnormal LV function
  - start small doses
  - dose titration to doses demonstrated to increase survival



ACE-I and CCBs

for coronary heart disease and stroke prevention in hypertensive and other high risk patients

- ACE-I = beta blockers + diuretics in CHD
- CCBs = beta blockers + diuretics in CHD

- ACE-I > CCBs for prevention of CHD
- CCBs > ACE-I for prevention of stroke

Possibly by decreasing the overall blood pressure

BP lowering is fundamental for prevention of IHD and stroke

Effect of **ACE-I (Ramipril)** on cardiovascular events in high risk patients (with any manifestation of coronary heart disease), despite NO LV dysfunction or heart failure

- Retards progression of both heart failure and atherosclerosis:
- Decreases risk of
  - MI (by 20%)
  - Stroke
  - Death from cardiovascular causes
  - Revascularisation procedures
  - Cardiac arrest
  - Heart failure
  - Complications related to diabetes and diabetes itself
- Treating 1000 patients for 4 years prevents 150 events in approx. 70 patients
- Recommend all patients at high risk, receive an ACE-I even if LV function normal!

Aspirin:

analgesic, antipyretic, anti-inflammatory, antiplatelet

1. 300mg o.d: At onset of acute MI to obtain rapid and complete inhibition of platelet cyclo-oxygenase
   - Improves survival in acute MI
2. 75mg -375mg o.d: for chronic prophylaxis
   - Reduces risk of MI in patients with unstable angina
   - Reduces risk of second MI
   - Prophylaxis for stable angina
   - Reduces risk of stroke in TIA

Aspirin continued

- Long term, Medium dose in high risk categories:
  - Unstable angina
  - Suspected acute MI
  - Past history of acute MI, stroke, Transient ischaemic attack
  - Other:
    - vascular procedures
    - Stable angina
    - Peripheral vascular disease
- PREVENTS:
  - MI by one third
  - Stroke by one third
  - Death by one sixth
  - Overall mortality

Aspirin resistance

- 16-30% patients resistant to Aspirin
- Regardless of underlying clinical symptoms, they are at a **4x greater risk** of clinically important cardiovascular morbidity compared to those sensitive to Aspirin
- Cause? (absorption, genetic, compliance, dose)
- No benefit derived from other anti-platelet agents either (clopidogrel, tirofiban)

Aspirin

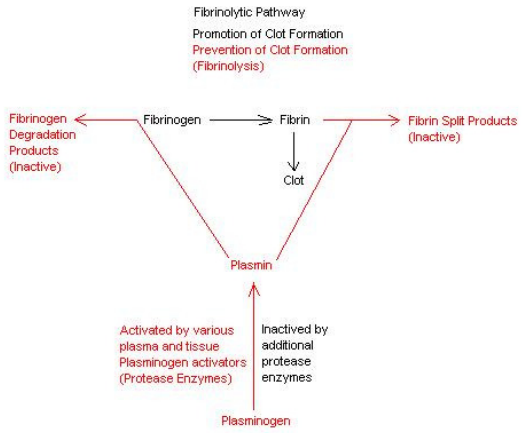
- Selective, irreversible inhibition of platelet COX
- COX needed for biosynthesis of
  - Prostaglandins
  - Platelet Thromboxane A2
    - Pro-aggretory
    - Vasoconstriction
- ↓COX
  - Anti-inflammatory
  - Antipyretic
  - Mild analgesic
  - Anti-aggretory

Aspirin kinetics

- Rapid absorption from GIT
- Rapid deacetylation→salicylate
- Hepatic metabolism
- Metabolites and unchanged salicylate excreted in urine

Aspirin adverse effects

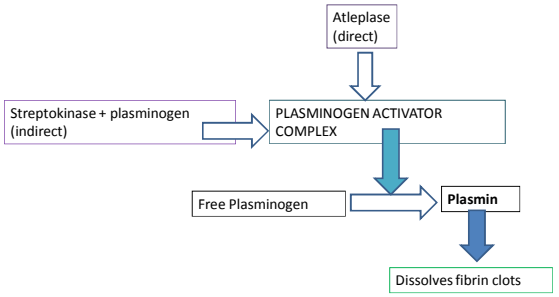
- Inhibition of PGE_2 biosynthesis in stomach and GIT: ulceration and haemorrhage
  - ↓ mucous secretion
  - ↑ acid secretion
  - Vasoconstriction of microvessels in submucosa
  - ↓GIT motility (constipation)
- Inhibition of platelet TXA_2
  - Bleeding tendency



Fibrinolytic Drugs

1. Streptokinase
   – Enzyme from streptococci that breaks down fibrin
2. Anistreplase
   – A prodrug that liberates streptokinase
3. Alteplase
   – Human plasminogen tissue activator made by bacteria via recombinant DNA technology
4. Urokinase
   – From human urine (unlicensed for MI)

Mechanism of Action Fibrinolytics



Streptokinase and MI

A. Indications:
   1. Patients with severe pain > 20 min and
   2. ST elevation or
   3. Bundle branch block on ECG

- Max benefit < 90 min of onset of pain
- May be given within 12hrs of onset of pain
- IV infusion
- Monitor BP for hypotension (activation of kinins and vasodilator peptides)

- Streptokinase + Aspirin
  1. Effective
  2. Relatively safe
  3. Inexpensive

Streptokinase and MI

- <u>Adverse effects:</u>

1. Bleeding
2. If treated with streptokinase in preceding year
   1. ↓efficacy
   2. ↑ hypersensitivity rxns

- <u>Contra-indications:</u>

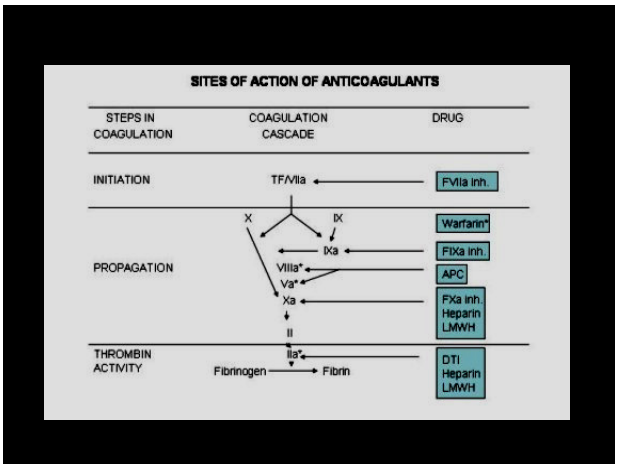
1. Recent surgery
2. Pregnancy
3. Active GI bleed / PUD
4. Severe liver disease (varices)
5. Head injury / stroke
6. Uncontrolled hypertension
7. Trauma

Alteplase and MI

- Selectively dissolves recently formed clot
- IV infusion given over 30 min
- Immediately followed by heparin

<u>DDI:</u>

- Fibrinolytics have additive effects with Aspirin
- Heparin required after Alteplase to prevent early reocclusion of affected artery



Heparin

- Present in mast cells
- Binds to antithrombin III and potentiates its inhibitory action on coagulation cascade:
  - Thrombin (IIa)
  - IXa
  - Xa
  - XIa
- Given as iv bolus (5000U) followed by constant iv infusion to Rx established thrombus (25000-30 000 IU over 24 hrs)
- Given subcut as prophylaxis (5000 units bd)
- Monitor **APTT** 4-6 hrs after initiating Rx until 2 consecutive readings within target range, then daily

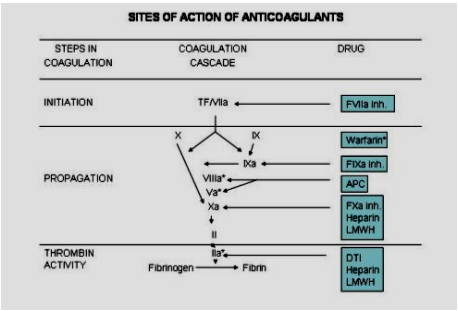
Low Molecular Weight Heparins

- Preferentially inhibit clotting factor Xa
- Release inhibitor of tissue factor pathway (TFPI)
- Lower risk of bleeding complications
- Do not prolong APTT
- Unfractionated preparations:
  - Enoxaparin
  - Dalteparin
  - Tinzaparin

Anticoagulants & Antiplatelet Drugs

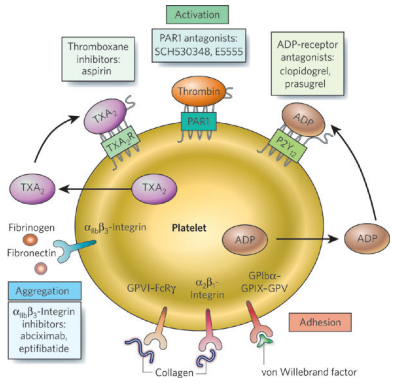
Quick summary

Dr K Outhoff



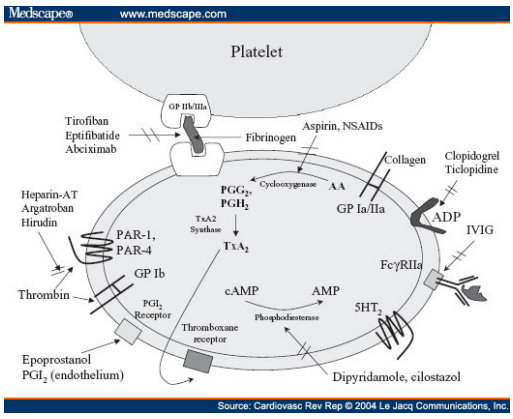
Anticoagulants

Drug	WARFARIN	HEPARIN	LMWH (Enoxaparin Dalteparin)	FONDAPARINUX	DIRECT THROMBIN INHIBITORS (lepirudin, hirudin, bevalirudin)
R.O.A	Oral	Sub cut / i.v	Sub cut	Sub cut	Oral
M.O.A	Inhibits hepatic synthesis of Vit K dependent clotting factors: II, VII, IX, X	Potentiates inhibitory effect of antithrombin III on clotting factors IIa, IXa, Xa, XIa, XIIa	Inhibition of factor Xa	Synthetic pentasaccharide; Specific inhibitor of Factor Xa	Bind to and inhibit fibrin-bound thrombin in the clot
Onset	Delayed 3-4 days (catabolism of preformed factors)	Instantaneous inactivation of thrombin (IIa)	Immediate	Immediate	
Monitor	PT → INR (2-3.5)	APTT (1.5-2.5)	Factor Xa assay (seldom required)	Factor Xa (seldom)	APTT
Antidote	Vit. K FFP	Protamine Sulphate	Protamine partially effective	None	None
Other	Teratogen Drug interactions +++	Zero order kinetics	Predictable kinetics	Used for orthopaedic ϕ	Anticoagulant of the leech!



Antiplatelet Drugs

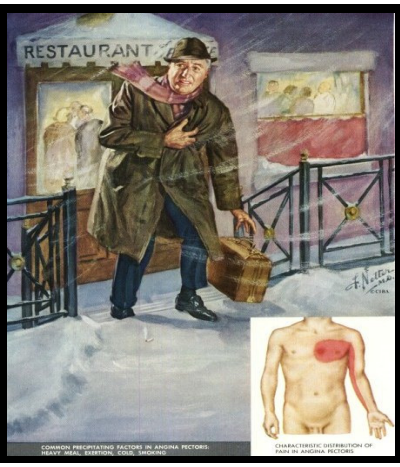
Drug	Aspirin (Thromboxane inhibitor)	Clopidogrel (ADP inhibitor)	Dipyramidole	Abciximab, Eptifibatide, Tirofiban
M.O.A	Irreversible inhibition of COX and therefore: TXA2 (pro-aggregatory) PGI2 (vasodilator)	Prodrug Binds to & irreversibly inhibits platelet adenosine receptors	Inhibition of phosphodiesterase, reduced breakdown of cAMP, increases potency and duration of action of adenosine, vasodilator.	Glycoprotein IIb/IIIa inhibitors
Comments	Gastric intolerance (inhibition of gastroprotective PGE2): Ulceration Bleeding	Sometimes used instead of aspirin, Or in combination for acute coronary syndromes. Haemorrhage GIT symptoms	Provokes angina (steal mechanism)	Reduce occlusion following angioplasty. Hypersensitivity reactions can occur



Case study

Jan, 57 yo, white, male,
Acute chest pain,
Myocardial infarction,

Management

- Acute treatment (infarct)
- BP
- Lipids
- Arrhythmia

- Chronic treatment