

ISCHEMIC HEART DISEASE

For Class- B.Pharmacy 2nd Semester
Subject- Pathophysiology (BP204T)

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Ischemic heart disease

- Also known as Coronary Artery Disease (CAD)
- Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium
- Imbalance between myocardial oxygen supply and demand.
- Caused mainly by Atherosclerosis of Coronary Artery
- It includes
 - Angina: Stable & Unstable
 - Myocardial infarction
 - Heart failure & Arrhythmia

Atherosclerosis

- Can affect any artery in the body
- Heart: angina, MI and sudden death;
- Brain: stroke and transient ischaemic attack;
- Limbs: claudication and critical limb ischaemia.



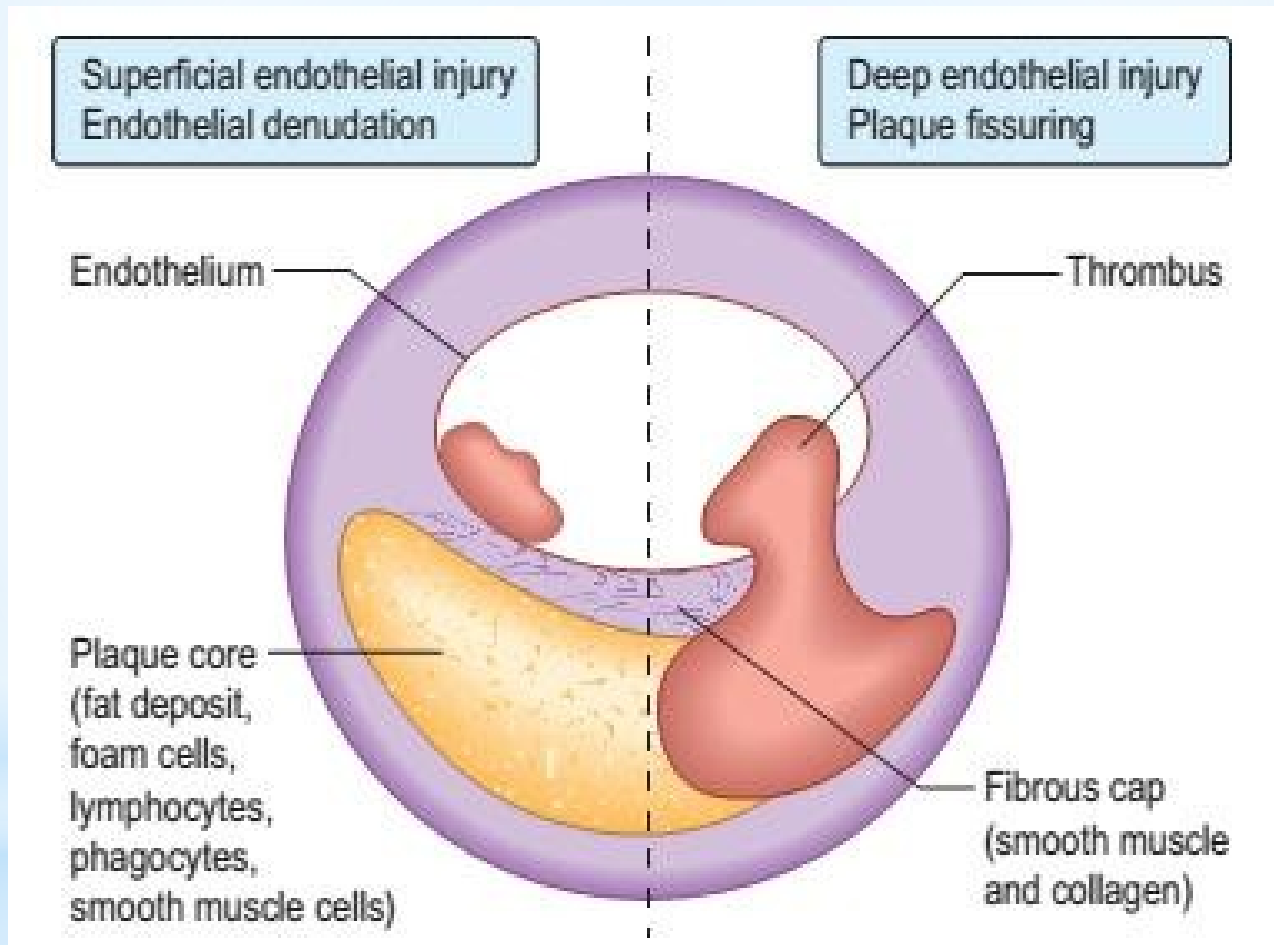
Atherosclerosis


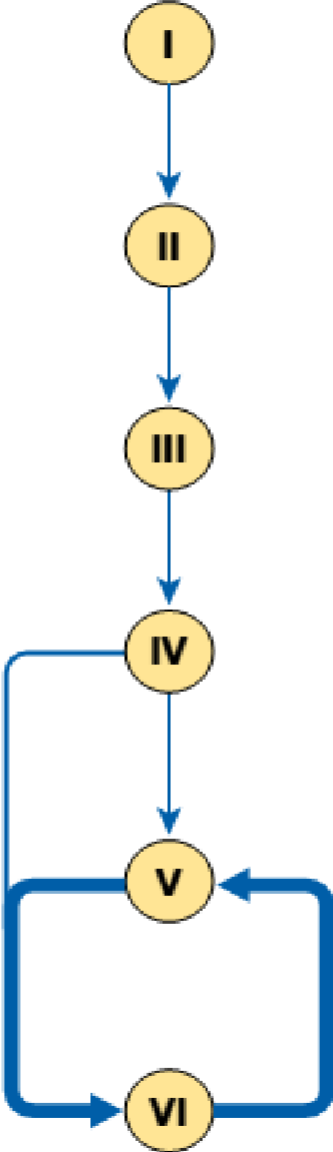





- Progressive inflammatory disorder of the arterial wall characterised by focal lipid rich deposits of atheroma
- Remain clinically asymptomatic until
 - large enough to impair tissue perfusion,
 - Ulceration and disruption of the lesion result in thrombotic occlusion
 - Distal embolisation of the vessel.
- Clinical manifestations depend upon the site of the lesion and the vulnerability of the organ supplied

Early Atherosclerosis

- Second and third decades of life
- Tend to occur at sites of altered arterial shear stress such as bifurcations
- Starts with any abnormal endothelial function
- Inflammatory cells, predominantly monocytes, bind to receptors expressed by endothelial cells,
- Migrate into the intima
- Take up oxidised low-density lipoprotein (LDL) particles
- Become lipid-laden macrophages or foam cells.
- As Foam cells dies, it releases its lipid pool in intimal space with cytokines and growth factor
- In response, smooth muscle cells migrate from the media of the arterial wall into the intima
- Lipid core will be covered by smooth muscle cells and matrix
- Forms stable atherosclerotic plaque that will remain asymptomatic until it becomes large enough to obstruct arterial flow

Early Atherosclerosis



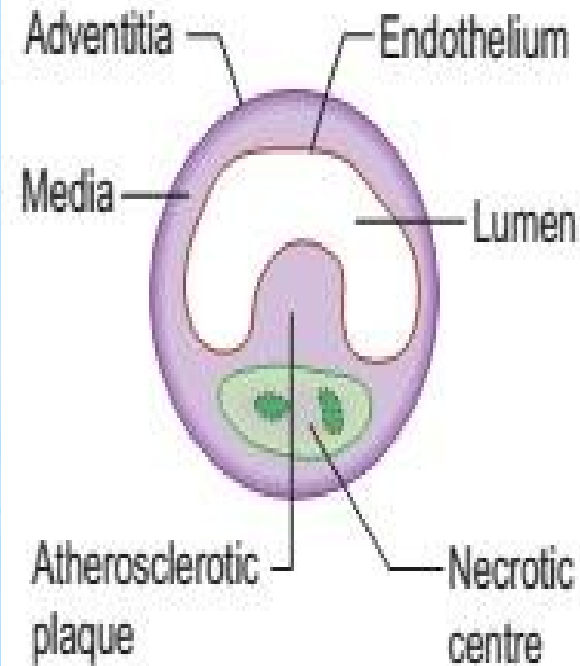
Nomenclature and main histology	Sequences in progression	Main growth mechanism	Earliest onset	Clinical correlation
Type I (initial) lesion Isolated macrophage foam cells 		Growth mainly by lipid accumulation	From first decade	Clinically silent
Type II (fatty streak) lesion Mainly intracellular lipid accumulation 				
Type III (intermediate) lesion Type II changes and small extracellular lipid pools 				
Type IV (atheroma) lesion Type II changes and core of extracellular lipid 		Accelerated smooth muscle and collagen increase	From fourth decade	Clinically silent or overt
Type V (fibroatheroma) lesion Lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic 		Thrombosis, haematoma		
Type VI (complicated) lesion Surface defect, haematoma-haemorrhage, thrombus 				

Advanced Atherosclerosis

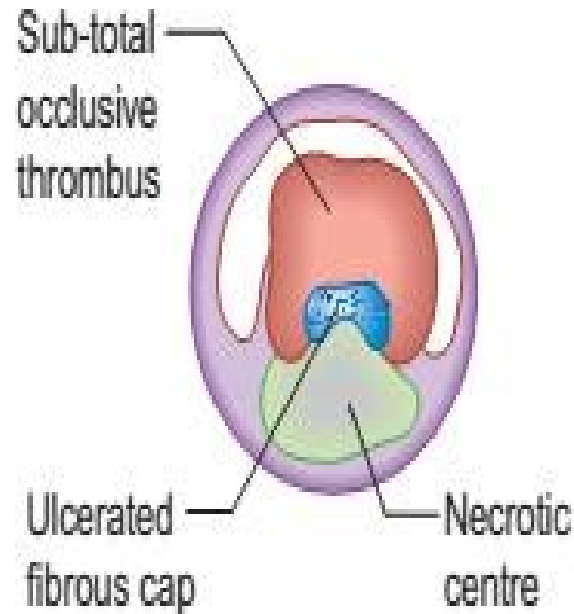
- In established atherosclerotic plaque, macrophages mediate inflammation and smooth muscle cells promote repair
- Cytokines released by macrophage starts degrading smooth muscle layered over plaque
- Now lesion remains vulnerable to mechanical stress that ultimately causes erosion, fissuring or rupture of the plaque surface.
- Any breach in the integrity of the plaque will expose its contents to blood
- Trigger platelet aggregation and thrombosis
- That extend into the atheromatous plaque and the arterial lumen.
 - cause partial or complete obstruction at the site of the lesion
 - distal embolisation resulting in infarction
 - ischaemia of the affected organ

Advanced Atherosclerosis

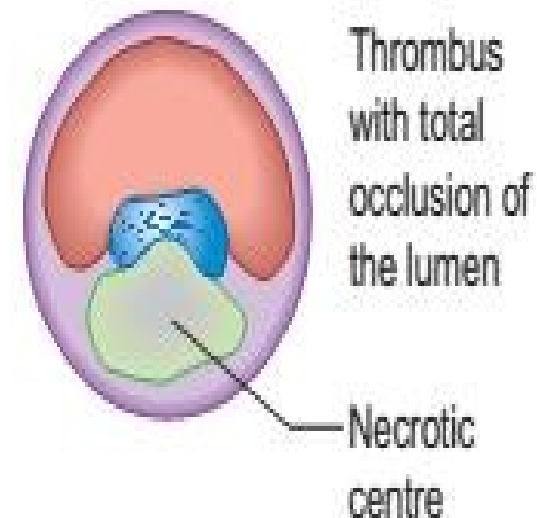
a Stable angina pectoris



b Unstable angina pectoris



c Myocardial infarction (STEM I)



Risk factor of Atherosclerosis

- Effect of risk factors is multiplicative rather than additive.
- It is important to distinguish between relative risk and absolute risk.
- **Absolute Risk**
 - Age
 - Male sex
 - Positive family history

Risk factor of Atherosclerosis

- Relative Risk
 - Smoking
 - Hypertension
 - Diabetes mellitus
 - Haemostatic factors.
 - Physical activity
 - Obesity
 - Alcohol
 - Other dietary factors
 - Personality
 - Social deprivation

Risk factor: Absolute Risk

- **Age & Sex**
 - Premenopausal women have lower rates of disease than men
 - Although this sex difference disappears after the menopause
- **Positive family history**
 - Runs in families,
 - Due to a combination of shared genetic, environmental and lifestyle factors.

Risk factor: Relative Risk

- **Smoking**
 - strong consistent
 - Dose linked relationship between cigarette smoking and IHD, especially in younger (< 70 years) individuals
- **Hypertension: directly proportional**
- **Hypercholesterolaemia: directly proportional to serum cholesterol concentrations (LDL)**
- **Diabetes mellitus: potent risk factor for all forms of atherosclerosis**
 - Men with type 2 diabetes: two- to four-fold greater annual risk of CAD,
 - Women with type 2 diabetes: (3–5-fold) risk

Risk factor: Relative Risk

- **Haemostatic factors**
 - Platelet activation and high levels of fibrinogen
 - Antiphospholipid antibodies - recurrent arterial thromboses
- **Physical activity**
 - Physical inactivity roughly doubles the risk of coronary heart disease
 - Regular exercise
 - Increased serum HDL cholesterol concentrations,
 - Lower BP,
 - Collateral vessel development
- **Obesity: often associated with HTN and cardiovascular disease**

Risk factor: Relative Risk

- Alcohol: excess consumption
- Other dietary factors
 - Diets deficient in fresh fruit, vegetables and polyunsaturated fatty acids (PUFA)
- Personality: little or no evidence to support the popular belief that stress is a major cause of CAD
- Social deprivation

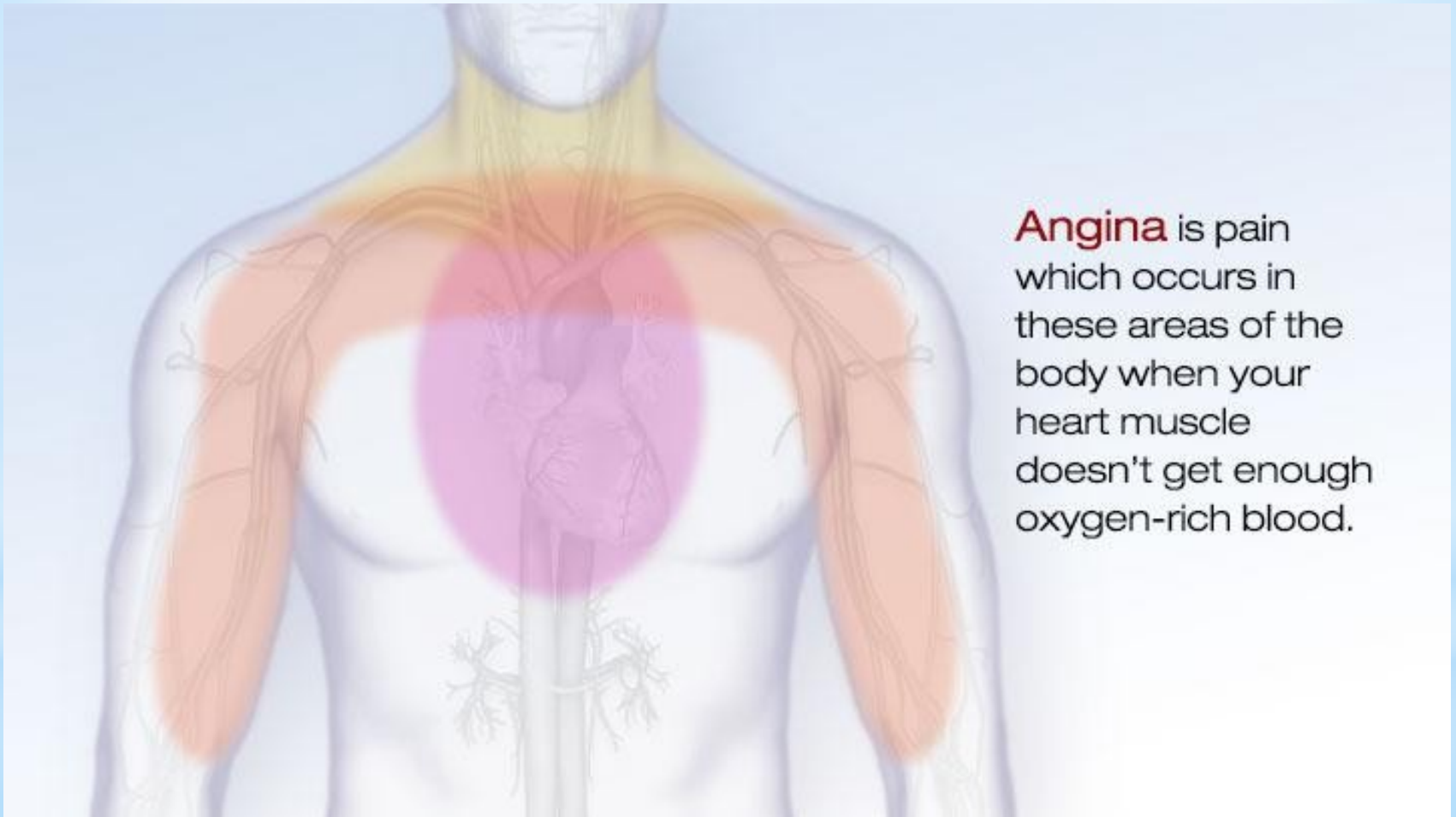
Primary Prevention

- Strategies taken before onset of disease in high risk individual.
- Two complementary strategies
- **Population strategies**
 - modify the risk factors of the whole population
 - through diet and lifestyle advice
 - For ex: Public restricting of smoking
- **Targeted strategies**
 - identify and treat high risk individuals who usually have a combination of risk factors
 - can be identified by using composite scoring system

Secondary Prevention

- Already have evidence of atheromatous vascular disease are at high risk of future cardiovascular events.
- Various secondary measures in this case
 - energetic correction of modifiable risk factors,
 - Smoking
 - Hypertension
 - Hypercholesterolaemia,
 - Statin therapy irrespective of their serum cholesterol concentration
 - Target BP of $\leq 140/85$ mmHg
 - Aspirin and ACE inhibitors
 - Beta-blockers: h/o MI or heart failure.

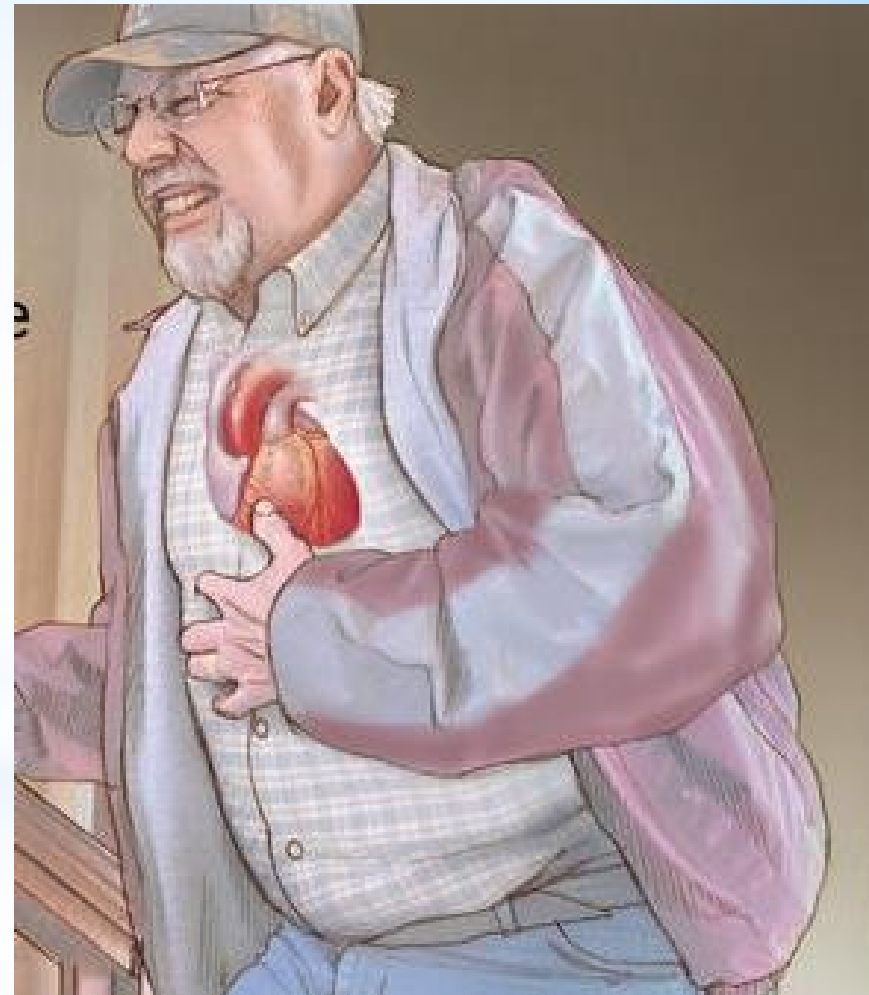
ANGINA



Angina is pain which occurs in these areas of the body when your heart muscle doesn't get enough oxygen-rich blood.

Introduction

- A type of chest pain
- Not a disease, its a symptom of an underlying heart problem specially IHD
- Described as 'heavy', 'tight' or 'gripping'.
- Typically, central/retrosternal
- Mild ache to most severe that provokes sweating and fear
- Associated breathlessness.



CLASSIFICATION

CLASS	Characteristic
Class I	No angina with ordinary activity. Angina with strenuous activity
Class II	Angina during ordinary activity, e.g. walking up hills, walking rapidly upstairs, with mild limitation of activities
Class III	Angina with low levels of activity, e.g. walking 50– 100 yards on the flat, walking up one flight of stairs, with marked restriction of activities
Class IV	Angina at rest or with any level of exercise

Classical or Exertional Angina Pectoris

- Characterized by
 - constricting discomfort in the front of the chest, arms, neck, jaw;
 - provoked by physical exertion, especially after meals and in cold, windy weather or by anger or excitement and
 - relieved (usually within minutes) with rest or glyceryl trinitrate. Occasionally, it disappears with continued exertion ('walking through the pain').
- Typical angina: all three features,
- Atypical angina: two out of the three,
- Non-anginal chest pain: one or less of these features

Types of Angina

- **Stable Angina:** episodic clinical syndrome where there is no change in severity of attacks.
- **Unstable angina:** Deterioration(24 hrs) in previous stable angina with symptoms frequently occurring at rest, i.e. acute coronary syndrome
- **Refractory angina:** patients with severe coronary disease in whom revascularization is not possible and angina is not controlled by medical therapy.
- **Variant (**Prinzmetal's**) angina:** occurs without provocation, usually at rest, as a result of coronary artery spasm, more frequently in women

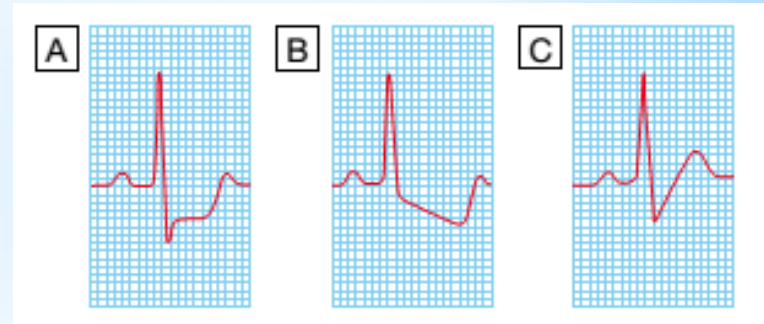
Stable Angina

- Characterised by central chest pain, discomfort or breathlessness that is precipitated by exertion or other forms of stress and is promptly relieved by rest
- **Activities precipitating angina**
 - Common
 - Physical exertion
 - Cold exposure
 - Heavy meals
 - Intense emotion
 - Uncommon
 - Lying flat (decubitus angina)
 - Vivid dreams (nocturnal angina)

Clinical Features

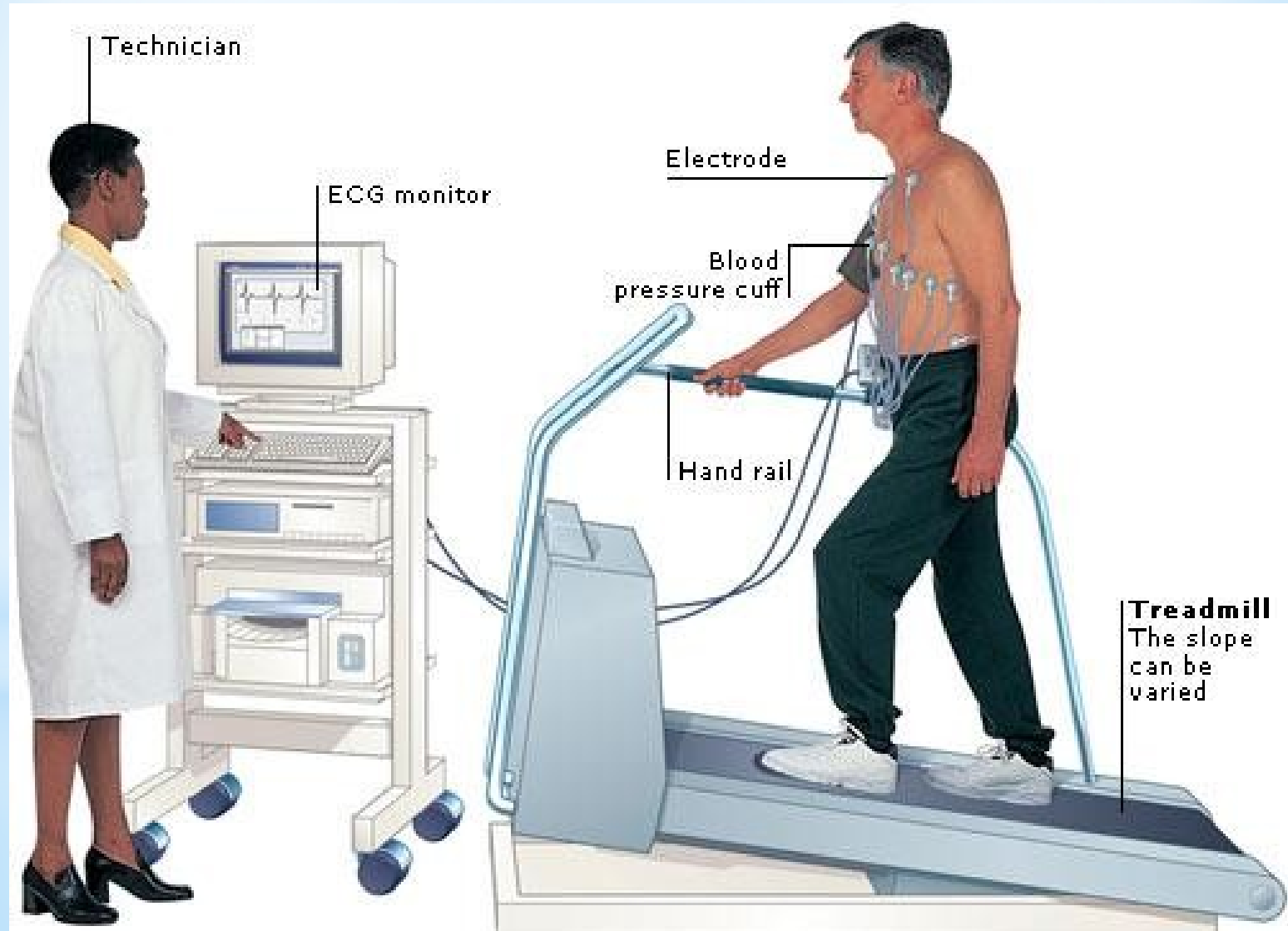
- History is by far the most important factor in making the diagnosis
- Physical examination is frequently unremarkable
- But careful search for evidence of
 - valve disease (particularly aortic),
 - left ventricular dysfunction (cardiomegaly, gallop rhythm)
 - arterial disease (carotid bruits, peripheral vascular disease)
 - unrelated conditions that may exacerbate angina (anaemia, thyrotoxicosis).
- Important assessment of risk factors e.g. hypertension, diabetes mellitus

Investigation



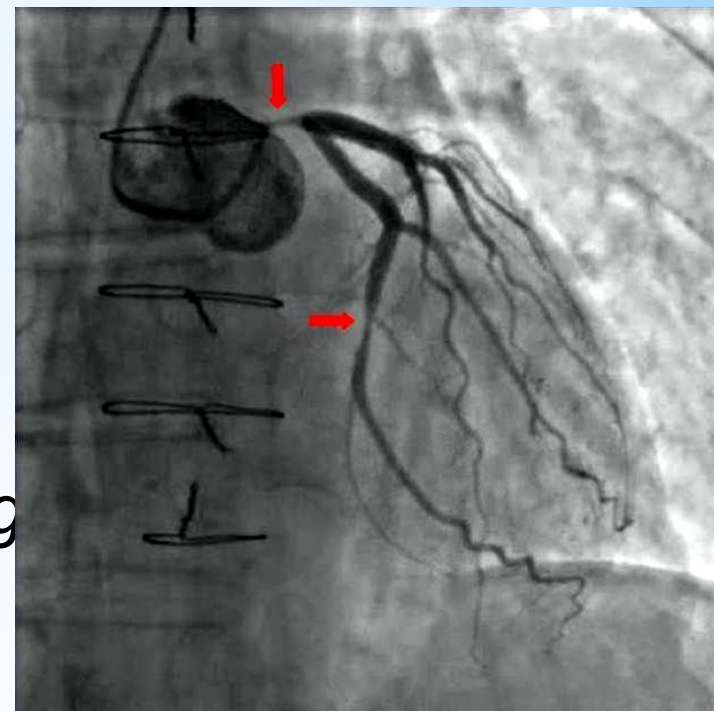
- **Resting ECG**
 - may show evidence of previous MI but is often normal, even in patients with severe CAD.
 - Occasionally, there is T-wave flattening or inversion in some leads, providing non-specific evidence of myocardial ischaemia or damage.
 - The most convincing evidence of myocardial ischaemia - reversible ST segment depression or elevation, with or without T-wave inversion, at the time the patient is experiencing symptoms
- **Exercise ECG**
 - Exercise tolerance test (ETT) - standard treadmill or bicycle while monitoring the patient's ECG, BP and general condition.
 - Planar or down-sloping ST segment depression of ≥ 1 mm is indicative of ischaemia (A, B)
 - Up-sloping ST depression is less specific and often occurs in normal individuals (C)

Investigation



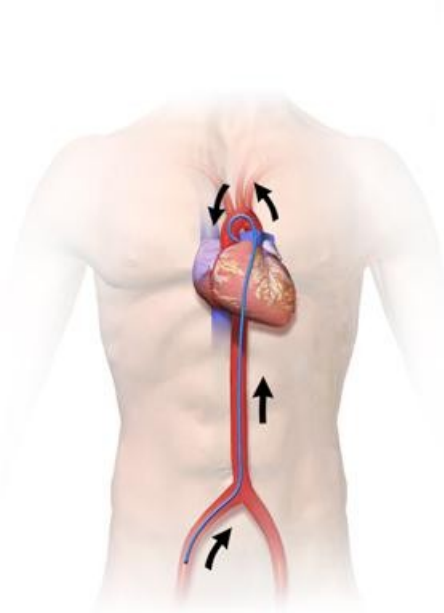
Investigation

- **Other forms of stress testing**
 - *Myocardial perfusion scanning*
 - *Stress echocardiography*
- **Coronary arteriography**
 - detailed anatomical information about the extent and nature of coronary artery disease
 - indicated when non-invasive tests have failed to establish the cause of atypical chest pain
 - under local anaesthesia
 - requires specialised radiological equipment, cardiac monitoring and an experienced operating team

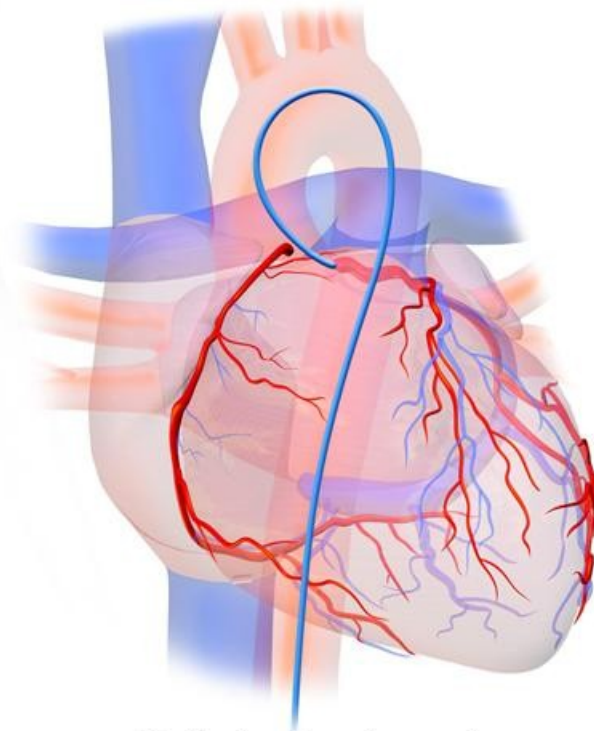


Investigation

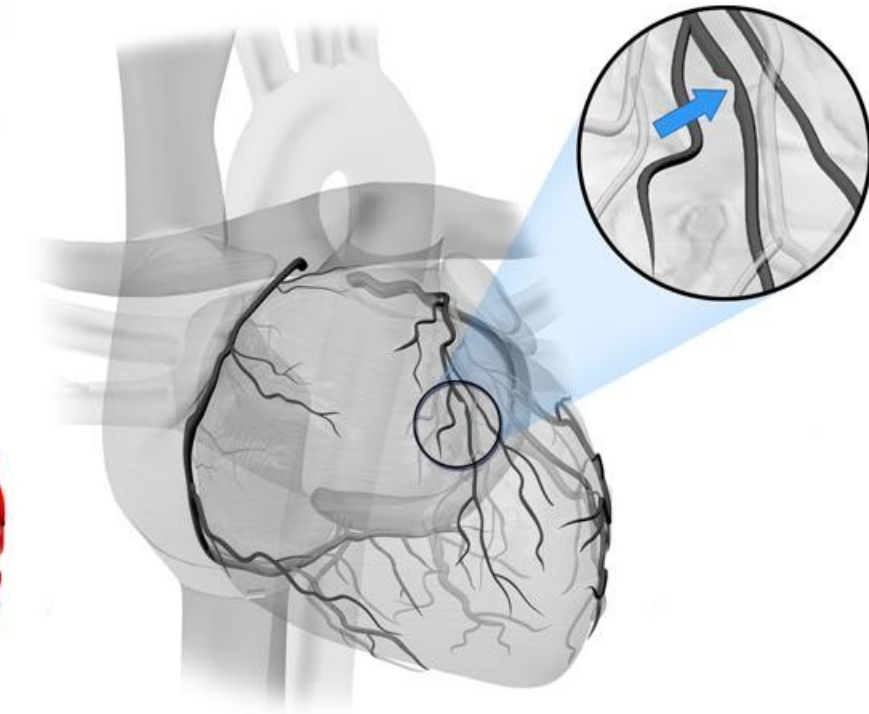
Coronary Angiography



Catheter inserted in leg and guided up the aorta



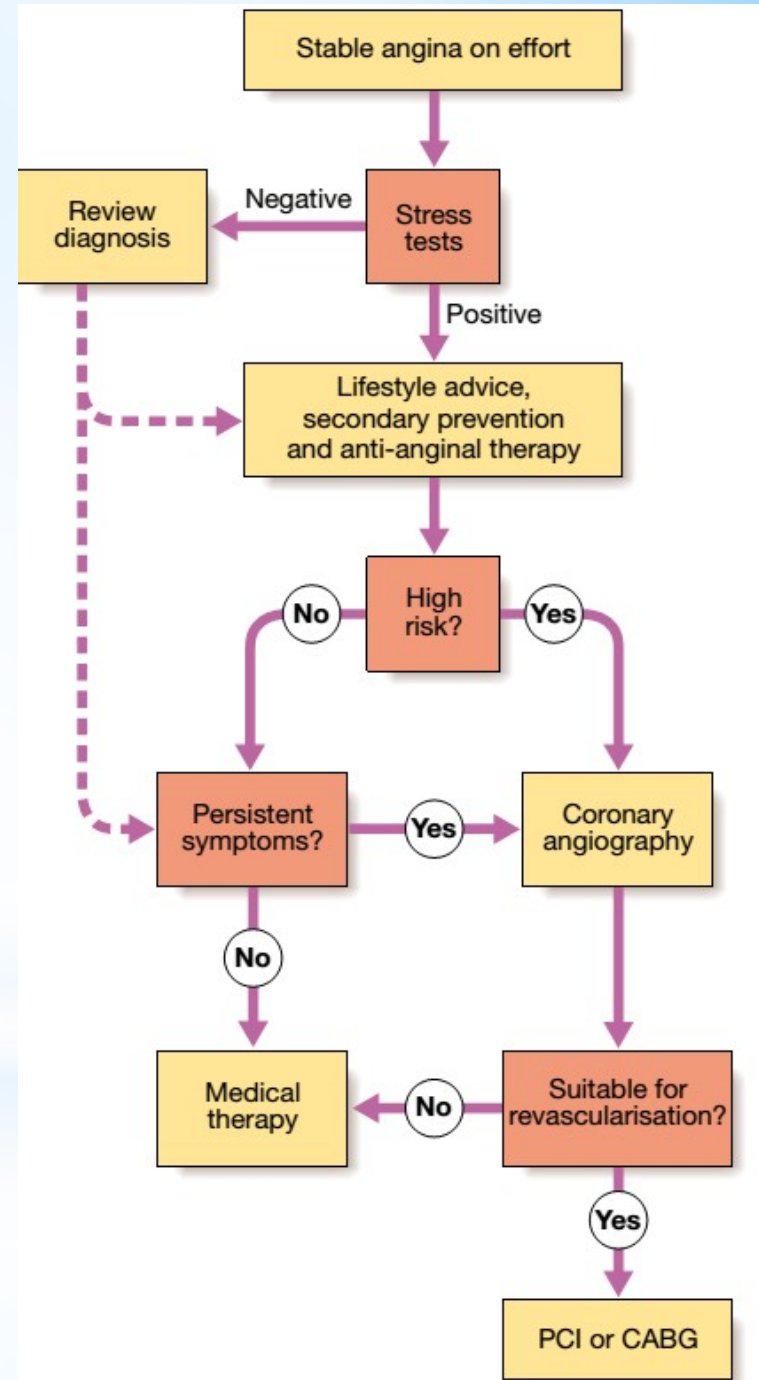
Catheter tip stops at left coronary artery



Contrast agent injected into arteries. X-ray imaging shows stenosis in left coronary artery

Management

- Management of angina pectoris involves
 - careful assessment of the likely extent and severity of arterial disease
 - identification and control of risk factors such as smoking, hypertension and hyperlipidaemia
 - use of measures to control symptoms
 - Identification of high-risk patients for treatment to improve life expectancy.



TREATMENT

- **Antiplatelet therapy**
 - Low-dose (75 mg) aspirin
 - reduces the risk of adverse events such as MI
 - prescribed for all patients with CAD indefinitely
 - Clopidogrel (75 mg daily)
 - equally effective ALTERNATIVE
 - if aspirin causes dyspepsia or other side-effects
- **Anti-anginal drug treatment: Five groups of drug**
 - Nitrates
 - β -blockers
 - calcium antagonists
 - potassium channel activators
 - I_f channel antagonist

Preparation	Peak action	Duration of action
Sublingual GTN	4–8 mins	10–30 mins
Buccal GTN	4–10 mins	30–300 mins
Transdermal GTN	1–3 hrs	Up to 24 hrs
Oral isosorbide dinitrate	45–120 mins	2–6 hrs
Oral isosorbide mononitrate	45–120 mins	6–10 hrs

- **Nitrates**

- act directly on vascular smooth muscle to produce venous and arteriolar dilatation
- reduction in myocardial oxygen demand
- Increase in myocardial oxygen supply
- prophylactically before taking exercise that is liable to provoke symptoms.
- Continuous nitrate therapy can cause pharmacological tolerance
 - avoided by a 6–8-hour nitrate-free period
 - Nocturnal angina: longacting nitrates can be given at the end of the day

- **β -blockers:** lower myocardial oxygen demand by reducing heart rate, BP and myocardial contractility
 - provoke bronchospasm in patients with asthma.
- **Calcium antagonists**
 - inhibit the slow inward current
 - caused by the entry of extracellular calcium through the cell membrane of excitable cells,
 - particularly cardiac and arteriolar smooth muscle
 - lower myocardial oxygen demand by reducing BP and myocardial contractility

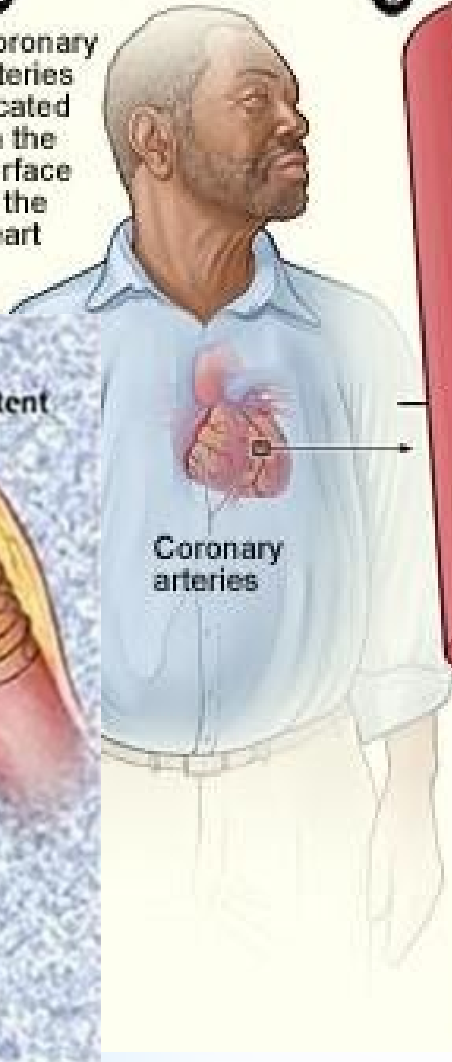
Drug	Dose	Feature
Nifedipine	5–20 mg 8-hourly*	May cause marked tachycardia
Nicardipine	20–40 mg 8-hourly	May cause less myocardial depression than the other calcium antagonists
Amlodipine	2.5–10 mg daily	Ultra long-acting
Verapamil	40–80 mg 8-hourly*	Commonly causes constipation; useful anti-arrhythmic properties (p. 572)
Diltiazem	60–120 mg 8-hourly*	Similar anti-arrhythmic properties to verapamil

- **Potassium channel activators**
 - arterial and venous dilating properties
 - but do not exhibit the tolerance seen with nitrates.
 - Nicorandil (10–30mg 12-hourly orally) - only drug in this class currently available for clinical use
- **I_f channel antagonist**
 - Ivabradine is the first of this class of drug
 - Induces bradycardia by modulating ion channels in the sinus node
 - Comparatively, does not have other cardiovascular effects
 - Safe to use in patients with heart failure

Percutaneous Coronary Intervention (PCI)

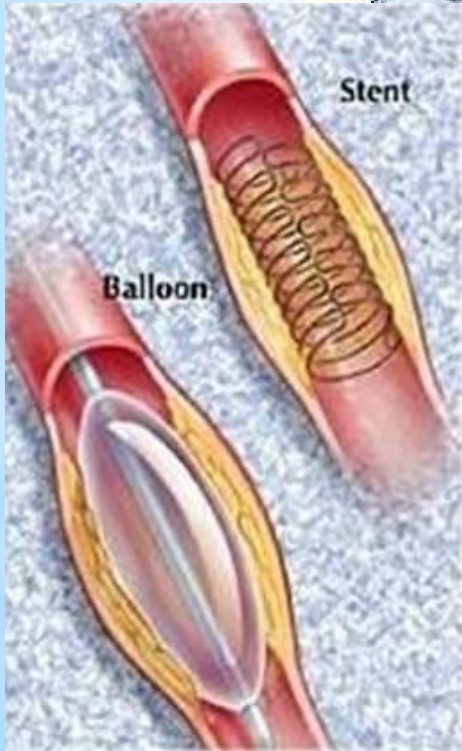
- Passing a fine guide-wire across a coronary stenosis under radiographic control
- Balloon is placed and then inflated to dilate the stenosis
- Then a coronary stent is deployed on a balloon
 - maximise and maintain dilatation of a stenosed vessel
 - reduces both acute complications and the incidence of clinically important restenosis
- Mainly used in single or two-vessel disease

A
Coronary arteries located on the surface of the heart



Stent

Balloon



B
Catheters
Coronary artery
Closed stent
Plaque

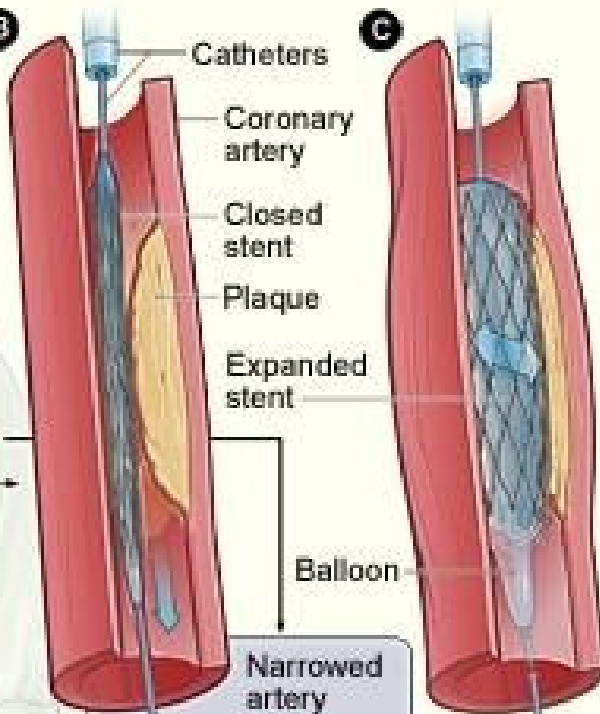
C

Expanded stent

Balloon

Narrowed artery

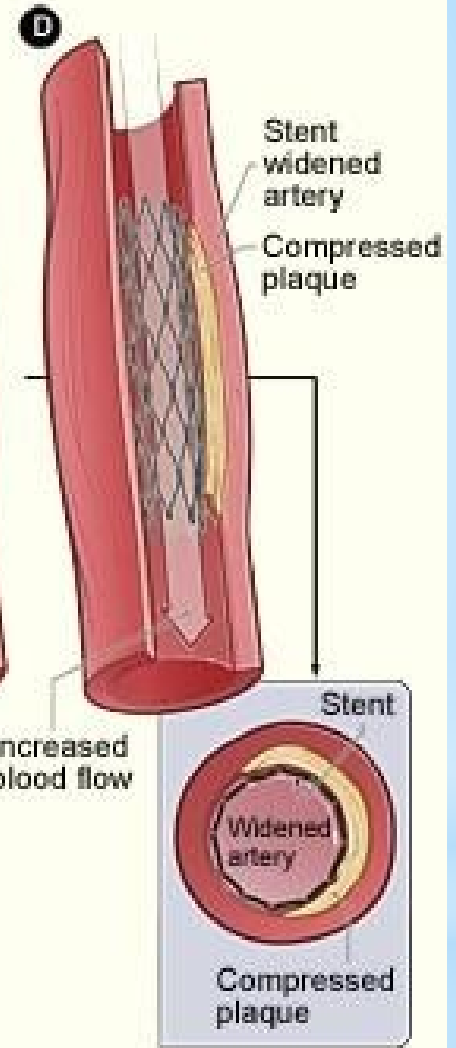
Closed stent around plaque
balloon catheter
Artery cross-section



D
Stent widened artery
Compressed plaque

Increased blood flow

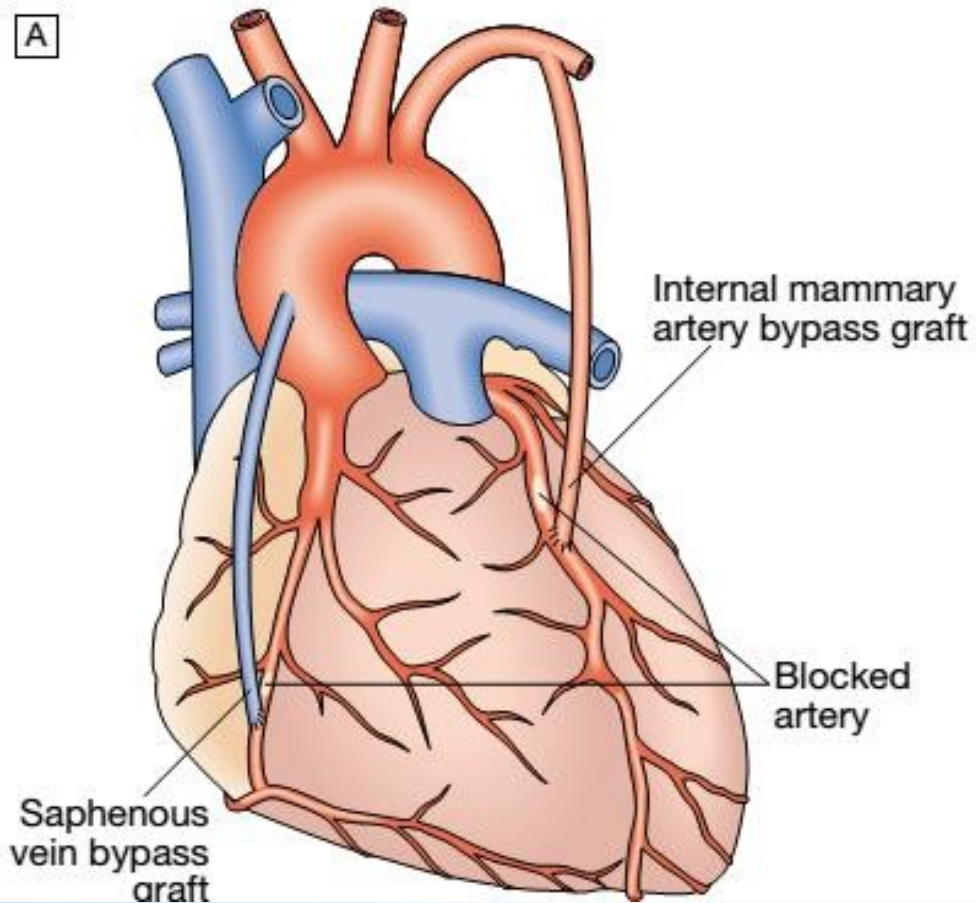
Stent
Widened artery
Compressed plaque



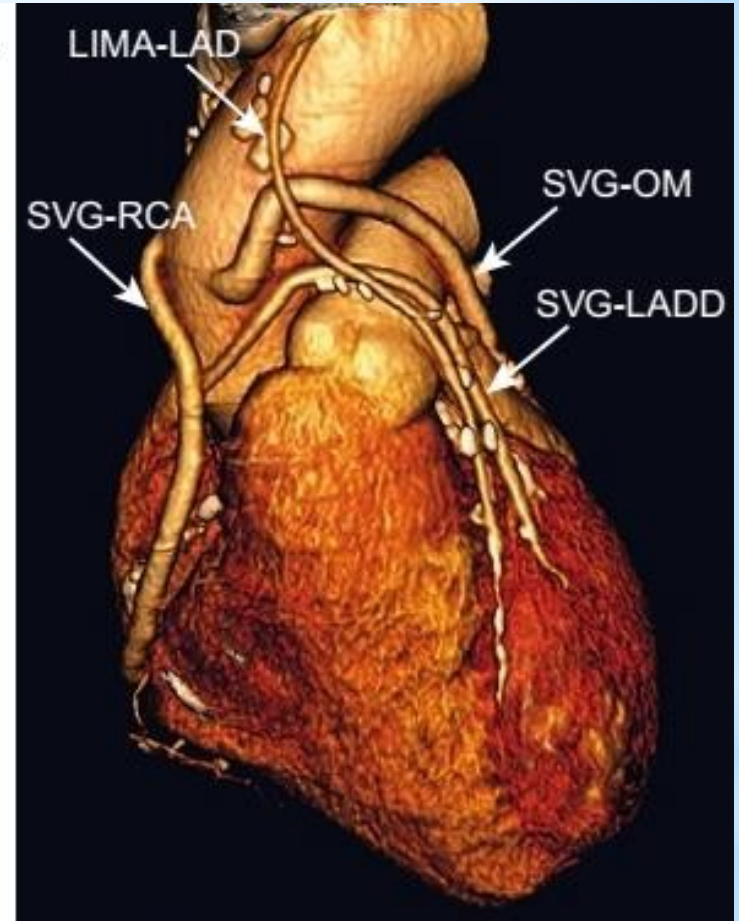
Coronary artery bypass grafting (CABG)

- Stenosed artery is by-passed with
 - internal mammary arteries
 - radial arteries
 - reversed segments of the patient's own saphenous vein
- Major surgery under cardiopulmonary bypass,
- But in some cases, grafts can be applied to the beating heart: **'off-pump' surgery**
- Operative mortality is approximately 1.5% but risks are higher
 - elderly patients,
 - with poor left ventricular function
 - those with significant comorbidity, such as renal failure
- 90% of patients are free of angina 1 year after CABG surgery, but fewer than 60% of patients are asymptomatic after 5 or more years.

A



B



Myocardial Infarction (MI)

- Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, in which case any one of the following meets the diagnosis for MI:
 - Detection of rise and/or fall of cardiac biomarkers (preferably troponin),
 - ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block)
 - Development of pathological Q waves
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Clinical features : Symptoms

- Pain is the cardinal symptom
- Prolonged cardiac pain: chest, throat, arms, epigastrium or back
- Anxiety and fear of impending death
- Nausea and vomiting
- Breathlessness
- Collapse/syncope

- Sympathetic activation: pallor, sweating, tachycardia
- Vagal activation: vomiting, bradycardia
- Signs of impaired myocardial function
- Hypotension, oliguria, cold peripheries
- Narrow pulse pressure
- Raised JVP
- Third heart sound
- Quiet first heart sound
- Diffuse apical impulse
- Lung crepitations
- Tissue damage: fever
- Other complications: e.g. mitral regurgitation, pericarditis

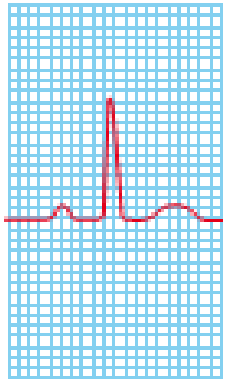
Types of MI

- There are three types of MIs:
- **Type 1** – spontaneous MI with ischaemia due to a primary coronary event, e.g. plaque erosion/rupture, fissuring or dissection
- **Type 2** – MI secondary to ischaemia due to increased oxygen demand or decreased supply, such as coronary spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
- **Type 3,4,5** – diagnosis of MI in sudden cardiac death, after percutaneous coronary intervention (PCI) and after coronary artery bypass graft (CABG), respectively.

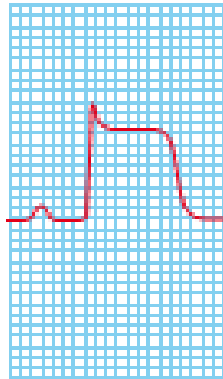
Investigations: Electrocardiography

- Confirmatory diagnosis
- But difficult to interpret if there is bundle branch block or previous MI.
- Repeated ECGs are important: initial ECG may be normal or non-diagnostic in one-third of cases
- ECG changes are best seen in the leads that 'face' the ischaemic or infarcted area
- ST-segment deviation
 - ST-segment elevation
 - T wave inversion - change in ventricular repolarisation
 - persists after the ST segment has returned to normal.
 - reliable for the approximate age of the infarct to be deduced.

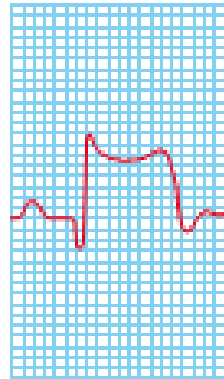
Investigations: Electrocardiography



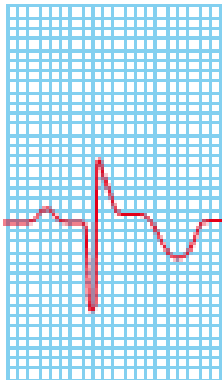
A



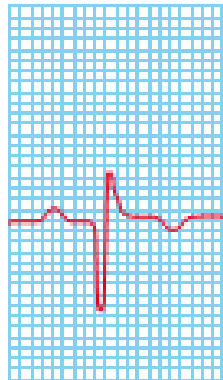
B



C



D



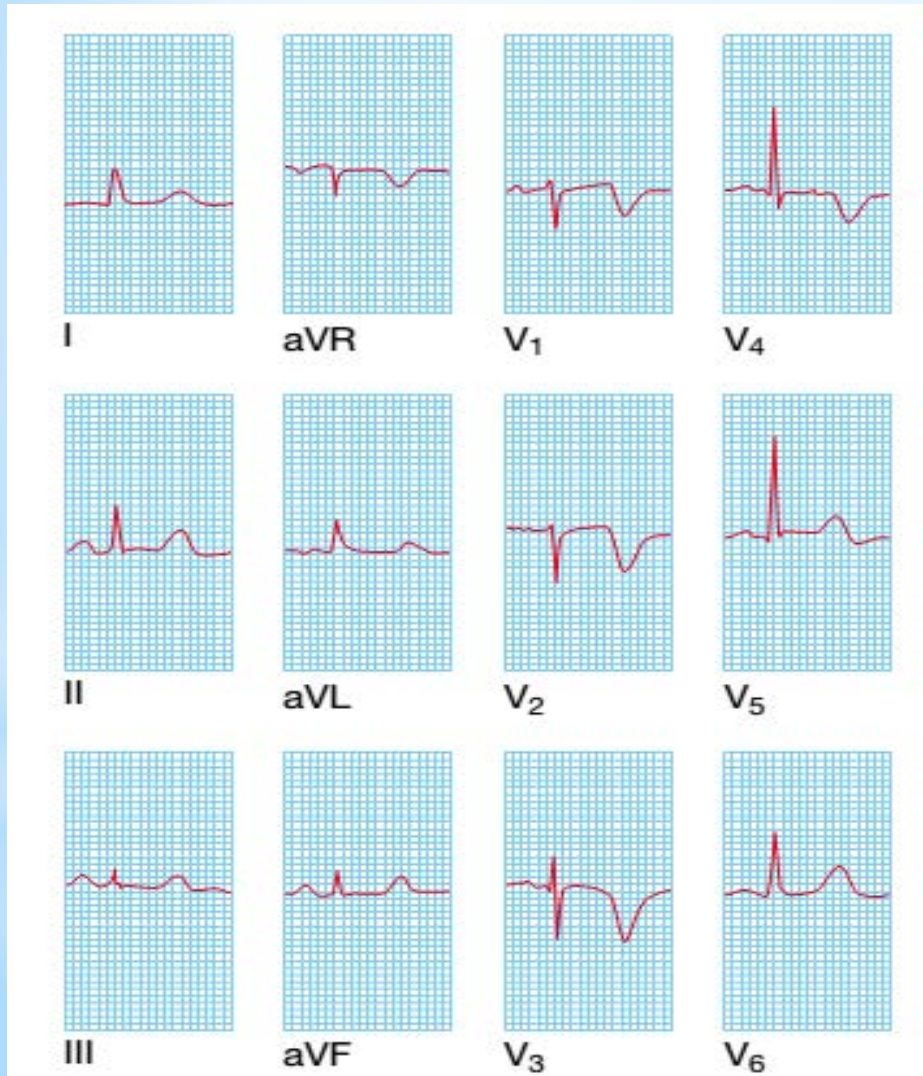
E

a Normal ECG complex. B Acute ST elevation ('the current of injury'). C Progressive loss of the R wave, developing Q wave, resolution of the ST elevation and terminal T wave inversion. d Deep Q wave and T- wave inversion. E Old or established infarct pattern

Investigations: Electrocardiography

- **Non-ST segment elevation ACS**
 - Partial occlusion of a major vessel or complete occlusion of a minor vessel,
 - unstable angina or partial thickness (subendocardial) MI.
 - ST-segment depression and T-wave changes.
 - Presence of infarction: loss of R waves in the absence of Q waves

Investigations: Electrocardiography



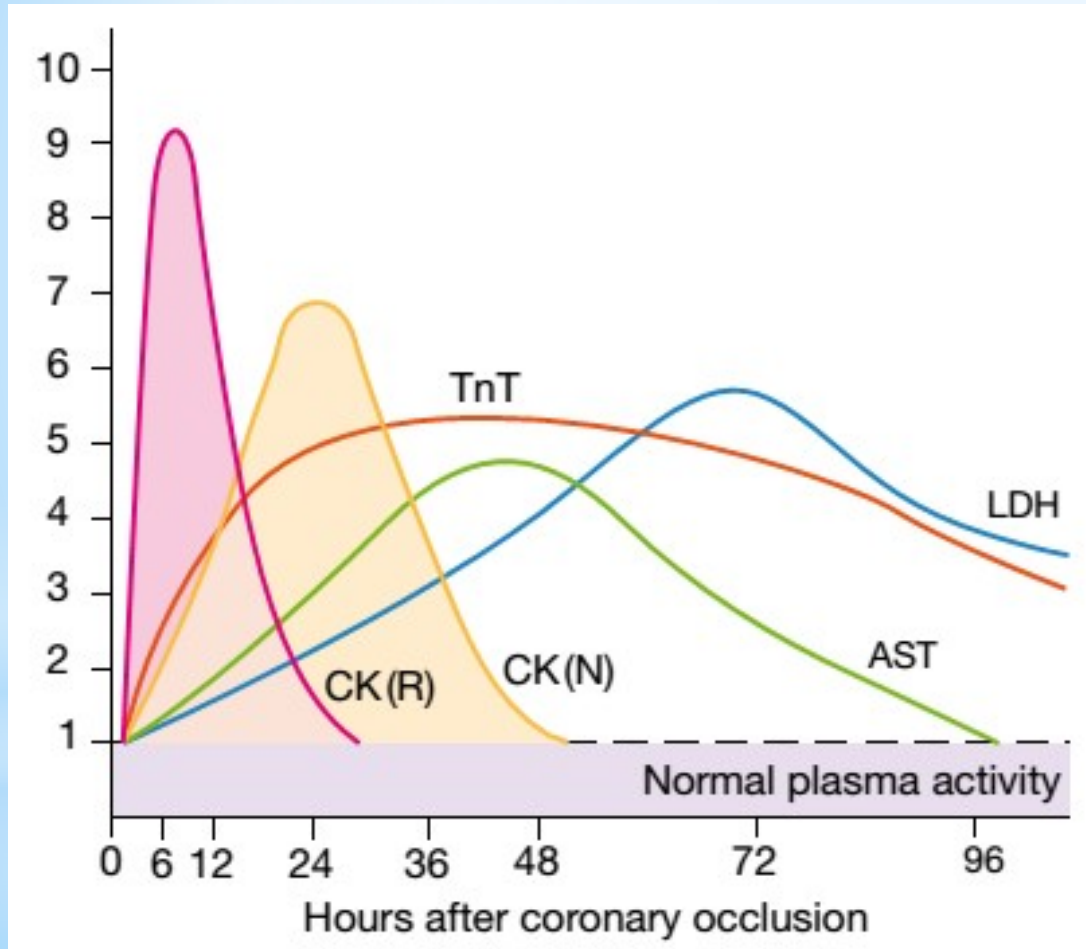
Recent anterior non-ST elevation (subendocardial) MI.

There is deep symmetrical T-wave inversion together with a reduction in the height of the R wave in leads V1, V2, V3 and V4

Investigations: Plasma Cardiac Markers

- **Unstable Angina:** no detectable rise in cardiac markers or enzymes
- **Myocardial Infarction:** creatine kinase (CK), a more sensitive and cardiospecific isoform of this enzyme (CK-MB), and the cardiospecific proteins, troponins T and I
- Also present in skeletal muscle but not CK-MB
 - intramuscular injection,
 - vigorous physical exercise
 - particularly in older people,
 - a fall

Investigations: Plasma Cardiac Markers



Creatine kinase (CK) and troponin T (TnT) are the first to rise, followed by aspartate aminotransferase (AST) and then lactate dehydrogenase (LDH)

Investigations

- **Other blood tests:** erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) are also elevated
- **Chest X-ray**
 - pulmonary oedema that is not evident on clinical examination
 - heart size is often normal
 - But there may be cardiomegaly due to pre-existing myocardial damage
- **Echocardiography**
 - assessing left and right ventricular function
 - detecting important complications such as
 - mural thrombus,
 - cardiac rupture,
 - ventricular septal defect,
 - mitral regurgitation and
 - Pericardial effusion.

Early Medical Management

- Admitted urgently to hospital because of significant risk of death or recurrent myocardial ischaemia
- Reduce the incidence by at least 60%
- Oxygen – nasal cannula 2–4 L/min if hypoxia is present
- Brief history/risk factors and immediate
 - Intravenous access + blood for markers
 - 12-lead ECG
- Aim of early management
 - Analgesia
 - Antithrombotic therapy
 - Anti-anginal therapy
 - Reperfusion therapy

Anti-anginal Therapy

- Sublingual glyceryl trinitrate (300–500 µg): valuable first-aid measure
- IV nitrates (GTN 0.6–1.2mg/hour or isosorbide dinitrate 1–2mg/hour): left ventricular failure and the relief of recurrent or persistent ischaemic pain
- IV β -blockers (Atenolol 5–10mg or Metoprolol 5–15 mg given over 5mins) : relieve pain, reduce arrhythmias and improve short-term mortality. Contraindicated in
 - Heart failure (pulmonary oedema),
 - Hypotension (systolic BP < 105mmHg)
 - Bradycardia (heart rate < 65/min).
- Dihydropyridine calcium channel antagonist: nifedipine or amlodipine can be added to the β -blocker if there is persistent chest discomfort
 - but may cause an unwanted tachycardia if used alone.
 - Because of their rate-limiting action, verapamil and diltiazem are the calcium channel antagonists of choice if a β -blocker is contraindicated.

Analgesia

- Essential not only to relieve distress, but also to lower adrenergic drive
- IV opiates: initially morphine sulphate 5– 10mg or diamorphine 2.5–5 mg)
- IV Antiemetics: initially metoclopramide 10mg
- Intramuscular injections should be avoided
 - Poor skeletal muscle perfusion
 - Painful haematoma

Antithrombotic Therapy

- ***Antiplatelet therapy***

- Aspirin: oral dose of 300mg first tablet within the first 12 hour, followed by 75 mg.
- Aspirin + clopidogrel 600 mg: early (within 12 hours), followed by 150 mg daily for 1 week and 75mg daily thereafter
- Ticagrelor (180 mg followed by 90 mg 12-hourly): more effective than clopidogrel
- Antiplatelet treatment with i.v. glycoprotein IIb/IIIa inhibitors reduces the combined endpoint of death or MI and used in context of PCI

Antithrombotic Therapy

- **Anticoagulants**
 - reduces the risk of thromboembolic complication
 - prevents reinfarction in the absence of reperfusion therapy or after successful thrombolysis
 - Unfractionated heparin, fractionated (low molecular weight) heparin or a pentasaccharide.
 - Continued for 8 days or until discharge from hospital or coronary revascularisation

Reperfusion therapy

- Depending on type of MI, outcome of reperfusion therapy varies
 - NSTEMI: No demonstrable benefit
 - STEMI: restores coronary artery patency and preserves left ventricular function and improves survival
- Medium- to high-risk patients do benefit but this does not need to take place in the first 12 hours.
- Primary percutaneous coronary intervention (PCI)

Reperfusion therapy

- **Thrombolysis**
 - reduce hospital mortality by 25–50%
 - this survival advantage is maintained for at least 10 years
 - **Alteplase** (human tissue plasminogen activator)
 - over 90 minutes (bolus dose of 15 mg)
 - Followed by 0.75 mg/kg body weight, but not exceeding 50mg, over 30 mins
 - then 0.5mg/kg body weight, but not exceeding 35mg, over 60mins
 - better survival rates than other thrombolytic agents, such as streptokinase,
 - **Analogues of tPA (tenecteplase and reteplase):** longer plasma half-life than alteplase and can be given as an intravenous bolus

Late Management of MI

- **Risk stratification and further investigation lifestyle modification**
 - Cessation of smoking
 - Regular exercise
 - Diet (weight control, lipid-lowering)
- **Secondary prevention drug therapy**
 - Antiplatelet therapy (aspirin and/or clopidogrel)
 - β -blocker
 - ACE inhibitor
 - Statin
 - Additional therapy for control of diabetes and hypertension
 - Aldosterone receptor antagonis
- **Rehabilitation devices: Implantable cardiac defibrillator (high-risk patients)**