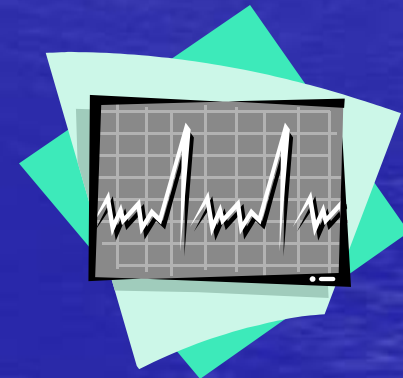


# Therapeutic Update: *Heart Disease*

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# Aims and Objectives

- To discuss ischaemic heart disease
- To describe treatment options and discuss:
  - aims of drug treatment
  - initiation of drug therapy
  - monitoring and long-term follow-up
  - dealing with adverse effects
- To highlight areas for increased pharmaceutical involvement

# Ischaemic Heart Disease (1)

- *What is ischaemic heart disease?*

- *Ischaemia*

- = pain resulting from insufficient oxygen supply to part of the body

- *Cardiac ischaemia* (Angina Pectoris)

- = results where the blood (and oxygen) supply to the coronary arteries is insufficient

- = is usually caused by atherosclerosis : narrowing of the arteries, due to fatty plaques

- = symptoms are chest pain (radiating),

# Ischaemic Heart Disease (2)

- Spectrum of disease
  - 'Stable' angina - narrowing / reduced blood supply
  - 'Unstable' angina - partial blood clot formation in arteries
  - Myocardial infarction (heart attack) - blockage of the artery with thrombus
- Aims of drug therapy
  - prevent clot formation
  - reduce cardiac workload and improve blood supply



# Anti-thrombotic Therapies

# Antiplatelet Therapies

- most arterial clots are 'platelet-mediated'
- atherosclerotic plaques - plaque rupture- platelet adhesion - activation - aggregation - partial or complete coronary occlusion
- Aim of therapy : prevent platelet aggregation
- Aspirin and Clopidogrel inhibit platelet aggregation
- **Antiplatelet therapy reduces the risk of serious vascular events (death/MI/stroke) by 25%**

# Aspirin

- Aspirin 75mg - 300mg daily for all; except where contraindicated
- Contraindications :
  - allergy - primarily bronchospasm
  - recent ulcer with significant blood loss
- Side effects:
  - nausea and vomiting or stomach 'upset'
- Take with or after food
- Consider e/c to reduce side effects

# Clopidogrel

- Clopidogrel 75mg daily is used:
  - as an alternative to aspirin, where aspirin is C/I
  - in addition to aspirin if unstable symptoms or post stent placement
- Acts via different mechanism to aspirin - synergy
- Adverse effects :
  - neutropenia (very rare)
  - bleeding (esp. in combination with aspirin)
  - rashes (antihistamines help)
- Clopidogrel is at least equivalent to aspirin

# Anti-anginal Therapies (1)

- **Beta-blockers:**
  - control heart rate
  - improve blood supply
  - reduce cardiac workload, therefore reducing oxygen requirements
- first-line in angina unless C/I
  - particularly hypotension, bradycardia
  - cardioselective agents vs non-cardioselective
- reduce mortality by up to 45% post-MI

# Anti-Anginal Therapies (2)

- **Calcium Channel Blockers**
  - reduce blood pressure
  - improve blood supply to myocardium
  - may slow heart rate (Diltiazem / Verapamil)
- Use first-line if beta-blockers C/I or add to beta-blockers if single agent is ineffective
- No mortality data - symptom control only
- Short-acting agents have been implicated in increased risk of stroke / MI

# Anti-Anginal Therapies (3)

- **Nitrates**

- improve blood supply to the myocardium
- reduce pre- and afterload : reduced cardiac workload
- Use as adjunct to beta-blocker / Calcium channel blocker therapy
- Unsuitable for monotherapy - development of TOLERANCE if given without 'nitrate-free' period
- No mortality data - symptom control only

# Anti-Anginal Therapies (4)

- **Nicorandil**

- reduces pre- and afterload - reducing cardiac workload
- improves blood supply to the myocardium
- Commonly used as an adjunct to first-line therapies
- New data from the IONA study indicates a reduction in the combined end-point of morbidity and mortality when added to standard therapy

# Secondary Prevention

- Therapies prescribed to reduce the risk of ischaemic events in patients known to have ischaemic heart disease
  - Antiplatelets
  - Lipid-lowering
  - Beta-blockers / ACE inhibitors
- Key area for pharmaceutical intervention / patient counselling

# Cholesterol - why worry ?

- UK now has a raised average plasma cholesterol compared to other countries

## **Raised plasma cholesterol :**

- is a risk factor in coronary heart disease
- leads to atherosclerosis (clogged arteries), unstable arteries, rupture of plaques and clotting in the arteries.
- can result in heart attack, stable or unstable angina

# High Risk Patients

- Target groups :
  - Patients post-MI
  - Patients with known cardiac disease (angina, unstable angina, CABG,) or vascular disease
  - Patients with no known vascular disease but a significant risk ( $>20\%$  /  $>30\%$ ) over the next 10 years
    - e.g. raised BP, family history, diabetes, obesity, etc.

# Cholesterol Levels

- Treat:
  - total cholesterol levels (TC) > 5.0mmol/L
  - low density lipoprotein (LDL) > 3.0mmol/L
  - triglycerides (TG) > 2.0mmol/L
  - high density lipoprotein (HDL) < 1.0mmol/L
- Check: Fasted levels
- Levels affected by:
  - AMI / stress / cardiac surgery

# Lipid Management: The Process

- Consider risk factors & measure cholesterol
  - If raised : Dietary trial then retest at 3 months
  - Still raised : Add drug therapy to diet then retest at 3 months
  - Still raised : Adjust dose / amend therapy
  - Retest at 3 monthly intervals until target achieved
- Once target achieved :
  - Repeat cholesterol test annually
  - Ensure liver function checked annually

# Drug Therapy

- Primarily statins
  - ~30% reduction in mortality with Simvastatin & Pravastatin
  - should be used first-line at proven doses
    - Simvastatin 20mg – 40mg at night
    - Pravastatin 40mg at night
- Once started statins should be continued indefinitely – don't stop once cholesterol is down

# Statin Therapy

- Side effects include :
  - GI Upset: Take with food
  - Insomnia: Take earlier in day
  - Liver problems : Rare; Annual LFT check
  - Muscle cramps : Check CK / Consider Dose reduction  
/withdrawal
  - Impotence : Rare

# ACE-I : CV risk reduction

- Activation of the renin-angiotensin system  
= increased risk of CV events
  - traditional role = treatment of CHF
  - post-MI with LV dysfunction - 23% reduction in mortality
- Data for Ramipril from HOPE study
  - 25% reduction in CV death in pts with
    - CV disease or diabetes plus one cardiac risk factor (high BP, smoking, high cholesterol)

# ACEI Therapy

- Role in all patients with CV disease (esp. diabetics) - controversial due to cost
  - Start at low dose to reduce risk of hypotension
  - Titrate to achieve clinical trial doses
  - Continue indefinitely
- Adverse effects and monitoring
  - cough - may resolve if persist, consider alternative
  - renal dysfunction - exclude stenosis, titrate slowly
  - can cause hyperkalaemia

# IHD Standard Regimen

- **Aspirin** - long-term
- **Statin** - according to lipid levels; long-term
- **Beta-blockers** or other anti-anginal - as need to prevent chest pain
- **Nitrate spray** (for symptom treatment)
- **ACE-Inhibitor** - long-term

# Post-MI : Standard regimen

- **Aspirin** (acute and long-term)
- **Beta-blockers** - initiate early and continue long-term
- **ACE-Inhibitors** - initiate in hospital and continue long-term
- **Statins** - initiate in hospital and continue long-term
- s/I Nitrates if previous angina

# Treatment Thresholds for Antihypertensive Therapy

- Drug therapy in all patients with sustained BP
  - $> 160\text{mmHg}$  systolic and / or
  - $> 100\text{mmHg}$  diastolic(after non-pharmacological measures)
- Treat where systolic  $> 140\text{mmHg}$  or diastolic  $> 90\text{mmHg}$  and:
  - Target organ damage
  - Established CV disease or 10 year CV risk  $> 15\%$
  - Diabetes

# Choice of Agent

1. Low dose thiazide as first-line therapy unless C/I or compelling reason for other drug class
2. Long-acting dihydropyridine if isolated systolic hypertension if low-dose thiazide not suitable
3. Choice of drug depends on relative indications / contraindications
4. Less than 50% patients are controlled on monotherapy and approximately 30% will require three or more agents

# Good Practice

- Use once daily agent
- Titrate doses according to license (not thiazides)
- Add drugs in stepwise approach until BP control is achieved (combination therapy is required in most patients)
- Small doses of two drugs result in larger BP reductions and fewer adverse effects than a maximal dose of one drug

# Thiazides

- Reduce circulating fluid volume / CO
- Low doses only (no dose response)
  - i.e. Bendrofluazide 2.5mg om
- First-line in all patients unless C/I or compelling reason for other class
  - effective, inexpensive
  - proven to reduce stroke and HF
- Compelling indication: the elderly
  - Plus obese pts, black pts
- Compelling contraindications: gout, diabetes, renal and liver impairment
- Monitor: U&Es – may cause dehydration

# AB/CD Algorithm for Hypertension

- Younger (55y)                      Older/Black
- Step 1:    A                              C or D
- Step 2:    A                      +              C or D
- Step 3:    A + C + D
- Step 4:    Add in B
- Step 5:    + Alpha Blocker/ Spironolactone
- A = ACE1 or A2RA; B = Beta blocker;  
C = Calcium channel blocker; D = Diuretic

# Beta-blockers

- Reduce CO, alter baroreceptor function, reduce sympathetic activation, reduce renin
- Suitable first-line where thiazides C/I
  - Especially post-MI, angina, anxiety, migraine
  - Increased efficacy in younger pts
  - Less effective as monotherapy in black pts
- Drug choice based on:
  - lipid solubility, duration of action, cardioselectivity
- Avoid in asthmatics / COPD
- Adverse effects: fatigue, cold peripheries, GI disturbance, depression, sleep disturbance, impaired glucose tolerance, effects lipid profile

# ACE Inhibitors

- Reduce Angiotensin II (vasoconstrictor), mild diuretic effects
- First line in pts with co-morbidities
  - Heart failure, LV dysfunction, post-MI, IHD
  - Diabetics: slow progression of renal disease
- Reduced efficacy in black pts
  - Low circulating renin levels
- C/I in renal artery or aortic stenosis
- Adverse effects:
  - first-dose hypotension (use long-acting agent)
  - dry cough
- Monitor: U&E's (esp. Creatinine)

# Calcium Channel Blockers

- Vasodilate peripherally and centrally
- Two classes
  - Dihydropyridine: Nifedipine, Amlodipine
  - Non-dihydropyridine: Diltiazem, Verapamil
- Alternative to thiazides in Isolated Systolic hypertension (ISH)
- Alternative to ACE-I in diabetes or if LV dysfunction
- Adjunct to first-line therapies where BP remains uncontrolled
- Caution: bradycardia and heart block with Verapamil, Diltiazem
- Avoid short-acting agents – Nifedipine S/L, capsules

# Additive Combinations

- Two drugs:
  - Beta-blocker plus thiazide
  - Thiazide plus ACEI
  - Beta-blocker plus calcium channel blocker
  - Calcium channel blocker plus ACEI

## Three drugs

- Diuretic, ACEI and calcium channel blocker
- Diuretic, beta-blocker, Calcium channel blocker

# Summary

- Hypertension is underdiagnosed and undertreated
- Drug therapy should be initiated if raised BP (+/- additional risk factors)
- Adequate BP control reduces mortality and morbidity
- All drug classes are effective – drug choice depends on co-morbidities and tolerability

# Pathophysiology

Poor Ventricular Function; Myocardial Damage- CAD, Arrhythmia, Dilated Cardiomyopathy



Heart Failure

Decreased Stroke Volume & Cardiac Output



Neurohormonal Response



1. Activation of Sympathetic System
2. Renin-Angiotensin Aldosterone System
3. Salt & water retention

# ACE inhibitors

- Decrease symptoms and signs of heart failure
- Slows the progression of all grades due to worsening heart failure
- Reduces hospital admissions due to worsening heart failure
- All patients with heart failure due to LVSD (unless contraindicated) should be treated with an ACE I

# ACE 1 Inhibitors

- Several large multicentre trials have shown ACE 1, in NYHA HF 11-1V:
  1. Improve symptoms and exercise tolerance
  2. Decrease risk of death
  3. Decrease disease progression
  4. Decrease hospital admission
- Initiated after renal function and electrolyte status
- Achievement of target dose to maximise effectiveness

# Beta Blockers

- Small doses of Beta Blockers started cautiously and increased very slowly
- Some initial clinical deterioration and little/no increase in exercise capacity
- Progression of heart failure is slowed and a decrease in hospitalisation
- Those already treated with an ACE I and diuretics and/or and who are clinically stable (NYHA class I-3)
- Carvedilol, Bisoprolol and Metoprolol
- Start low dose and titrate up

# Digoxin

- Digoxin used with diuretics can decrease the signs and symptoms of heart failure
- Digoxin does not reduce mortality
- Used in all patients with AF and heart failure
- Use in severely symptomatic (NYHA class 3-4) heart failure who remain symptomatic with diuretics and ACE I or who have had hospital admissions
- Patients treated with diuretics but intolerant of ACE I and A 2 A

# Other Treatments

## Angiotensin 2 receptor antagonists

- Used in those intolerant to ACE I
- Hypotension and renal dysfunction can still occur
- Monitor and titrate as you would ACE I

## Hydralazine and ISDN

- Use in patients treated with a diuretic and/or digoxin but intolerant of an ACE I
- Can increase exercise capacity and reduce mortality

# Other Treatments cont...

## Cholesterol lowering drugs

- Statins can be used in patients with coronary heart disease
- Shown to reduce risk of further coronary events and development of heart failure

## Anticoagulant and antiplatelet therapy

- Advocated in patients with heart disease and arrhythmias to prevent thromboembolism

# Atrial Fibrillation – Rate Control

- Digoxin is ineffective in controlling ventricular rate during acute, paroxysmal episodes, & in cardioversion
- In patients with good LVF, metoprolol, propranolol, atenolol or verapamil & diltiazem are drugs of choice
- In patients with acute/chronic heart failure, amiodarone should be used – limited by s/e, e.g., pulmonary toxicity
- Digoxin effective in persistent AF in combination with with b-blockers & rate-limiting Ca antagonists
- Target heart rates vary with age – 60-90 beats/min at rest; 90-115 during exercise. This requires careful dose titration

# Atrial Fibrillation- Rhythm Control

- Identify & treat all reversible causes of AF before drug treatment for maintenance of sinus rhythm
- In patients with good LVEF and no CAD, flecainide and propafenone can be used; also, sotalol or amiodarone
- Amiodarone maintains sinus rhythm in HF patients; b-blockers in CAD
- Aim to prevent embolism and cardiomyopathy

# AF - Conclusions

- AF is associated with increased risk of morbidity and mortality from CVD, esp. stroke
- Risk of stroke increases with age and presence of other CVD risk factors
- Rate control is preferable alternative for most patients, as lower risk of adverse events and hospitalisation
- Rhythm control option in early AF, but attrition rate is high
- Antithrombotic therapy is essential in all cases