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CARDIOVASCULAR SYSTEM

The Hands–on Guide to Clinical Pharmacology, 3rd Edition. By S Chatu.
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Furosemide
Heparin
Methyldopa
Nicorandil, nitrates (glyceryl trinitrate [GTN], isosorbide dinitrate [ISDN], isosorbide mononitrate [ISMN])
Sildenafil, simvastatin, spironolactone
Tenecteplase
Verapamil
Warfarin

Management guidelines

ANAPHYLACTIC SHOCK

- Give 0.5 mg (0.5 ml of 1:1000) epinephrine intramuscular (IM) (given intravenous [IV] if there is no central pulse or if severely unwell) if any compromise in airway (stridor, tongue swelling), breathing (low oxygen saturations, wheeze) or circulation (hypotensive, pale, clammy).
- Most ideal site to inject IM epinephrine is the middle third of thigh on the anterolateral aspect.
- Give high-flow oxygen through face mask.
- Gain IV access.
- Give 10 mg of IV chlorpheniramine.
- Give 100–200 mg IV hydrocortisone.
- Consider salbutamol nebulizer and IV aminophylline if bronchospasm present.
- Administer IV fluids if required to maintain blood pressure (BP).
- Repeat IM epinephrine every 5 minutes if no improvement, as guided by BP, pulse and respiratory function.
- If still no improvement, consider intubation and mechanical ventilation.
- Follow-up:
  - Suggest a medic alert bracelet naming culprit allergen.
  - Identify allergen with skin prick testing and consider referral to an allergy clinic at a later stage.
  - Self-injected epinephrine may be necessary for the future.

DYSRHYTHMIAS

Bradycardia

- Look for and treat underlying cause (e.g. drugs, hypothyroidism, post MI).
- If pulse rate <40 bpm and patient symptomatic, give IV atropine up to a maximum dose of 3 mg.
- If no response, consider external, percussion or temporary venous pacing until underlying cause corrected or permanent pacemaker inserted.

Atrial fibrillation (AF)

- Look for and treat any underlying cause.
- Antiarrhythmic agents are used to restore sinus rhythm or control ventricular rate.

- Consider anticoagulation with warfarin (aspirin if warfarin contraindicated or inappropriate) to prevent thromboembolic events. The CHAD score can help in making a decision however all those with valvular heart disease should be anticoagulated
- *Paroxysmal AF*:
  - Self-terminating, usually lasts less than 48 hours.
  - If recurrent, consider warfarin and antiarrhythmic drugs (e.g. sotalol, amiodarone).
- *Persistent AF*:
  - Lasts more than 48 hours and can be converted to sinus rhythm either chemically (amiodarone, beta blocker or flecainide) or with synchronized direct current (DC) shock.
  - In cases of synchronized DC shock, administer warfarin for 1 month, then give DC shock under general anaesthetic to revert to sinus rhythm (only if no structural heart lesions are present) and continue warfarin for 1 month thereafter. If haemodynamically unstable, DC cardiovert with IV heparin or LMWH.
- *Permanent AF*:
  - To control the ventricular rate use digoxin, a rate-limiting calcium-channel blocker, beta blocker or amiodarone as monotherapy or in combination.
  - Warfarin for anticoagulation (give aspirin if warfarin is contraindicated or inappropriate) if risk of emboli is high
  - Consider pacemaker or radiofrequency ablation if all else fails.

Atrial flutter

- Look for and treat any underlying cause.
- Treat as for acute AF.
- In chronic atrial flutter, maintain on warfarin to prevent thromboembolic events and antiarrhythmic medication (e.g. sotalol, amiodarone) and consider radiofrequency ablation.

Paroxysmal supraventricular tachycardia (PSVT)

- Most terminate spontaneously, if not perform vagal manoeuvres (e.g. carotid sinus massage if no bruits, Valsalva manoeuvre), which transiently increase atrioventricular (AV) block.
- If this fails, give IV adenosine in incremental doses.
- If this fails, or adenosine is contraindicated, give IV verapamil.
- If the patient is haemodynamically compromised, give synchronized DC shock under sedation or short-acting general anaesthetic (e.g. propofol).
- Other antiarrhythmics that can be tried are beta blockers, amiodarone, flecainide, disopyramide, propafenone after seeking expert advice.
- In recurrent PSVT consider regular antiarrhythmics (commonly used drugs: beta blockers, rate-limiting calcium-channel blockers, amiodarone) or refer for radiofrequency ablation of abnormal foci.

Ventricular fibrillation (VF), pulseless ventricular tachycardia (VT)

- Protocols for the management of VF and pulseless VT are subject to constant updates. Consult current European Resuscitation Council guidelines.

Ventricular tachycardia (VT) with a pulse

- Look for and treat underlying cause and correct electrolyte imbalances.
- Give IV amiodarone or IV lidocaine.
- If this fails, consider other antiarrhythmics after expert advice (i.e. disopyramide, flecainide, procainamide, propafenone) or perform overdrive pacing.
- Proceed to synchronized DC shock if patient is symptomatic, in cases of haemodynamic compromise, or if there is no response to antiarrhythmic drugs.
- Once recovered, consider implantable cardiac defibrillator (ICD) or electrical ablation of abnormal foci or prophylaxis with a regular antiarrhythmic agent.

HEART FAILURE – ACUTE

- Sit patient up to improve oxygenation.
- Give high-flow oxygen through non-rebreathing face mask (caution in chronic obstructive pulmonary disease [COPD]).
- Consider non-invasive ventilation with positive end expiratory pressure (i.e. continuous positive airways pressure [CPAP]) if still hypoxic.
- Give IV furosemide, which initially causes venodilatation, reducing cardiac preload, and then reduces intravascular volume by diuresis.
- Give IV morphine, which relieves dyspnoea, anxiety and also cardiac preload via its venodilatory effect.
- If no improvement, consider IV GTN infusion (only if systolic BP > 100 mmHg).
- In cardiogenic shock (signified by falling BP), consider positive inotropes (dopamine, dobutamine), intra-aortic balloon pump and revascularization (percutaneous coronary intervention [PCI]), coronary artery bypass graft [CABG]) if due to an acute coronary syndrome.

HEART FAILURE – CHRONIC

- Treat any underlying cause (e.g. hypertension, valvular heart disease, ischaemic heart disease [IHD]).
- Reduce salt intake by educating patients about salt intake of common foods and alter modifiable risk factors (e.g. smoking, obesity).
- Loop diuretic (e.g. furosemide, bumetanide) for pulmonary congestion and systemic fluid overload (i.e. lower limb oedema, pleural effusions, ascites); a thiazide diuretic can be added (e.g. bendroflumethiazide or metolazone).
- Regular review and dose adjustment of diuretics required to maintain dry weight and prevent renal impairment.
- Digoxin, loop and thiazide diuretics improve symptoms only.
- All doses should be increased to target dose or maximum tolerated.
- All those with symptomatic heart failure or with asymptomatic reduced left ventricular ejection fraction (LVEF) should be started on an ACE inhibitor (e.g. ramipril).

- Beta blockers added in next, if still symptomatic.
- Aldosterone antagonist added if still symptomatic (spironolactone, eplerenone) to improve symptoms and increase survival.
- Digoxin is used first line if heart failure is associated with AF and added in sinus rhythm if still symptomatic on ACE inhibitor, beta blocker and diuretics.
- Vasodilators hydralazine and oral nitrates can be used in combination if ACE inhibitor and ARB are contraindicated or not tolerated; combination can be added to ACE inhibitor if ARB or aldosterone antagonist not tolerated.
- Start warfarin to prevent thromboembolic events if AF is present, or if there is significant cardiomegaly, left ventricle aneurysm or history of mural thrombus.
- ACE inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, spironolactone, hydralazine and nitrates improve symptoms and survival in heart failure.
- Consider cardiac transplant, biventricular pacing, ICD, revascularization in IHD, valvular surgery, ventricular surgery and left ventricular assist devices (if patient meets criteria).
- Offer annual influenza and pneumococcal vaccine (only required once).
- Add aspirin if IHD also present.
- In advanced heart failure, consider palliative care.

HYPERLIPIDAEMIA

- Advise low-fat diet, substitute chicken and turkey for red meat and encourage fish, fruit, vegetables and fibre.
- Treat any underlying causes of hyperlipidaemia: hypothyroidism, chronic alcohol intake, drugs (e.g. thiazide diuretics, beta blockers).
- Medication only indicated when dietary modification fails.
- Treat for primary prevention of cardiovascular disease (MI, stroke, transient ischaemic attack [TIA], peripheral vascular disease [PVD]) in adults who have a 20% or greater 10-year risk of developing cardiovascular disease (use risk calculators).
- If cholesterol >5.5 mmol/L, start patient on a statin for primary prevention if above criteria met (use fibrate, ezetimibe, or a bile acid resin if statin not tolerated).
- Treat regardless of lipid levels if established cardiovascular disease (IHD, stroke, TIA, PVD) or diabetes present, aiming for total cholesterol of less than 4 mmol/L and low-density lipoprotein (LDL)-cholesterol of less than 2 mmol/L.
- Bile acid resins (e.g. colestyramine), nicotinic acid, ezetimibe and fibrates can also be used to decrease cholesterol levels.
- In *hypertriglyceridaemia*, fibrates (e.g. bezafibrate) are first-line therapy but nicotinic acid can also be used.
- In *mixed hyperlipidaemia* (high cholesterol and high triglycerides), statins can be used in combination with a fibrate, bile acid resin, nicotinic acid or ezetimibe.
- Omacor (omega-3-acid ethyl esters) can be used to treat hypertriglyceridaemia.

HYPERTENSION

- Alter modifiable risk factors (e.g. smoking, obesity, alcohol, salt intake).
- Rule out secondary causes of hypertension (e.g. renal disease, endocrine diseases, drugs, coarctation of the aorta).
- Indications for treatment vary but generally treat if:
  - Systolic BP sustained >160 mmHg, or
  - Diastolic BP sustained >100 mmHg.
- Treat if diastolic BP 90–99 mmHg or systolic BP 140–159 mmHg in the presence of end-organ damage (brain, heart, kidney, retina), diabetes or at high risk of IHD assessed by risk calculators.
- In diabetes and chronic kidney injury, aim for BP <130/80 mmHg.
- The following classes of antihypertensives are used in various combinations and as a general rule if under 55 years old, first line is ACE inhibitor (ARB if ACE inhibitor is contraindicated or not tolerated) and if 55 years or over, and in black patients of any age consider calcium-channel blockers and diuretics:
  1. Thiazide diuretics (e.g. bendroflumethiazide).
  2. Beta blockers (e.g. atenolol).
  3. ACE inhibitors (e.g. captopril).
  4. Calcium-channel blockers (e.g. nifedipine).
  5. ARBs (e.g. losartan).
  6. Alpha blockers (e.g. doxazosin).
  7. Centrally acting agents (e.g. methyldopa, moxonidine).

ISCHAEMIC HEART DISEASE (IHD)

Stable angina

- Alter modifiable risk factors (smoking, hypertension, hyperlipidaemia, diabetes mellitus, obesity, diet, lack of exercise).
- First-line therapy: sublingual GTN spray/tablet for acute attacks.
- Regular aspirin (if allergic or unable to tolerate aspirin, give clopidogrel).
- Maintenance therapy: beta blocker (e.g. atenolol).
- If still symptomatic, add a dihydropyridine calcium-channel blocker or a long-acting oral nitrate (isosorbide mononitrate or isosorbide dinitrate).
- If still symptomatic, give maintenance triple therapy (beta blocker, dihydropyridine calcium-channel blocker and a long-acting nitrate) + GTN for acute attacks.
- *Note*: do not give beta blockers with verapamil and exercise caution with diltiazem due to serious interactions.
- Nicorandil, a potassium-channel activator with vasodilator properties, is being increasingly used in the management of angina.
- Last resort is revascularization with percutaneous coronary intervention (PCI) or coronary bypass surgery.

Unstable angina / non-ST elevation MI / ST elevation MI

- Grouped together as acute coronary syndromes. These conditions are initially controlled medically and then investigated with a view to PCI or coronary bypass surgery.

- Sit the patient up (to ease breathing and reduce venous return to the heart).
- Give high-flow oxygen through non-rebreathing face mask (caution in COPD).
- Attach cardiac monitor and perform 12-lead electrocardiogram (ECG).
- Oral aspirin loading dose 300 mg (antiplatelet effect).
- Give oral clopidogrel loading dose 300 mg (antiplatelet activity).
- If ST elevation MI, needs urgent PCI or thrombolytic therapy if PCI not available.
- Take blood for full blood count (FBC), urea and electrolytes (U&Es), cardiac enzymes, lipids and random glucose.
- If patient is diabetic, commence on insulin sliding scale for at least 24 hours.
- Give subcutaneous (SC) low-molecular-weight heparin (LMWH) or IV heparin (to prevent infarction in acute attack) but not if having PCI.
- For pain relief, give IV morphine with IV antiemetic (e.g. metoclopramide).
- Give IV nitrates (e.g. GTN) if still symptomatic.
- If still symptomatic, start glycoprotein IIb/IIIa receptor antagonist (e.g. tirofiban – antiplatelet activity); usually started if intervention is anticipated, these drugs reduce events during and after PCI.
- If still symptomatic, consider emergency PCI or CABG surgery.
- Give IV beta blocker if not contraindicated and if haemodynamically stable (aim to maintain heart rate of 55–65 bpm to reduce myocardial work load).
- Admit to coronary care unit (CCU).

Post myocardial infarction MI

- Heparin infusion or LMWH (enoxaparin or dalteparin) may be given to maintain vessel patency (usually for 5 days).
- Some centres are using a synthetic factor X inhibitor, fondaparinux, in the treatment of acute coronary syndromes in place of heparin and LMWH.
- If pain persists, IV nitrates (e.g. GTN) and morphine can be given.
- If ST elevation persists, consider repeat thrombolysis or emergency angiogram with PCI or CABG surgery.
- Look for and treat any complications:
  - *Tachydysrhythmias*: antiarrhythmic drugs, DC shock or overdrive pacing.
  - *Bradydysrhythmias*: IV atropine, temporary pacing.
  - *LVF with pulmonary oedema*: IV furosemide followed by long-term ACE inhibitor.
  - *Cardiogenic shock*: IV dobutamine.
  - *Ventricular septal rupture/rupture of papillary muscle*: urgent surgery.
- Prevention of reinfarction:
  - Alter modifiable risk factors (smoking, obesity, hyperlipidaemia, hypertension, diabetes mellitus).
  - Daily aspirin for life, and a beta blocker (e.g. atenolol) for a minimum of 2–3 years.

  - Long-term ACE inhibitor (e.g. ramipril) regardless of left ventricular (LV) function.
  - If patient had a non-ST elevation MI, should continue with clopidogrel for 1 year.
  - Add a statin (e.g. simvastatin).
- Advise no driving for 1 month and no work for 2 months.
- Usually stay in CCU for 5 days.
- ECG stress test on day 5:
  - If satisfactory, follow up in clinic 4–6 weeks later.
  - If positive, or if ischaemic chest pain post MI, consider coronary angiogram and appropriate intervention with surgery or PCI as in- or outpatient.

THROMBOEMBOLISM

Deep vein thrombosis (DVT)

- Give IV or SC LMWH with oral warfarin.
- Alternatively use fondaparinux (synthetic factor X inhibitor) instead of heparin until adequately anticoagulated with warfarin.
- Discontinue heparin/fondaparinux when international normalized ratio (INR) reaches therapeutic range.
- Consider thrombolytic therapy (e.g. tenecteplase) in cases of large thrombi.
- Continue warfarin for a minimum of 3–6 months.
- Look for and treat underlying cause.
- Consider thrombophilia screen if no risk factors for DVT are present.

Pulmonary embolism (PE)

- Perform investigations to help confirm diagnosis (d-dimer, arterial blood gas [ABG], ECG, chest X-ray [CXR], ventilation/perfusion [V/Q] scan, computerized tomography [CT] pulmonary angiogram).
- Give high-flow oxygen through face mask.
- Give a non-steroidal anti-inflammatory drug (NSAID) for pleuritic pain.
- Give an IV heparin loading dose followed by heparin infusion or low-molecular-weight heparin or, alternatively, use fondaparinux.
- Start oral warfarin at the same time as heparin and continue warfarin for 6 months (discontinue heparin when INR reaches therapeutic range).
- Consider thrombolytic therapy (e.g. tenecteplase) if patient is haemodynamically unstable or PE suspected in cardiac arrest.
- Consider vena caval filter in recurrent PE despite adequate anticoagulation.
- Look for and treat any underlying cause.

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Drug types

BETA BLOCKERS

- There are two types of beta receptors: $beta_1$ and $beta_2$.
- $Beta_1$ receptors are found in the heart.
- Most other beta receptors are $beta_2$ receptors and are found in the peripheral vasculature, kidneys, skeletal muscle and airways.

Types of beta blockers

1. *Selective* (blocking $beta_1$ receptors): atenolol, bisoprolol and metoprolol.
2. *Non-selective* (blocking both $beta_1$ and $beta_2$ receptors): nadolol, propranolol and timolol.

Indications

- Main indications:
  - Hypertension.
  - IHD.
  - Cardiac dysrhythmias.
  - Secondary prophylaxis in MI.
  - Heart failure.
- Non-selective beta blockers can further be used in:
  - Thyrotoxicosis (for symptom control).
  - Prophylaxis of migraine.
  - Glaucoma.
  - Anxiety (for prevention of palpitations, tremor and tachycardia).
  - Essential tremor.
  - Primary and secondary prophylaxis of oesophageal variceal bleeding.

Effects

- Beta blockers can cause the following effects:
  - *$Beta_1$ receptor blockade*: decreased force of myocardial contraction and decreased heart rate.
  - *$Beta_2$ receptor blockade in the kidneys*: decreased renin release and hence lowered BP.
  - *$Beta_2$ receptor blockade in skeletal muscle*: tiredness.
  - *$Beta_2$ receptor blockade in the airways*: bronchospasm.
  - *$Beta_2$ receptor blockade in blood vessels*: peripheral vasoconstriction (i.e. cold extremities).
  - Lipid-soluble beta blockers cross the blood–brain barrier and can cause sleep disturbance and nightmares (this also applies to water-soluble beta blockers, but to a lesser extent).

Note

- Selective $beta_1$ blockers may also block $beta_2$ receptors to some extent, especially in high doses.
- Beta blockers can also be either water soluble, which are excreted renally unchanged (atenolol, celiprolol, nadolol, sotalol), or lipid soluble, which are metabolized by the liver prior to excretion (metoprolol, propranolol).

- Some act as partial agonists (i.e. have intrinsic sympathomimetic activity [ISA] properties), such as celiprolol, oxprenolol and pindolol. They can simultaneously block and stimulate beta receptors. This results in less bradycardia and less peripheral vasoconstriction than with other beta blockers.
- Labetalol and carvedilol block both alpha and beta receptors.

CALCIUM-CHANNEL BLOCKERS

Types of calcium-channel blockers:

1. *Dihydropyridines*: amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, isradipine.
2. *Phenylalkalamines*: verapamil.
3. *Benzothiazepines*: diltiazem.

Indications

- Hypertension.
- Angina.
- Supraventricular dysrhythmias (verapamil or diltiazem).

Mechanism of action

- All calcium-channel blockers act on L-type calcium channels at different sites:
  - Myocardium.
  - The conducting system of the heart.
  - Vascular smooth muscle.

Dihydropyridines

- Dihydropyridines act mainly on peripheral and coronary vasculature and are therefore used to treat angina (usually combined with a beta blocker).
- Dihydropyridines can be used alone in the treatment of hypertension or can be safely combined with a beta blocker.
- Dihydropyridines have very few cardiac effects.

Verapamil and diltiazem

- Verapamil and diltiazem act both on the heart and on peripheral blood vessels. They decrease heart rate, force of contraction and have antiarrhythmic properties. They also cause peripheral vasodilatation and dilatation of coronary arteries.
- Verapamil and diltiazem must be used with extreme caution if given with beta blockers, due to hazardous interactions such as asystole and AV-node block.

DIURETICS

Types of diuretics

1. *Thiazides*: bendroflumethiazide, benzthiazide, chlorthalidone, clopamide, cyclopenthiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, metolazone, xipamide.
2. *Loop*: furosemide, bumetanide, torasemide.
3. *Potassium-sparing*: spironolactone, eplerenone, amiloride, triamterene.
4. *Carbonic anhydrase inhibitors*: acetazolamide, dorzolamide.
5. *Osmotic*: mannitol.

Indications

- Hypertension (thiazides).
- Chronic heart failure (loop diuretics, thiazides or in combination).
- Fluid overload in renal or liver disease (loop diuretics, thiazides or in combination).
- Glaucoma (acetazolamide, dorzolamide or mannitol).
- Raised intracranial pressure (mannitol).

Note

- Loop diuretics are the most effective diuretics, followed by thiazides.
- Potassium-sparing diuretics are weak and not normally used on their own. They are usually given with loop diuretics or thiazides to prevent hypokalaemia.
- Loop and thiazide diuretics act synergistically and are effective in the treatment of resistant fluid overload.

Drugs

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

(Captopril, lisinopril, perindopril, ramipril)

Class: Angiotensin-converting enzyme (ACE) inhibitor

Indications

- Hypertension.
- Heart failure.
- Post MI in high-risk patients and if LV dysfunction.
- Diabetic nephropathy to prevent progression.

Mechanism of action

- ACE inhibitors inhibit ACE, leading to decreased synthesis of angiotensin II, a vasoconstrictor, and accumulation of bradykinin, a vasodilator, resulting in a dual antihypertensive effect. The reduction in angiotensin II leads to reduced formation of aldosterone and hence reduced sodium and water retention.
- ACE inhibitors prevent glomerular injury in the kidneys.
- ACE inhibitors are given post MI to reduce myocardial damage and prevent further coronary events as thought to:
    - Prevent atherogenesis and thrombosis in blood vessels.
    - Prevent LV hypertrophy and dysfunction.

Adverse effects

- *Common*: postural hypotension, dry cough, rash.
- *Rare*: hyperkalaemia, worsening of renal function (in those with underlying renal ischaemia or severe heart failure), angioneurotic oedema, haematological toxicity (e.g. neutropenia, agranulocytosis).

Contraindications

- Renal vascular disease (e.g. renal artery stenosis).
- Pregnancy.

Interactions

- *NSAIDs*: these increase the risk of renal impairment.
- *Potassium-sparing diuretics*: concomitant use with an ACE inhibitor increases the risk of hyperkalaemia.

Route of administration

- Oral.

Note

- Microalbuminuria is an early sign of nephropathy in diabetics. ACE inhibitors reduce the risk of further renal deterioration.
- Patients should be advised to take the first dose just before bedtime to prevent first-dose hypotension.
- ACE inhibitors improve exercise tolerance and symptoms in heart failure. They also prolong life expectancy in these patients.

Related drugs

- Cilazapril, fosinopril, imidapril, moexipril, quinapril, trandolapril.

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ADENOSINE

Class: Antiarrhythmic agent

Indications

- Paroxysmal supraventricular tachycardia (PSVT).
- To differentiate between PSVT with aberrant conduction and VT.

Mechanism of action

- Adenosine acts on the sinoatrial (SA) and AV nodes by binding to adenosine receptors in the conducting tissue of the heart and by activating potassium channels. This slows conduction in the heart and causes a decrease in the heart rate.

Adverse effects

- *Common*: chest pain, bronchospasm, flushing, light-headedness, nausea (all transient, usually lasting a few seconds).
- *Rare*: severe bradycardia, transient asystole, hypotension.

Contraindications

- Asthma.
- 2nd or 3rd degree heart block (unless pacemaker *in situ*).
- Sick sinus syndrome.

Interactions

- *Dipyridamole*: enhances adenosine effects.
- *Theophylline*: inhibits the action of adenosine by blocking adenosine receptors.

Route of administration

- IV.

Note

- Prior to administration of adenosine the patient should be warned about the transient adverse effects such as chest pain, as they may cause great distress. This drug is best administrated via a large bore cannulae followed by a rapid saline flush, whilst recording a rhythm strip.
- Adenosine has a very short duration of action (about 8 seconds), therefore adverse effects are mostly short-lived. Adenosine is used in incremental amounts up to the maximum dose until the desired effect is reached.

ALPHA$_1$ BLOCKERS

(Doxazosin, prazosin, indoramine, terazosin, tamsulosin, alfuzosin)

Class: Alpha$_1$ blocker

Indications

- Hypertension.
- Benign prostatic hypertrophy (BPH).

Mechanism of action

- They inhibit alpha$_1$-mediated vasoconstriction, thus causing reduction in peripheral resistance with a subsequent fall in BP.
- Alpha$_1$ blockers relax smooth muscle in the internal urethral sphincter, resulting in increased urinary outflow in BPH.

Adverse effects

- *Common*: postural hypotension, dizziness, headache, gastrointestinal (GI) upset, fatigue.
- *Rare*: impotence, flu-like symptoms, rash.

Contraindications

- Heart failure, postural hypotension, micturition syncope.
- Caution:
  - Hepatic impairment.
  - Pregnancy.
  - Breastfeeding.

Interactions

- *Beta blockers, calcium-channel blockers, diuretics*: alpha$_1$ blockers enhance the hypotensive effect if used concomitantly.

Route of administration

- Oral.

Note

- Long-term therapy with doxazosin lowers plasma LDL, very low-density lipoprotein (VLDL) and triglyceride levels. It also increases high-density lipoprotein (HDL) levels and is therefore considered beneficial in patients with IHD.
- Used third line for hypertension or when other drugs are contraindicated or not tolerated.
- Doxazosin, indoramin, prazosin or terazosin can be used in the treatment of hypertension.
- Alfuzosin and tamsulosin are used in the treatment of BPH.

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AMIODARONE

Class: Antiarrhythmic agent

Indications

- Supraventricular dysrhythmias.
- Ventricular dysrhythmias (including VF and pulseless VT in cardiac arrest).

Mechanism of action

- Amiodarone prolongs the refractory period in all parts of the conducting system of the heart. This decreases the speed of impulses moving through the heart.
- Amiodarone also has some beta-blocking, alpha-blocking and some weak calcium-channel-blocking properties.

Adverse effects

- *Common*: reversible corneal deposits (in long-term use), photosensitive rash.
- *Rare*: hypo- or hyperthyroidism, pulmonary fibrosis, hepatitis, neurological symptoms (e.g. tremor, ataxia), peripheral neuropathy, grey skin colour, metallic taste in the mouth, myopathy.

Contraindications

- Cardiac conduction defects (e.g. sick sinus syndrome).
- Thyroid disease.
- Pregnancy.
- Breastfeeding.
- Iodine allergy (as amiodarone contains iodine).

Interactions

- *Beta blockers*: concomitant use of amiodarone and beta blockers increases the risk of AV block, bradycardia and myocardial depression.
- *Digoxin*: amiodarone increases the plasma concentration of digoxin.
- *Diltiazem*, *verapamil*: concomitant use of amiodarone with diltiazem or verapamil increases the risk of AV block, bradycardia and myocardial depression.
- *Phenytoin*: amiodarone inhibits the metabolism of phenytoin.
- *Warfarin*: amiodarone enhances the effect of warfarin by inhibiting its metabolism.

Route of administration

- Oral, IV.

Note

- Thyroid function and liver function tests (LFTs) should be monitored every 6 months while on treatment with amiodarone.
- Pulmonary function tests should be performed prior to and during treatment with amiodarone in order to detect any developing pulmonary fibrosis.
- Patients should be advised to use sun block to prevent photosensitivity rash.
- Amiodarone has a half-life of about 36 days and therefore interactions can occur long after the drug has been stopped. In the emergency treatment of dysrhythmias an IV loading dose is followed by an infusion.

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AMLODIPINE

Class: Calcium-channel blocker

Indications

- Hypertension.
- Prophylaxis and treatment of angina.

Mechanism of action

- Amlodipine inhibits the influx of calcium into vascular smooth muscle (and, to a lesser extent, into myocardium) by binding to the L-type calcium channels, especially in arterioles. This results in relaxation of vascular smooth muscle with a subsequent decrease in peripheral resistance and BP.
- Amlodipine dilates coronary arteries, which contributes to its antianginal effect.

Adverse effects

- *Common*: headache, flushing, ankle swelling.
- *Rare*: urinary frequency, GI disturbance, mood changes, palpitations, impotence.

Contraindications

- Breastfeeding.
- Cardiogenic shock.
- Advanced aortic stenosis.
- Unstable angina.
- Acute porphyria.

Interactions

- *Antihypertensives*: amlodipine increases the hypotensive effect.

Route of administration

- Oral.

Note

- Amlodipine can safely be used in asthmatics, for whom beta blockers are contraindicated.
- Dihydropyridine calcium-channel blockers have no antiarrhythmic properties, unlike diltiazem and verapamil.

Related drugs

- Other dihydropyridine calcium-channel blockers: felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine.

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ANGIOTENSIN-RECEPTOR BLOCKERS (ARBs)

(Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)

Class: Angiotensin II-receptor blocker

Indications

- Hypertension.
- Diabetic nephropathy in type 2 diabetes mellitus to prevent progression.
- Heart failure (in combination with ACE inhibitor, or if ACE inhibitor intolerant).

Mechanism of action

- ARBs are reversible competitive antagonists at angiotensin II receptors (confusingly known as AT_1 receptors), which are found in vascular smooth muscle and in the adrenal glands. This action blocks the vasoconstrictor effects of angiotensin II, and it reduces aldosterone secretion from the adrenal cortex. These actions in turn result in an antihypertensive effect.
- ARBs do not inhibit breakdown of kinins unlike ACE inhibitors thus are rarely associated with a dry cough and angioneurotic oedema, which can make ACE inhibitors intolerable. See also Mechanism of action of ACE inhibitors.
- When the ARBs block AT_1 receptors the increased levels of angiotensin II result in stimulation of AT_2 receptors. The clinical significance of this is unknown.

Adverse effects

- *Common*: headaches, dizziness, diarrhoea.
- *Rare*: myalgia, vasculitis, hepatitis, taste disturbance, hyperkalaemia, rash, pruritus.

Contraindications

- Breastfeeding.
- Pregnancy.

Interactions

- *ACE inhibitors, ciclosporin, potassium-sparing diuretics*: concomitant use of ARBs with either of these drugs increases the risk of hyperkalaemia.

Route of administration

- Oral.

Note

- Currently only losartan and valsartan can be used to prevent renal failure in type 2 diabetes.
- Usually prescribed in clinical practice when ACE inhibitors are not tolerated or are contraindicated.

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ASPIRIN

Class: Non-steroidal anti-inflammatory drug (NSAID)

Indications

- Acute coronary syndrome, acute ischaemic stroke, PVD.
- Prophylaxis of MI, ischaemic stroke, TIAs in high-risk patients.
- Mild to moderate pain and inflammation.
- In AF to prevent thromboembolic events.

Mechanism of action

- Aspirin irreversibly inhibits the cyclo-oxygenase enzymes COX-1 and COX-2. This leads to the inhibition of prostaglandin (mostly pro-inflammatory) and thromboxane (promotes clotting) synthesis leading to its effects:

1. Decrease in vascular permeability and vasodilatation (anti-inflammatory effect).
2. Decrease in sensitization of pain afferents (analgesic effect).
3. Decrease in the effect of prostaglandins on the hypothalamus (antipyretic effect).

- Platelets contain a high concentration of COX-1, which is necessary for thromboxane A_2 production. Aspirin inhibits this process and hence inhibits platelet aggregation and thrombus formation (antiplatelet effect).

Adverse effects

- *Common*: GI irritation (gastritis, duodenitis, peptic ulcer).
- *Rare*: bronchospasm, rash, thrombocytopenia, renal failure.

Contraindications

- Children under 16 years (as aspirin may cause Reye's syndrome), except when specifically indicated (e.g. juvenile arthritis).
- Active peptic ulcer or GI bleeding.
- Gout (aspirin inhibits uric acid excretion).
- Bleeding disorders (e.g. haemophilia).
- Breastfeeding.
- History of hypersensitivity.
- Intracerebral bleed.
- Uncontrolled hypertension (risk of intracerebral bleed).

Interactions

- *Selective serotonin reuptake inhibitors (SSRIs)*: concomitant use of aspirin and SSRIs increases the risk of GI bleeding.
- *Warfarin*: concomitant use of aspirin and warfarin increases the risk of bleeding.

Route of administration

- Oral, rectal.

Note

- The risk of GI irritation can be reduced by taking aspirin after food or by using the enteric-coated form.
- In high doses, aspirin can lead to salicylate intoxication (dizziness, tinnitus, deafness).

Related drugs

- Clopidogrel, dipyridamole.

ATENOLOL

Class: Beta blocker

Indications

- Hypertension.
- Angina.
- Supraventricular dysrhythmias.
- Secondary prophylaxis of MI.

Mechanism of action

- Atenolol reduces heart rate and force of myocardial contraction by acting on $beta_1$ receptors in the heart. This results in decreased workload of the heart; hence its use in angina.
- Renin production by the kidney is also reduced by atenolol, which contributes to its antihypertensive effect.
- Atenolol decreases the effects of sympathetic activity on the heart with a resulting decrease in conduction and in action potential initiation; hence its use as an antiarrhythmic.

Adverse effects

- *Common*: lethargy (usually ceases after long-term use), bradycardia and AV block, hypotension, cold peripheries.
- *Rare*: bronchospasm, worsened or precipitated heart failure, nightmares, impotence.

Contraindications

- Asthma.
- Uncontrolled heart failure (including cardiogenic shock).
- Cardiac conduction defects (e.g. 2^{nd} and 3^{rd} degree heart block).
- Bradycardia.
- COPD.
- Severe PVD.
- Hypotension.
- Phaeochromocytoma (can use with alpha blocker).

Interactions

- *Diltiazem*: concomitant use of diltiazem and atenolol increases the risk of bradycardia and AV block.
- *Verapamil*: the risk of heart failure, severe hypotension and asystole is increased if atenolol is given with verapamil.

Route of administration

- Oral, IV.

Note

- Atenolol is selective for $beta_1$ receptors, but at high doses it can also block $beta_2$ receptors, thus causing bronchospasm.
- Abrupt withdrawal of atenolol may worsen angina.
- Beta blockers may mask the symptoms of hypoglycaemia caused by oral hypoglycaemics or insulin.
- Bisoprolol, carvedilol or metoprolol can be used in the treatment of chronic heart failure.

Related drugs

- Bisoprolol, carvedilol, celiprolol, esmolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, timolol.

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ATROPINE

Class: Muscarinic antagonist

Indications

- Cardiac arrest (asystole, pulseless electrical activity if rate <60 bpm).
- Bradycardia.
- Organophosphorus poisoning.
- For paralysis of the ciliary muscle (allowing measurement of the refractive error in children).
- Anterior uveitis.

Mechanism of action

- Atropine decreases the activity of the parasympathetic nervous system by blocking the action of acetylcholine on muscarinic receptors. This leads to pupillary dilatation, bronchodilatation, increase in heart rate and decreased secretions from sweat, salivary and bronchial glands.
- Atropine also reduces gut motility and bronchial secretions.

Adverse effects

- *Common*: antimuscarinic effects (e.g. dry mouth, blurred vision, constipation, dilated pupils).
- *Rare*: confusion (especially in the elderly), palpitations, irritation of the eye (when given as eye drops), acute urinary retention.

Contraindications

- BPH.
- Closed-angle glaucoma.
- Paralytic ileus.
- Myasthenia gravis.
- Pyloric stenosis.

Interactions

- *Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and antihistamines*: increased risk of antimuscarinic side-effects.

Route of administration

- IV (bradycardia, cardiac arrest), IM (organophosphorus poisoning), eye drops.

Note

- Atropine can be used to reverse the adverse effects of neostigmine (e.g. excessive bradycardia). In this case it is given IV.
- When used in anterior uveitis, aim of treatment is to prevent complications.
- Occasionally, atropine is given with anaesthetics such as propofol, halothane and suxamethonium to prevent bradycardia and hypotension during general anaesthesia.
- Atropine is also used to decrease salivary and bronchial secretions that are increased during intubation prior to surgery.

BENDROFLUMETHIAZIDE

Class: Thiazide diuretic

Indications

- Hypertension.
- Chronic heart failure.
- Oedema secondary to liver disease, nephrotic syndrome or low-protein diet.
- Prophylaxis of calcium-containing renal stones.

Mechanism of action

- Bendroflumethiazide acts on the proximal part of the distal tubule in the nephron where it inhibits Na^+ and Cl^- reabsorption. This leads to increased excretion of Na^+, Cl^- and water, which stimulates potassium excretion further down in the distal tubule. All these events lead to hypokalaemia, hyponatraemia and a decrease in intravascular volume.
- Reduced intravascular volume causes an initial decrease in cardiac output (hence initial antihypertensive effect), but a reduction in peripheral resistance is responsible for lowering BP in the long term.

Adverse effects

- *Common*: hypokalaemia, hyponatraemia, dehydration, postural hypotension.
- *Rare*: impotence, hyperuricaemia, hyperglycaemia, hyperlipidaemia, hypercalcaemia, thrombocytopenia, photosensitivity, acute pancreatitis.

Contraindications

- Hypokalaemia, hyponatraemia, hypercalcaemia.
- Gout.
- Addison's disease.

Interactions

- *Digoxin*: hypokalaemia caused by bendroflumethiazide potentiates the effects of digoxin.
- *Lithium*: bendroflumethiazide increases the plasma concentration of lithium.

Route of administration

- Oral.

Note

- Low doses of bendroflumethiazide cause minimal biochemical disturbance and are fully effective at lowering BP. Higher doses do not decrease BP any further, but make biochemical adverse effects more likely.
- Prolonged use at high doses may lead to hypokalaemia, which may cause cardiac dysrhythmias (hence potassium levels must be monitored). If high doses are prescribed, it is recommended to combine bendroflumethiazide with either potassium supplements, a potassium-sparing diuretic (e.g. amiloride) or an ACE inhibitor.

Related drugs

- Chlorthalidone, cyclopenthiazide, hydrochlorothiazide, indapamide, metolazone, xipamide.

BEZAFIBRATE

Class: Fibrate

Indications

- Hyperlipidaemia.

Mechanism of action

- Bezafibrate reduces triglyceride levels by stimulating the enzyme lipoprotein lipase, which converts triglycerides into fatty acids and glycerol.
- Bezafibrate also reduces cholesterol levels (to a lesser extent than triglycerides) by reducing cholesterol production in the liver. It decreases circulating LDL levels and also increases the levels of beneficial HDL.

Adverse effects

- *Common*: nausea, abdominal discomfort, headache.
- *Rare*: myositis syndrome (muscle pain, stiffness, weakness), impotence, rash, pruritus, gallstones.

Contraindications

- Hepatic impairment.
- Pregnancy and breastfeeding.
- Nephrotic syndrome.
- Gallbladder disease.
- Primary biliary cirrhosis.

Interactions

- *Statins*: concomitant use of bezafibrate and statins increases the risk of myositis syndrome.
- *Warfarin*: bezafibrate potentiates the anticoagulant effect of warfarin by displacing it from plasma protein binding sites.

Route of administration

- Oral.

Note

- Drug treatment of hyperlipidaemia is recommended when patients fail to respond to dietary measures.
- It has been shown that fibrates are less effective than statins in the prevention of cardiovascular events (e.g. MI, stroke).

Related drugs

- Ciprofibrate, fenofibrate, gemfibrozil.

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CLOPIDOGREL

Class: Antiplatelet drug

Indications

- Prevention of vascular events after ischaemic stroke, after MI and in PVD.
- Acute coronary syndrome.
- Post coronary artery stent (1 year for drug eluted, up to 3 months for bare metal stent).

Mechanism of action

- Clopidogrel irreversibly modifies adenosine diphosphate (ADP) receptors on platelets and thus prevents ADP from binding to them. This prevents activation of glycoprotein GpIIb/IIIa complex and therefore prevents platelet aggregation.
- Platelets exposed to clopidogrel are affected for the rest of their lifespan, which is 8–10 days.

Adverse effects

- *Common*: GI symptoms, rash.
- *Rare*: bleeding (GI tract, intracranial), neutropenia, thrombotic thrombocytopenic purpura, hepatic impairment.

Contraindications

- Active bleeding.
- Breastfeeding.
- Intracranial bleed.

Interactions

- Anticoagulants or *other antiplatelet drugs*: increase the risk of bleeding.
- *NSAIDs:* increase the risk of bleeding.

Route of administration

- Oral.

Note

- Clopidogrel is used when aspirin is contraindicated or not tolerated.
- Clopidogrel can be combined with aspirin in the treatment of acute coronary syndromes for a more effective antiplatelet effect.

Related drugs

- Other antiplatelet drugs: abciximab, aspirin, dipyridamole, eptifibatide, tirofiban.

DIGOXIN

Class: Cardiac glycoside

Indications

- Supraventricular dysrhythmias.
- Chronic heart failure.

Mechanism of action

- Increases the force of myocardial contraction by inhibiting the Na^+/K^+ adenosine triphosphate (ATP) pump in the heart. This increases intracellular Na^+ concentration, which in turn inhibits the Na^+/Ca^{2+} exchanger and hence the amount of calcium pumped out of the cell. These events lead to increased intracellular calcium in myocardial cells, which increases myocardial contraction.
- Digoxin slows the heart rate by increasing vagal activity. It also slows conduction through the AV node (hence its use in dysrhythmias).

Adverse effects

- *Common*: nausea, vomiting, anorexia, diarrhoea, arrhythmias.
- *Rare*: gynaecomastia in chronic use, confusion, hallucinations, yellow vision, thrombocytopenia.

Contraindications

- 2^{nd} or 3^{rd} degree heart block.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- AV accessory pathway, e.g. Wolff–Parkinson–White (WPW) syndrome.
- VT or VF.

Interactions

- *Amiodarone*, *propafenone*, *quinidine*: these antiarrhythmic drugs increase the risk of digoxin toxicity.
- *Diltiazem*, *nicardipine*, *verapamil*: increase the risk of digoxin toxicity.

Route of administration

- Oral, IV (for emergency loading dose).

Note

- In chronic heart failure, digoxin does not reduce mortality but improves symptoms and reduces the frequency of hospital admissions.
- For treatment of dysrhythmias, a loading dose is given IV or orally but this is not required in the treatment of chronic heart failure.
- Digoxin has a narrow therapeutic window and therefore requires therapeutic drug monitoring.
- The risk of digoxin toxicity is greater in hypokalaemia. Patients receiving digoxin and potassium-losing diuretics may therefore require potassium supplements or a potassium-sparing diuretic.
- Hypomagnesaemia, hypercalcaemia and hypothyroidism also increase the risk of digoxin toxicity.
- Digoxin can cause ST depression and T wave changes on the ECG, which do not indicate toxicity.

Related drugs

- Digitoxin.

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DILTIAZEM

Class: Calcium-channel blocker

Indications

- Prophylaxis and treatment of angina.
- Hypertension.
- Paroxysmal supraventricular dysrhythmias (treatment and prophylaxis).
- Rate control in AF and atrial flutter.

Mechanism of action

- Diltiazem inhibits the influx of calcium into vascular smooth muscle and myocardium by binding to the L-type calcium channels. This results in:

1. Relaxation of vascular smooth muscle with subsequent decrease in peripheral resistance and BP.
2. Decreased myocardial contractility.
3. Slowed conduction at the AV node and prolonged refractory period (hence its use as an antiarrhythmic).

- Reduction in afterload, myocardial contractility and heart rate lead to reduced oxygen consumption, thereby relieving angina.

Adverse effects

- *Common*: headache, dizziness, hypotension, bradycardia, ankle swelling, constipation.
- *Rare*: lethargy, rash, AV block.

Contraindications

- Severe bradycardia.
- 2nd and 3rd degree heart block (unless pacemaker).
- Sick sinus syndrome, WPW syndrome, accessory pathways.
- Heart failure.
- Pregnancy and breastfeeding.
- Acute porphyria.

Interactions

- *Antiarrhythmics*: diltiazem may potentiate the myocardial depression caused by other antiarrhythmic drugs.
- *Beta blockers*: these increase the risk of AV block and bradycardia if given with diltiazem.
- *Digoxin*: diltiazem increases the plasma concentration of digoxin.
- *Theophylline*: diltiazem enhances the effects of theophylline.

Route of administration

- Oral.

Note

- Diltiazem can be used in patients with coronary artery spasm (Prinzmetal's angina).
- Diltiazem has the fewest adverse effects of all calcium-channel blockers.
- It has a short half-life due to extensive first-pass metabolism.
- Topical diltiazem can be used to treat chronic anal fissure.

Related drugs

- Verapamil.

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DOBUTAMINE

Class: Inotropic sympathomimetic.

Indications

- Inotropic support in the following:
  - Cardiogenic shock.
  - Cardiac surgery.
  - Septic shock.
- Pharmacological cardiac stress testing.

Mechanism of action

- Dobutamine stimulates beta$_1$ receptors in the heart. This results in increased cardiac contractility.
- Unlike dopamine, dobutamine does not cause release of norepinephrine.

Adverse effects

- *Common*: tachycardia (dobutamine has a lesser tendency to cause tachycardia than dopamine), temporary premature ventricular beats, temporary rise in BP.
- *Rare*: cardiac dysrhythmias, shortness of breath.

Contraindications

- None.

Interactions

- *Beta blockers*: severe hypertension may occur.

Route of administration

- IV.

Note

- Dobutamine does not reduce renal perfusion and for this reason is preferred to beta agonists in the treatment of shock.
- Other vasoconstrictor agents used in the intensive therapy unit (ITU) setting to correct hypotension are the alpha$_1$ receptor agonists: ephedrine, metaraminol, phenylephrine.

Related drugs

- Dopamine, dopexamine.

DOPAMINE

Class: Inotropic sympathomimetic.

Indications

- Cardiogenic shock following MI.
- Hypotension following cardiac surgery.
- Initiation of diuresis in chronic heart failure.

Mechanism of action

- The actions of dopamine are dose dependent.
- In low doses (<5 μg/kg/min), dopamine acts on dopamine receptors resulting in renal, coronary and mesenteric vasodilatation. This improves perfusion in those areas.
- In moderate doses (5–20 μg/kg/min), dopamine increases cardiac contractility and causes tachycardia by acting on cardiac $beta_1$ adrenoceptors.
- In high doses (>20 μg/kg/min), dopamine causes vasoconstriction by acting on alpha adrenoceptors.

Adverse effects

- *Common:*
  - Low doses: nausea, vomiting.
  - Moderate to high doses: tachycardia, ventricular ectopic beats, peripheral vasoconstriction, hypotension or hypertension.

Contraindications

- Untreated tachydysrhythmias.
- Phaeochromocytoma.

Interactions

- *MAOIs*: dopamine can cause a hypertensive crisis if given with MAOIs.

Route of administration

- IV.

Note

- Moderate and high doses of dopamine must be administered through a central venous line.
- BP, heart rate and urine output must be monitored during treatment.
- Dopamine should not be infused into alkaline solutions as this would render it inactive.
- Extravasation of dopamine can cause skin necrosis. If this occurs, phentolamine should be infiltrated into the ischaemic area because this neutralizes the dopamine.

Related drugs

- Dobutamine, dopexamine.

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EPINEPHRINE (ADRENALINE)

Class: Sympathomimetic agent

Indications

- Anaphylaxis.
- Cardiac arrest.
- Prolongation of the effects of local anaesthetics.
- Open-angle glaucoma.
- Severe asthma and croup.
- Endoscopic therapy, e.g. bleeding peptic ulcer.

Mechanism of action

- Epinephrine has various effects due to stimulation of the sympathetic nervous system. It is a potent alpha and beta receptor agonist. It is more $beta_2$ selective, but does not distinguish between $alpha_1$ and $alpha_2$ receptors.
- $Beta_1$ receptor stimulation increases the heart rate and force of myocardial contraction. $Beta_2$ receptor stimulation results in vasodilatation, bronchodilatation and uterine relaxation.
- Alpha receptor stimulation causes vasoconstriction, which prolongs the action of local anaesthetics by preventing their spread from the site of application.
- In anaphylactic shock, epinephrine raises BP and causes bronchodilatation.
- Epinephrine is thought to decrease the production of aqueous humour and increase its outflow from the anterior chamber of the eye, hence its use in glaucoma.
- In asthma and croup, epinephrine reduces bronchial muscle spasm and decreases airway swelling, respectively.

Adverse effects

- *Common*: anxiety, restlessness, tremor, tachycardia, hypertension.
- *Rare*: cardiac dysrhythmias, cerebral haemorrhage, pulmonary oedema (all in overdose).

Contraindications

- Closed-angle glaucoma.

Interactions

- *Beta blockers*: can cause severe hypertension if given with epinephrine.
- *Tricyclic antidepressants*: increase the risk of cardiac dysrhythmias and hypertension if given with epinephrine (local anaesthetics with adrenaline are safe).

Route of administration

- IM (anaphylactic shock), IV (cardiac arrest), SC (with local anaesthetics), inhalation (asthma, croup), eye drops (open-angle glaucoma).

Note

- Epinephrine is frequently administered with local anaesthetics (e.g. lidocaine) except in the fingers, toes and penis where prolonged vasoconstriction may result in gangrene.
- In cardiac arrest, epinephrine can be given through an endotracheal tube if IV access is unobtainable. In this case the dose should be doubled.

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EZETIMIBE

Class: Cholesterol-absorption inhibitor

Indications

- Hypercholesterolaemia.

Mechanism of action

- Reduces cholesterol absorption from the intestine, which leads to reduced cholesterol delivery to the liver. This causes increased hepatic LDL-receptor activity, thereby increasing clearance of plasma LDL cholesterol.
- Ezetimibe is absorbed form the intestine and is transferred to the liver via the portal circulation and is excreted back into the duodenum with bile. This repeated enterohepatic metabolism accounts for its long half-life of about 22 hours.

Adverse effects

- *Common*: GI symptoms, headache.
- *Rare*: myalgia, myopathy, rhabdomyolysis, hepatitis, gallstones, cholecystitis.

Contraindications

- Nil.

Interactions

- *Ciclosporin*: plasma concentration of both drugs is increased.
- *Fibrates*: increased risk of gallstones if used with ezetimibe.

Route of administration

- Oral.

Note

- Usually used in conjunction with a statin due to their additive effect but can be used as monotherapy.
- Ezetimibe also causes a reduction in triglyceride levels.

FUROSEMIDE (FRUSEMIDE)

Class: Loop diuretic

Indications

- Acute and chronic heart failure.
- Fluid overload (i.e. acute or chronic kidney injury, ascites in cirrhosis).
- Hypercalcaemia.

Mechanism of action

- Furosemide inhibits reabsorption of Na^+, K^+ , Cl^-, H^+ and water in the ascending limb of the loop of Henle in the kidneys by inhibiting the $Na^+/K^+/2Cl^-$ pump at this site. This leads to increased salt, water and potassium loss and can lead to side-effects of hyponatraemia, hypokalaemia and hypochloraemia.
- Furosemide further decreases preload by causing venodilatation. This reduces ventricular filling pressures in the heart thereby reducing myocardial work load. This effect occurs before the diuretic response.

Adverse effects

- *Common*: hypovolaemia, hypokalaemia, hyponatraemia, hyperuricaemia and gout.
- *Rare*: bone marrow suppression, GI disturbance, reversible deafness (only in high doses or in patients with renal failure), hypocalcaemia, acute pancreatitis.

Contraindications

- Renal failure with anuria.

Interactions

- *Antibacterials*: furosemide increases the risk of ototoxicity associated with aminoglycosides and vancomycin.
- *Digoxin*: furosemide-induced hypokalaemia enhances the effects of digoxin, thus increasing the risk of digoxin-induced dysrhythmias.
- *Lithium*: furosemide decreases lithium excretion, leading to an increased risk of lithium toxicity.
- *NSAIDs*: concomitant use increases the risk of nephrotoxicity and reduces response of loop diuretics.

Route of administration

- Oral, IM, IV.

Note

- Furosemide causes potassium loss. A potassium-sparing diuretic (e.g. amiloride), potassium supplements or an ACE inhibitor should be prescribed with it.
- Relief of breathlessness in acute pulmonary oedema results from venodilatation and preload reduction before diuresis.
- Loop diuretics are more effective than thiazide diuretics.
- In renal impairment, higher doses of diuretics are required as there is reduced luminal excretion of the drug, reducing its effects.

Related drugs

- Bumetanide, torasemide.

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HEPARIN

Class: Anticoagulant

Indications

- Prophylaxis and treatment of DVT and PE.
- Acute coronary syndrome.
- Acute occlusion of peripheral arteries.
- Extracorporeal circuits (e.g. haemodialysis, cardiopulmonary bypass).

Mechanism of action

- Heparin potentiates the action of antithrombin III, which inactivates thrombin and other clotting factors (especially Xa) involved in the clotting pathway. This inhibits thrombus formation.
- Heparin has an antiplatelet effect by binding to and inhibiting von Willebrand factor.

Adverse effects

- *Common*: haemorrhage.
- *Rare*: osteoporosis or alopecia with long-term use, skin necrosis, rash, anaphylaxis, heparin-induced thrombocytopenia, hyperkalaemia.

Contraindications

- Haemorrhage.
- Haemophilia/thrombocytopenia.
- Active peptic ulceration.
- Following major trauma.
- Recent haemorrhagic stroke or recent surgery.
- Severe hypertension.
- Severe liver disease.
- Renal impairment (caution with LMWH).

Interactions

- *Aspirin and clopidogrel*: both increase the risk of haemorrhage if given with heparin.
- *Glyceryl trinitrate*: a GTN infusion increases the excretion of heparin.

Route of administration

- IV, SC.

Note

- Two types of heparin are available: unfractionated heparin and LMWH. They are both of equal efficacy, but LMWH has a longer duration of action (e.g. dalteparin).
- LMWH is preferred because it can be given SC and avoids the need for activated partial thromboplastin time (APTT) monitoring.
- Heparin-induced thrombocytopenia usually occurs day 5–10 after treatment and is characterized by a reduction in platelet count, thrombosis and a skin reaction. Heparin must be stopped and an alternative anticoagulant used.

Related drugs

- Other LMWHs: bemiparin, dalteparin, enoxaparin, tinzaparin.

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METHYLDOPA

Class: Centrally acting antihypertensive agent

Indications

- Hypertension.

Mechanism of action

- Methyldopa is converted to its active component, alpha-methylnorepinephrine, within adrenergic nerve endings. This compound stimulates alpha$_2$ adrenoceptors of the vasomotor centre in the medulla, causing reduced sympathetic outflow. Subsequently, this leads to vasodilatation and a fall in BP.

Adverse effects

- *Common*: drowsiness, headache, postural hypotension, depression, impotence.
- *Rare*: haemolytic anaemia, diarrhoea, nasal congestion, hepatitis, gynaecomastia.

Contraindications

- Depression.
- Active liver disease.
- Acute porphyria.
- Phaeochromocytoma.

Interactions

- *Anaesthetics*: these enhance the hypotensive effect of methyldopa.
- *Antidepressants*: these enhance the hypotensive effect of methyldopa.
- *Lithium*: concomitant use of methyldopa and lithium may cause neurotoxicity.

Route of administration

- Oral, IV.

Note

- Methyldopa is commonly prescribed for hypertension in pregnancy. It crosses the placenta and appears in breast milk but has no adverse effects on the fetus.
- Treatment with methyldopa may result in a positive direct Coombs test.

Related drugs

- Clonidine, moxonidine.

NICORANDIL

Class: Potassium-channel activator

Indications

- Prevention and treatment of stable angina.

Mechanism of action

- Nicorandil's actions include both nitrate-like effects and activation of ATP-sensitive potassium channels in vascular smooth muscle. This leads to vasodilatation in coronary, arterial and venous systems, which in turn reduces preload, afterload and myocardial oxygen consumption.
- Nicorandil has no significant effects on myocardial contractility.

Adverse effects

- *Common*: headache, nausea, vomiting, dizziness, facial flushing.
- *Rare*: angina, palpitations, GI tract and anal ulceration, myalgia, angioedema, bronchitis, dyspnoea.

Contraindications

- Cardiogenic shock.
- Hypotension.
- LVF.
- Breastfeeding.

Interactions

- *MAOIs*: enhance the hypotensive effect.
- *Sildenafil, tadalafil, vardenafil*: enhance the hypotensive effect.

Route of administration

- Oral.

Note

- Headaches usually diminish with continued use.
- Nicorandil has been shown to reduce the incidence of VTs/PSVTs and myocardial ischaemia in patients already on maximum conventional antianginal therapy. This effect is believed to be due to nicorandil mimicking the natural process of ischaemic preconditioning, whereby the heart's inbuilt mechanism makes it more and more resistant to ischaemic episodes.
- Nicorandil is currently the only potassium-channel activator in use.
- Nicorandil should be considered as a possible cause in patients who present with symptoms of perianal or GI ulceration. They will only respond to treatment withdrawal.

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NITRATES

(Glyceryl trinitrate, isosorbide mononitrate, isosorbide dinitrate)

Class: Organic nitrates

Indications

- Angina and acute coronary syndromes.
- Heart failure (acute LVF, chronic heart failure).
- Malignant hypertension.
- Anal fissure (applied as GTN ointment).

Mechanism of action

- Nitrates are metabolized into nitric oxide within vascular smooth muscle cells. This compound causes relaxation of vascular smooth muscle through activation of guanylyl cyclase. As a result, coronary arteries and systemic veins vasodilate, with ensuing decrease in preload and improved oxygen supply to the myocardium, which reduces LV work load.
- Nitrates also reduce afterload to some extent. This is useful in the treatment of heart failure.

Adverse effects

- *Common*: headache, dizziness, postural hypotension, flushing, tachycardia.

Contraindications

- Hypotension or hypovolaemia.
- Aortic or mitral stenosis.
- Constrictive pericarditis.
- Cardiac tamponade.
- HOCM.
- Closed-angle glaucoma
- Taking sildenafil, tadalafil, or vardenafil.

Interactions

- *Sildenafil, tadalafil, vardenafil*: enhance the hypotensive effect of nitrates.

Route of administration

- Sublingual, skin patch or skin ointment (all for angina), IV (for unstable angina, acute heart failure, malignant hypertension), oral (for angina, heart failure).

Note

- Sublingual GTN or a GTN skin patch can be used prophylactically before exercise to prevent angina.
- Properties of isosorbide dinitrate and isosorbide mononitrate are similar to those of GTN but they can be taken orally and have a longer duration of action.
- Tolerance to long-acting nitrates (ISDN and ISMN) develops after as little as 24 hours of continued administration. Their effects thus become progressively weaker. This can be minimized by allowing drug-free periods of 8 hours.

SILDENAFIL

Class: Phosphodiesterase type 5 (PDE_5) inhibitor

Indications

- Male erectile dysfunction.
- Primary pulmonary hypertension.

Mechanism of action

- Penile erection in a healthy male involves nitric oxide release within the corpus cavernosum in response to sexual stimulation. Nitric oxide increases the levels of cyclic guanosine monophosphate (cGMP) through activation of guanylate cyclase. This leads to relaxation of smooth muscle within the corpus cavernosum and allows influx of blood.
- The role of phosphodiesterase type 5 (PDE_5) is to degrade cGMP within the corpus cavernosum. Sildenafil selectively inhibits PDE_5, leading to increased cGMP resulting in prolonged relaxation of smooth muscle in the penis and maintenance of an erection in response to sexual stimulation.
- Sildenafil leads to vasodilatation of pulmonary blood vessels, hence is used in primary pulmonary hypertension.

Adverse effects

- *Common*: headache, flushing, nasal congestion, dyspepsia.
- *Rare*: cardiovascular events (acute coronary syndromes, arrhythmias), priapism, dizziness, hypersensitivity reactions, visual disturbance.

Contraindications

- Concomitant use of nitrates.
- Hypotension (systolic <90 mmHg).
- Recent stroke.
- MI and unstable angina.
- Hereditary degenerative disorders of the retina.

Interactions

- *Nicorandil*: concomitant use may lead to profound hypotension.
- *Nitrates*: concomitant use may lead to profound hypotension.
- *Ritonavir*: this raises the plasma concentration of sildenafil.

Route of administration

- Oral.

Note

- At recommended doses, sildenafil will not produce an erection without sexual stimulation.
- Important to illicit cause of impotence before prescribing medication, e.g. vascular, endocrine, neurological, psychological or drug induced.
- After taking a dose of sildenafil, the patient has a 4-hour window to engage in sexual intercourse. Other PDE_5 inhibitors have a longer duration of action (16 hours for vardenafil, 3 days for tadalafil).
- If prolonged erection (priapism >4 hours) urgent treatment is required to prevent irreversible damage with penile aspiration of blood, lavage, medical or surgical treatment.

Related drugs

- Tadalafil, vardenafil.

SIMVASTATIN

Class: HMG CoA reductase inhibitor

Indications

- Hypercholesterolaemia.
- Mixed hyperlipidaemia.

Mechanism of action

- Statins mainly target hepatocytes in the liver and reversibly inhibit HMG CoA reductase, the rate-limiting enzyme in cholesterol synthesis by the liver. The liver responds by increasing expression of LDL receptors, which increases LDL uptake from the plasma. These actions reduce plasma LDL cholesterol and therefore total cholesterol.
- Simvastatin causes a small decrease in the plasma concentration of triglycerides.
- Statins also have other non-lipid effects that provide benefit apart from lipid reduction, e.g. improve endothelial function, plaque stabilization, anti-inflammatory effects.

Adverse effects

- *Common*: headache, muscle cramps, flatulence.
- *Rare*: reversible myositis, GI disturbance (diarrhoea, abdominal pain), rash, alopecia, altered LFTs, hepatitis, acute pancreatitis.

Contraindications

- Acute liver disease or unexplained persistent abnormal LFTs.
- Pregnancy and breastfeeding.
- Acute porphyria.

Interactions

- *Ciclosporin, clarithromycin, erythromycin*: increase risk of myositis if given with simvastatin.
- *Fibrates*: increase the risk of myositis if given with simvastatin.
- *Itraconazole and ketoconazole*: increase the risk of myopathy if given with simvastatin.
- *Warfarin*: simvastatin enhances the effect of warfarin.

Route of administration

- Oral.

Note

- Simvastatin has been shown to be effective in reducing cardiovascular events and mortality in patients with known, or at high risk of, cardiovascular disease.
- Simvastatin should only be prescribed if the patient has not responded sufficiently to diet modification and after secondary causes of hyperlipidaemia have been ruled out (e.g. hypothyroidism, chronic alcohol abuse).
- LFTs should be carried out before, and 3 months after, starting therapy and yearly after unless clinically indicated.
- Statins should be taken at night as cholesterol is synthesized mainly during sleep (atorvastatin can be taken at any time).
- The patient should be advised to immediately report unexplained muscle pain, tenderness or weakness.

Related drugs

- Atorvastatin, fluvastatin, pravastatin, rosuvastatin.

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SPIRONOLACTONE

Class: Aldosterone antagonist

Indications

- Chronic heart failure.
- Conn's syndrome.
- Treatment of ascites in cirrhosis.
- Hypertension.

Mechanism of action

- Aldosterone causes sodium and therefore fluid retention and potassium excretion. Spironolactone is a competitive antagonist of aldosterone and acts on the distal tubule in the kidneys to inhibit its effects. This leads to a diuretic action with sodium excretion and potassium retention.
- There are high levels of aldosterone in heart failure thought to cause myocardial fibrosis, endothelial dysfunction and arrhythmias; spironolactone inhibits these processes by acting on the myocardium.

Adverse effects

- *Common*: hyperkalaemia, gynaecomastia, male sexual dysfunction, menstrual irregularities.
- *Rare*: hepatotoxicity, osteomalacia, headache, confusion, rashes.

Contraindications

- Hyperkalaemia.
- Addison's disease.

Interactions

- *ACE inhibitors, ARBs, potassium supplements*: these drugs increase the risk of hyperkalaemia if used concomitantly with spironolactone.

Route of administration

- Oral.

Note

- Monitor renal function and serum potassium during treatment and if hyperkalaemia develops the dose should be halved or treatment stopped.
- Low doses are used in chronic heart failure but in ascites due to cirrhosis higher doses are usually required.

Related drugs

- Eplerenone.

TENECTEPLASE

Class: Fibrinolytic agent

Indications

- Acute myocardial infarction (ST elevation MI).
- Acute PE with haemodynamic compromise.
- Acute ischaemic stroke (only alteplase licensed).

Mechanism of action

- Tenecteplase is a tissue plasminogen activator (tPA).
- It binds to circulating plasminogen in the blood and forms an activator complex that converts plasminogen to plasmin. Plasmin then lyses the fibrin within the thrombus, thus dissolving it.

Adverse effects

- *Common*: bleeding from vascular puncture sites, GI bleed from occult peptic ulcers, nausea, vomiting, hypotension.
- *Rare*: intracerebral haemorrhage, allergic reaction.

Contraindications

- Recent haemorrhage.
- Bleeding disorders.
- Recent trauma or surgery.
- Aortic dissection.
- Severe hepatic impairment.
- Acute pancreatitis.
- Coma.
- Severe hypertension.
- Suspected peptic ulcer.

Interactions

- *Warfarin*: this increases the risk of haemorrhage if given with fibrinolytic agents.

Route of administration

- IV.

Note

- Patients presenting with acute ischaemic stroke should be thrombolysed if certain criteria are met.
- Fresh frozen plasma with tranexamic acid (an antifibrinolytic agent) may be given if treatment results in excessive bleeding.
- Use of thrombolysis in ST elevation MI is decreasing as primary PCI is the preferred treatment and this is more readably accessible.
- Alteplase and streptokinase can be used in PE. Streptokinase can also be used in DVT, acute arterial thromboembolism, thrombosed arteriovenous shunts and central retinal venous or arterial thrombosis.
- Tenecteplase, alteplase or reteplase are preferred over streptokinase if the patient presents within 6 hours of onset of chest pain with evidence of an anterior MI. They are also used if the patient has had streptokinase in the past because of possible antibodies.

Related drugs

- Alteplase (rt-PA), reteplase, streptokinase, urokinase.

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VERAPAMIL

Class: Calcium-channel blocker

Indications

- Hypertension.
- Angina.
- Paroxysmal supraventricular tachycardia.
- Rate control in AF or atrial flutter.

Mechanism of action

- Verapamil inhibits influx of calcium into vascular smooth muscle and myocardium by binding to the L-type calcium channels. This results in:
  1. Relaxation of vascular smooth muscle with subsequent decrease in peripheral resistance and BP.
  2. Decreased myocardial contractility.
  3. Slowed conduction through the AV node and prolonged refractory period (antiarrhythmic properties).
- Angina is relieved by reduction in afterload, heart rate and myocardial contractility, which all reduce myocardial workload.

Adverse effects

- *Common*: constipation, headache, ankle swelling.
- *Rare*: cardiac failure, hypotension, AV-node block.

Contraindications

- Heart failure/cardiogenic shock.
- Hypotension.
- Myocardial conduction defects (e.g. bradycardia, AV-node block, accessory pathway).
- Acute porphyria.

Interactions

- *Amiodarone*: concomitant use of amiodarone and verapamil increases the risk of AV block, bradycardia and myocardial depression.
- *Beta blockers*: if beta blockers are given with, or prior to, verapamil there is an increased risk of AV-node block, which may be complete and result in asystole, heart failure and severe hypotension.
- *Digoxin*: verapamil increases the plasma concentration of digoxin.

Route of administration

- IV (only in paroxysmal tachydysrhythmias), oral.

Note

- Beta blockers are the preferred treatment in unstable angina, as they have been shown to reduce the associated risk of MI. However, if beta blockers are contraindicated or ineffective, verapamil or diltiazem can be used.
- Verapamil and diltiazem should be avoided in heart failure as they can cause marked clinical deterioration due to their negative inotropic effect.

Related drugs

- Diltiazem.

WARFARIN

Class: Oral anticoagulant (vitamin K antagonist)

Indications

- Prevention of thromboembolism (e.g. in AF, prosthetic heart valves).
- Treatment and prevention of DVT and PE.
- Prevention of TIAs and ischaemic stroke in selected patients.

Mechanism of action

- Vitamin K is an essential cofactor for synthesis of clotting factors II, VII, IX and X, and proteins C and S. Warfarin inhibits reduction of vitamin K by inhibiting the enzyme vitamin K epoxide reductase, thereby reducing production of the clotting factors.
- Warfarin takes at least 48–72 hours to achieve its full anticoagulant effect (this reflects the half-life of the clotting factors).

Adverse effects

- *Common*: haemorrhage.
- *Rare*: skin necrosis, liver impairment, alopecia, acute pancreatitis, rash.

Contraindications

- Pregnancy.
- Severe hypertension.
- Active peptic ulcer disease.

Interactions

- *Alcohol, amiodarone, cimetidine, omeprazole, simvastatin*: these increase the anticoagulant effect of warfarin.
- *Aspirin, clopidogrel*: increased risk of haemorrhage.
- *Carbamazepine, rifampicin, spironolactone*: these decrease the anticoagulant effect of warfarin.
- *Combined oral contraceptive (COC) pill*: decreased anticoagulant effect.
- *Note*: warfarin is metabolized by hepatic enzymes that can be induced or inhibited by other drugs, hence a wide range of further interactions exists.

Route of administration

- Oral.

Note

- Therapy should be assessed regularly by measuring INR. The target INR varies with different conditions.
- Warfarin may rarely cause fetal abnormalities if taken during pregnancy (e.g. chondrodysplasia punctata), particularly in the first trimester, and also increases risk of fetal bleeding during delivery hence only used in special circumstances in pregnancy.
- In severe haemorrhage warfarin should be stopped and IV vitamin K with clotting factors II, VII, IX and X should be given. If clotting factors are unavailable, fresh frozen plasma can be used.
- Usually heparin is continued until the therapeutic INR has been achieved with warfarin.
- Over-anticoagulation usually results from a drug interaction with an antibiotic or certain foods.

Related drugs

- Dabigatran, nicoumalone, phenindione.