

Chapter 2

Cardiovascular System

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Chapter 2

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1 ARRHYTHMIAS

1.1 DRUGS FOR ARRHYTHMIAS

The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore, special care should be taken if two or more are used, especially if myocardial function is impaired. Moreover, hypokalaemia enhances the pro-arrhythmic effect of many drugs.

1.1.1 Drug treatment

Life-threatening new-onset atrial fibrillation should undergo emergency electrical cardioversion.

If not life-threatening, pharmacological or electrical cardioversion should be considered. Ventricular rate can be controlled with a standard beta-blocker (not sotalol), rate-limiting calcium channel blocker such as diltiazem or verapamil as monotherapy. If monotherapy fail, a combination of two drugs including a beta-blocker, digoxin, or diltiazem can be used.

Sinus rhythm can be maintained post-cardioversion with a standard beta-blocker. Alternatively, sotalol, flecainide, propafenone, or amiodarone may be considered.

(Avoid Verapamil in patients treated with beta-blockers; increased risk of severe hypotension and asystole)

1.1.2 Cardioversion

Cardioversion is a medical procedure by which an abnormally fast heart rate (tachycardia) or other cardiac arrhythmia is converted to a normal rhythm using electricity or drugs.

If atrial fibrillation present for more than 48 hours, electrical is preferred. Patient should be fully anticoagulated for at least 3 weeks before, and 4 weeks after electrical cardioversion.

1.1.3 Stroke prevention

All patients with atrial fibrillation should be assessed for their risk of stroke and the need for thromboprophylaxis; this needs to be balanced with the patient's risk of bleeding.

Chadsvasc (stroke) risk factors

RISK FACTORS	SCORE
Congestive heart failure	1
Hypertension	1
Age \geq 75	2
Age 65-74	1
Diabetes mellitus	1
Vascular disease	1
Stroke/TIA/thrombo-embolism	2
Sex Female	1

HASBLED (haemorrhage) clinical characteristic

CLINICAL CHARACTERISTIC	SCORE
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Alcohol (\geq 8u / week)	1
Stroke	1
Bleeding	1
Labile INRs (<60%)	1
Elderly (Age >65)	1
Drugs (antiplatelets or NSAIDs)	1

CHA2DS2-VASc score of 0 for men, or 1 for women, constitutes a very low risk of stroke and does not require an antithrombotic for stroke prevention.

1.2 AMIODARONE (HIGH RISK)

(alters sinus rhythm to restore normal heart beat; long half-life, loading doses may be required)

1.2.1 Warning signs

Side effects can occur up to a year after stopping treatment due to long half-life of amiodarone

- Corneal microdeposits
(reversible on withdrawal, very common, rarely interferes with vision, drivers may be dazzled by headlights at night)
- Impaired vision
(optic neuritis or optic neuropathy, stop treatment to prevent blindness)
- Thyroid function
(contains iodine which can cause hypo- or hyperthyroidism, replacement therapy can also be given, may need to stop treatment and initiate carbimazole to treat thyrotoxicosis)
- Hepatotoxicity
(stop if clinical signs of liver disease develop e.g. jaundice)
- Pulmonary toxicity
(pneumonitis suspected if new or progressive shortness of breath or cough, pulmonary fibrosis also possible)
- Neurological effects
(tremor, peripheral neuropathy)
- Phototoxic skin reactions
(burning sensation, erythema, persistent slate grey skin discoloration, patients advised to cover skin and use wide-spectrum sunscreen)

1.2.2 Monitoring

- Thyroid function test
(before treatment and then every 6 months)
- Liver function tests
(before treatment and then every 6 months)
- Serum K⁺
(measured before treatment)
- Chest x-ray
(measured before treatment)
- ECG with IV use
(resuscitation facilities must be available)

1.2.3 Pregnancy

risk of neonatal goitre; use only if no alternative

1.2.4 Breastfeeding

avoid; present in milk in significant amounts; theoretical risk of neonatal hypothyroidism from release of iodine

1.2.5 Drug Interactions

- Can occur several weeks after treatment stopped due to long half life
- Risk of severe bradycardia and heart block when Sofosbuvir with daclatasvir or ledipasvir or simeprevir taken with amiodarone; avoid concomitant use unless other antiarrhythmics cannot be given
- Increased plasma concentration of coumarins, dabigatran, digoxin, flecainide, phenindione, phenytoin
- Increased risk of ventricular arrhythmias when amiodarone given with amisulpride, atomoxetine, chloroquine, citalopram, disopyramide, escitalopram, haloperidol, hydroxychloroquine, levofloxacin, lithium, mizolastine, mefloquine, moxifloxacin, phenothiazines, pimozone, quinine, sulpiride, telithromycin, tolterodine, tricyclics
- Increased risk of bradycardia, AV block and myocardial depression when amiodarone given with beta-blockers, diltiazem, verapamil
- Increased risk of myopathy when amiodarone given with simvastatin

1.3 SOTALOL

(beta-blocker used to reduce heart rate in arrhythmias)

1.3.1 Safety information

Sotalol can prolong the QT interval which can occasionally lead to life threatening ventricular arrhythmias

1.3.2 Monitoring

- ECG and measurement of corrected QT interval
- Serum electrolytes (K⁺, Mg²⁺, Ca²⁺)
(electrolyte disturbance i.e. hypokalaemia, hypomagnesaemia, and hypercalcaemia, should be corrected before starting sotalol and during its use)

2 CARDIAC GLYCOSIDES

2.1 DIGOXIN (HIGH RISK)

(slows down heart rate whilst increasing force of heart contraction; long half-life, loading doses may be required, therapeutic range 1 to 2 mcg/L, dosage forms have different bioavailabilities: IV 100%, Tablet 50-90%, Elixir 75%)

2.1.1 Warning signs

(patients advised to report all to doctor immediately)

- **Cardiac**
(arrhythmias and heart block)
- **Neurological**
(weakness, lethargy, dizziness, headache, mental confusion and psychosis)
- **Gastrointestinal**
(anorexia, nausea, vomiting, diarrhoea, abdominal pain; avoided by dividing larger doses)
- **Visual**
(blurred and/yellow vision)
- **Overdose**
(stop immediately, toxicity difficult to differentiate from clinical deterioration, toxicity likely through range of 1.5 to 3 mcg/L)

2.1.2 Monitoring

- **Serum electrolytes (K^+ , Mg^{2+} , Ca^{2+})**
(toxicity increased by electrolyte disturbance i.e. hypokalaemia, hypomagnesaemia, and hypercalcaemia)
- **Renal function**
(renal excretion of drug; reduce dose in renal impairment to reduce accumulation of metabolite)
- **Plasma-digoxin**
(mainly in renal impairment, blood should be taken at least 6 hours after dose)
- **Heart rate**
(should be maintained above 60 beats/min)

2.1.3 Renal impairment

Reduce dose, monitor plasma concentration in renal impairment

2.1.4 Drug interactions

- **Increased plasma concentration with** alprazolam, amiodarone, ciclosporin, diltiazem, itraconazole, lercanidipine, macrolides, mirabegron, nicardipine, nifedipine, quinine, spironolactone and verapamil

- **Reduced plasma conc with St. John's Wort**
- **Concomitant administration of acetazolamide, amphotericin, loop diuretics or thiazides/related diuretics can cause hypokalaemia that increases the risk of cardiac toxicity & digoxin toxicity**
- **Drugs that impair renal function can affect plasma digoxin conc e.g. NSAIDs, ACE inhibitors**

3 VENOUS THROMBOEMBOLISM

This includes deep-vein thrombosis and pulmonary embolism, and occurs as a result of thrombus formation in a vein.

3.1 PROPHYLAXIS

All patients admitted to hospital should undergo a risk assessment on admission. Patients considered to be at high risk include those anticipated to have a substantial reduction in mobility, those with obesity, malignant disease, history of venous thromboembolism, thrombophilic disorder, or patients over 60 years. High risk patients should be offered pharmacological prophylaxis. Patients should receive either a low molecular weight heparin, unfractionated heparin (if patient in renal failure), or fondaparinux. Prophylaxis should continue until the patient is no longer considered to be at significant risk of venous thromboembolism. Mechanical prophylaxis (e.g. anti-embolism stockings) can be offered to medical patients in whom pharmacological prophylaxis is contra-indicated, and continued until the patient is sufficiently mobile.

3.2 TREATMENT

Initial treatment of deep-vein thrombosis and pulmonary embolism uses a low molecular weight heparin or unfractionated heparin IV infusion. Warfarin is usually started at the same time (the heparin needs to be continued for at least 5 days and until the INR is ≥ 2 for at least 24 hours). Laboratory monitoring for unfractionated heparin, preferably on a daily basis, is essential.

3.3 PREGNANCY

Heparins are used in pregnancy as they do not cross the placenta. Low molecular weight heparins are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Treatment should be stopped at

the onset of labour and advice sought from a specialist

3.4 HAEMORRHAGE

If haemorrhage occurs, withdraw heparin. If rapid reversal of the effects is required, protamine sulfate is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

3.5 HEPARIN

Unfractionated heparin initiates anticoagulation rapidly but has a short duration of action, compared to low molecular weight heparins (LMWH) which have a longer duration of action.

LMWHs (dalteparin, enoxaparin, and tinzaparin) are generally preferred as they are effective and have a lower risk of heparin-induced thrombocytopenia. Due to its long duration of action, dosing is less frequent and monitoring is often not required, therefore they are also more convenient to use.

Unfractionated heparin can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion. However due to its short duration of action, frequent dosing is necessary.

3.5.1 Heparin-induced thrombocytopenia

Usually develops after 5–10 days. Platelet counts should be measured just before treatment, and during treatment if given for longer than 4 days. Signs of heparin-induced thrombocytopenia include a 30% reduction of platelet count, thrombosis, or skin allergy. If thrombocytopenia occurs, heparin should be stopped and an alternative anticoagulant, such as argatroban or danaparoid, given. Ensure platelet counts return to normal range in those who require warfarin.

3.5.2 Hyperkalaemia

Heparins inhibit aldosterone secretion which can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs are more susceptible. In these patients, plasma-potassium concentration should be monitored before and during treatment, particularly if treatment is to be continued for longer than 7 days.

4 STROKE

4.1 TRANSIENT ISCHAEMIC ATTACK

Aspirin 300 mg immediately (if aspirin contraindicated clopidogrel 75 mg immediately). Long-term management should then be offered.

4.2 ISCHAEMIC STROKE

4.2.1 Initial management

Alteplase recommended if it can be administered within 4.5 hours of symptom onset. Treatment with aspirin 300 mg once daily for 14 days should be initiated 24 hours after thrombolysis (clopidogrel 75mg once daily if aspirin contraindicated). Anticoagulants should be considered in patients with atrial fibrillation, after initial aspirin treatment.

4.2.2 Long-term management

Transient ischaemic attack

Modified-release dipyridamole in combination with aspirin; if aspirin contraindicated modified-release dipyridamole alone; if both contraindicated clopidogrel alone

Ischaemic stroke

Clopidogrel is recommended as long-term treatment; if clopidogrel is contra-indicated, modified-release dipyridamole in combination with aspirin. Stroke associated with atrial fibrillation should be reviewed for long-term treatment with warfarin. A statin should be initiated 48 hours after stroke symptom onset. Hypertension should be treated; beta-blockers should not be used unless they are indicated for a co-existing condition. All patients should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight, alcohol intake, and smoking.

5 WARFARIN (HIGH RISK)

Take at least 48 to 72 hours for the anticoagulant effect to develop fully.

5.1 TARGET INR

- 1.1 or below in healthy people
- 2.5 for most indications
- 3.5 for recurrent DVT or PE

5.2 DURATION

- 6 weeks for isolated calf-vein DVT
- 3 months for venous thromboembolism provoked by surgery or other transient risk factor (e.g. combined oral contraceptive use, pregnancy, plaster cast)
- at least 3 months for unprovoked proximal DVT or PE; may be required long-term

5.3 WARNING SIGNS

(report immediately to a doctor)

- Haemorrhage – reversed with phytomenadione (nosebleeds, bleeding from wounds, bruising)
- Deep-vein thrombosis / Pulmonary embolism (pain, swelling, tenderness usually in calf, redness of skin, chest pain, shortness of breath)
- Haemorrhagic stroke (Headaches, confusion)
- Rash, skin necrosis, purple toes
- Diarrhoea and vomiting (may lead to poor absorption)

5.4 MONITORING

- INR: on alternate days in early days of treatment, then at longer intervals up to every 12 weeks
- Liver function
- Renal function
- Full blood count
- Blood pressure
- Thyroid function

5.5 PREGNANCY AND BREASTFEEDING

Teratogenic; avoid in pregnancy especially in the first and third trimesters. Risk of congenital malformations, and placental, foetal, or neonatal haemorrhage.

Significant amounts of warfarin is not present in breast milk and appears safe, but there is an increased risk of haemorrhage, especially in vitamin K deficiency.

5.6 INTERACTIONS

- Anticoagulant effect enhanced by amiodarone, anabolic steroids, azithromycin, cephalosporins, cimetidine, clarithromycin, clopidogrel, high dose corticosteroids, cranberry juice, dipyridamole, disulfiram, entacapone, erythromycin, esomeprazole, fibrates, fluconazole, fluvastatin, glucosamine, itraconazole, methylphenidate, metronidazole, miconazole (including topical), nalidixic acid, norfloxacin, NSAIDs, ofloxacin, omeprazole, propafenone, rosuvastatin, SSRIs, St John's wort, sulphonamides, tamoxifen, testosterone, tetracyclines, thyroid hormones, tramadol, tricyclics, venlafaxine and vitamin E
- Anticoagulant effect reduced by acitretin, azathioprine, carbamazepine, clopidogrel, Griseofulvin, mercaptopurine, phenobarbital, phenytoin, rifamycin's, sucralfate, vitamin K
- Anticoagulant effect may be enhanced and/or reduced by corticosteroids and cholestyramine

5.7 HEPATIC IMPAIRMENT

Use with caution in mild to moderate impairment; avoid in severe impairment.

5.8 RENAL IMPAIRMENT

Use with caution in mild to moderate impairment; in severe impairment monitor INR more frequently.

5.9 OTHER POINTS

- Anticoagulant treatment booklets and alert cards should be issued to all patients
- Take at the same time of day, once a day with a full glass of water, if a dose is missed DO NOT double the dose the next day
- Patient should notify their anticoagulation clinic of any changes to medication, lifestyle or diet
- Brown tablets = 1mg
Blue tablets = 3mg
Pink tablets = 5mg
- Ensure warfarin dose is expressed in milligrams and not the number of tablets

6 ANTIPLATELET DRUGS

Aspirin is only proven to be beneficial in the secondary prevention of cardiovascular disease, not primary; clopidogrel is an alternative. Dipyridamole is licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks.

Prasugrel or Ticagrelor, in combination with aspirin, is licensed in patients with acute coronary syndrome, and is usually given for up to 12 months.

6.1 ASPIRIN

6.1.1 Reye's syndrome (liver and brain damage)

Aspirin-containing preparations should not be given to children under 16 years, due to a risk of Reye's syndrome (vomiting, fatigue, seizures)

6.1.2 Hypersensitivity

Aspirin and other NSAIDs are contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID.

6.2 ORAL ANTIPLATELETS (HIGH RISK)

6.2.1 Warning signs

(report immediately to GP)

- *Chronic gastrointestinal bleeding (severe abdominal pain, vomiting blood, tarry black or blood mixed with stools, feeling out of breath and dizziness)*
- *Haemorrhage (unusual bruising or bleeding)*
- *Hypersensitivity (aspirin) (severe itching or rash)*
- *Heaviness in the centre of chest*
- *Pregnancy (risk of haemorrhage & impaired platelet activity)*
- *Breastfeeding (risk of Reye's syndrome)*

6.2.2 Monitoring

Renal and hepatic function- increased risk of GI bleeds

6.2.1 Other points

- *Discard m/r dipyridamole capsule after 6 weeks*
- *Take all antiplatelets with or just after food (except dipyridamole which should be taken 30-60mins before food)*

6.2.2 Interactions

- *Clopidogrel antiplatelet activity possibly reduced by carbamazepine, cimetidine, ciprofloxacin, erythromycin, fluconazole, fluoxetine, itraconazole, ketoconazole, oxcabazepine, moclobemide, lansoprazole, pantoprazole, reabprazole, etravirine*
- *Clopidogrel antiplatelet effect reduced by omeprazole, esomeprazole*
- *Clopidogrel enhances the anticoagulant effect of coumarins and phenindione (avoid)*
- *Clopidogrel increases plasma concentration of rosuvastatin*
- *Dipyridamole enhances effects of adenosine (toxicity risk), coumarins and phenindione, heparin*
- *An increased risk of bleeding with concomitant use of other antiplatelet drugs, NSAIDs, SSRIs, methotrexate, anticoagulants*

7 HYPERTENSION

High blood pressure increases the risk of stroke, coronary events, heart failure, and renal impairment. Lifestyle changes include smoking cessation, weight reduction, reduction of alcohol and caffeine, reduction of dietary salt, reduction of total and saturated fat, increasing exercise, and increasing fruit and vegetable intake.

7.1 THRESHOLDS

120/80 mmHg is normal blood pressure

Stage 1

clinic blood pressure 140/90 mmHg; or ambulatory daytime or home average 135/85 mmHg; (Treat under 80 years who have target-organ damage, cardiovascular disease, renal disease, diabetes, or 10-year cardiovascular risk (QRISK2) \geq 20%)

Stage 2

clinic blood pressure 160/100 mmHg; or ambulatory daytime or home average 150/95 mmHg (Treat all patients, regardless of age)

Severe hypertension

clinic systolic blood pressure \geq 180 mmHg; or clinic diastolic blood pressure \geq 110 mmHg; (treat promptly – see hypertensive crisis below)

7.2 TARGETS FOR TREATMENT

Over 80

≤ 150/90 mmHg; or
 ≤ 145/85 mmHg ambulatory or home average

Under 80

≤ 140/90 mmHg; or
 ≤ 135/85 mmHg ambulatory or home average

Cardiovascular disease, or diabetes in the presence of kidney, eye, or cerebrovascular disease

≤ 130/80 mmHg

7.3 DRUG TREATMENT (NICE 2107)

Under 55

1. ACE inhibitor; or ARB; or Beta-blocker
2. ACE or ARB *plus* CCB; or ACE or ARB *plus* thiazide-related diuretic; or beta-blocker *plus* CCB
3. ACE or ARB with CCB *plus* thiazide
4. Consider specialist advice

Over 55, and patients of African or Caribbean origin

1. CCB; or thiazide-related diuretic (e.g. chlortalidone or indapamide)
2. CCB or thiazide *plus* an ACE or ARB (ARB *plus* CCB preferred in African or Caribbean family origin)
3. Same as under 55
4. Same as under 55

7.4 REDUCING CARDIOVASCULAR RISK

Use of aspirin in primary prevention of cardiovascular events, is of unproven benefit. However, primary prevention with a statin is recommended in individuals with a high risk of developing cardiovascular disease.

7.5 DIABETES AND RENAL DISEASE

Use of an ACE or ARB regardless of blood pressure is recommended to minimise the risk of renal deterioration; use with caution in renal impairment (risk of hyperkalaemia)

7.6 HYPERTENSION AND PREGNANCY

Labetalol and methyldopa are considered safe for use in pregnancy. In uncomplicated chronic hypertension, a target blood pressure of <150/100 mmHg is recommended.

7.7 HYPERTENSIVE CRISIS

Hypertensive emergency is defined as severe hypertension with acute damage to the target organs. Prompt treatment with IV antihypertensive therapy is generally required. Over the first few minutes or within 2 hours, blood pressure should be reduced by 20–25%.

Hypertensive urgency is severe hypertension acute target-organ damage. Blood pressure should be reduced gradually over 24–48 hours with oral antihypertensive therapy, such as labetalol or amlodipine.

7.8 ANTIHYPERTENSIVES (HIGH RISK)

7.8.1 Warning signs

(report immediately to GP)

- Water retention
- Heaviness in the centre of chest triggered by effort or emotion
- Depression
- Extreme tiredness, thirst or excessive urination
- Irregular heartbeat, muscle weakness, nausea
- Pain or tightness in legs while exercising that disappears at rest
- Dizziness, light-headedness on standing, blurred vision (postural hypotension)

7.8.2 Monitoring

- Blood pressure
- Heart rate
- Renal function
- Serum electrolytes

7.8.3 Interactions

- Diltiazem, verapamil, amlodipine, ranolazine and high dose statins can increase risk of myopathy. Recommended maximum concomitant daily dose of simvastatin 20mg
- Increased plasma concentration of ivabradine, aliskerin, calcium channel blockers when given with grapefruit juice

7.8.4 Other points

- Prevent postural hypotension in the morning by sitting and standing up slowly
- Drink adequate volume of fluid daily
- Avoid soluble OTC preparations e.g. analgesics due to high sodium
- Maintain same brand of diltiazem & nifedipine

7.9 DRUGS AFFECTING THE RENIN-ANGIOTENSIN SYSTEM

7.9.1 Initiation under specialist supervision

Careful clinical monitoring in those with severe heart failure or in those:

- receiving multiple or high-dose diuretic therapy (e.g. more than 80 mg of furosemide daily or its equivalent);
- receiving concomitant angiotensin-II receptor antagonist or aliskiren;
- with hypovolaemia;
- with hyponatraemia (plasma-sodium concentration below 130 mmol/litre);
- with hypotension (systolic blood pressure below 90 mmHg);
- with unstable heart failure;
- receiving high-dose vasodilator therapy;
- known renovascular disease.

7.9.2 Renal effects

ACE inhibitors best avoided in patients with known or suspected renovascular disease due to risks of hyperkalaemia. If used under specialist supervision, renal function should be monitored regularly. Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.

7.9.3 Cautions

New onset cough

Indicates bradykinin build-up

Anaphylactoid reactions

To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; they should also be withheld before desensitisation with wasp or bee venom.

Concomitant diuretics

ACE inhibitors can cause a very rapid fall in blood pressure, treatment should therefore be initiated with very low doses. If the dose of diuretic is greater than 80 mg furosemide or equivalent, the ACE inhibitor should be initiated under close supervision.

Hepatic effects

If jaundice or marked elevations of hepatic enzymes occur during treatment then the ACE inhibitor should be discontinued—risk of hepatic necrosis.

Concomitant use of drugs affecting the renin-angiotensin system

Combination therapy with two drugs affecting the renin-angiotensin system (ACE and ARB) is not recommended due to an increased risk of hyperkalaemia, hypotension, and renal impairment. Patients with diabetic nephropathy are particularly susceptible.

7.10 BETA-ADRENOCEPTOR BLOCKING DRUGS

Beta blockers with intrinsic sympathomimetic activity tend to cause less bradycardia and may also cause less coldness of the extremities (e.g. oxprenolol, pindolol). Atenolol, and sotalol are the most water-soluble; they are less likely to enter the brain, and may therefore cause less sleep disturbance and nightmares. Beta-blockers can affect carbohydrate metabolism, causing hypoglycaemia or hyperglycaemia in patients with or without diabetes. They also mask the symptoms of a hypo in diabetic patients.

Bronchospasm

Beta-blockers, including those considered to be cardioselective, should usually be avoided in patients with a history of asthma or bronchospasm. However, when there is no alternative, a cardioselective beta-blocker (atenolol, bisoprolol, metoprolol, nebivolol) can be given to these patients with caution and under specialist supervision.

Bradycardia

Excessive bradycardia can occur with IV injection; symptoms include light headedness, dizziness, syncope, and may be countered with IV atropine sulfate.

Verapamil and beta-blockers

Should not be given due to a risk of hypotension and asystole.

Labetalol - Liver damage

Monitor liver function due to risk of severe hepatocellular damage; associated with both short-term and long-term treatment. If hepatotoxicity confirmed, discontinue permanently.

7.11 CALCIUM CHANNEL BLOCKERS

Verapamil and diltiazem are non-dihydropyridine calcium channel blockers and exert their effect on cardiac muscle. Dihydropyridine CCBs (amlodipine, felodipine, lacidipine, lercanidipine, and nifedipine) cause relaxation of peripheral blood vessels.

Verapamil and diltiazem should be avoided in heart failure because they may further depress cardiac function and cause clinically significant deterioration.

Nifedipine

Different versions of m/r preparations may not have the same clinical effect. To avoid confusion between these different formulations, prescribers should specify the brand to be dispensed. Modified-release formulations may not be suitable for dose titration in hepatic disease.

Dose form not appropriate for use in hepatic impairment, or where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, inflammatory bowel disease, or ileostomy after proctocolectomy. Dose reduction may be required in severe liver disease.

7.12 HYPOTENSION AND SHOCK

Shock is a medical emergency associated with a high mortality. The use of sympathomimetic inotropes and vasoconstrictors should be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

Vasoconstrictor sympathomimetics

Noradrenaline/norepinephrine, and phenylephrine are examples. The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney.

Phenylephrine has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure

Adrenaline/epinephrine

Used in CPR for cardiac arrest; IV administration with extreme care by specialist.

8 HEART FAILURE

An ACE inhibitor together with a beta-blocker, form the basis of treatment for all patients with heart failure due to left ventricular systolic dysfunction. An aldosterone antagonist (spironolactone, eplerenone) can be added to an ACE inhibitor and a beta-blocker in patients who continue to remain symptomatic. Digoxin is reserved for patients with worsening or severe heart failure despite the above treatment. Patients with fluid overload should also receive either a loop or a thiazide diuretic (with salt or fluid restriction where appropriate).

If an ARB is used as an adjunct to ACE, there is an increased risk of hyperkalaemia, hypotension, and renal impairment.

NOTE: Potassium sparing diuretics (aldosterone antagonists) can cause severe hyperkalaemia with ACE and ARBs; potassium supplements should be avoided.

9 HYPERLIPIDAEMIA

9.1 RISK CALCULATORS

QRISK[®]2: 10-year risk (over 10% warrants treatment)

JBS3: lifetime risk of cardiovascular event

9.2 PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

Fibrates, nicotinic acid, bile acid sequestrants, and omega-3 fatty acid compounds are not recommended for primary or secondary prevention.

Primary prevention

Individuals at high risk of developing cardiovascular disease include those who have diabetes mellitus, hypertension, smoking habit, chronic kidney disease, familial hypercholesterolaemia, and those aged ≥ 85.

All patients at high risk should make lifestyle modifications to diet, exercise, weight management, alcohol consumption, and smoking cessation. Offer a statin as first-line drug treatment combined with diet and lifestyle measures, if lifestyle modifications are inappropriate or ineffective.

Secondary prevention

Statin should be offered to all patients, including the elderly, with cardiovascular disease. Treatment must be combined with advice on diet and lifestyle measures (as above).

9.3 CHOLESTEROL TESTS

Total cholesterol, HDL-cholesterol, and non-HDL cholesterol concentrations should be checked before treatment, and 3 months after starting treatment:

- Total Cholesterol: ≤ 5 mmol/L
- Non-HDL Cholesterol: ≤ 4 mmol/L
- LDL-Cholesterol: ≤ 3 mmol/L
- HDL-Cholesterol: ≥ 1 mmol/L

9.4 HYPERCHOLESTEROLAEMIA, HYPERTRIGLYCERIDAEMIA, AND FAMILIAL HYPERCHOLESTEROLAEMIA

A statin is also the drug of first choice for treatment, severe hyperlipidaemia, if not controlled with a statin an additional lipid-regulating drug such as ezetimibe may be required. Fenofibrates and nicotinic acid may also be used to treat resistant hyperlipidaemia.

9.5 STATINS

Muscle effects

The risk of myopathy, myositis, and rhabdomyolysis associated with statin use is rare. Muscle toxicity is most likely at higher doses, and in certain patients. Patients at increased risk of muscle toxicity, include those with a personal or family history of muscular disorders, previous history of muscular toxicity, a high alcohol intake, renal impairment, hypothyroidism, and in the elderly.

A combination of a statin with a fibrate or nicotinic acid carries an increased risk of myopathy; a statin and gemfibrozil should be avoided. Fusidic acid should be avoided; temporarily discontinue statin and restart 7 days after last dose); drugs that increase the plasma-statin concentration, include macrolide antibiotics, imidazole and triazole antifungals, and ciclosporin.

Close monitoring of liver function and, if muscular symptoms occur, of creatine kinase is necessary. If severe muscular symptoms or raised creatine kinase occur during treatment, treatment should be discontinued. The statin should be reintroduced at a lower dose and the patient monitored closely; an alternative statin may be prescribed if not tolerated.

Interstitial lung disease

Very rare risk; If patients develop symptoms such as dyspnoea, cough, and weight loss, they should seek medical attention.

Hypothyroidism

Correcting hypothyroidism before lipid-regulating treatment may resolve the lipid abnormality; untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.

Monitoring

Statins can alter liver function tests, and rarely cause hepatitis and jaundice. Liver enzymes should be measured before treatment, and repeated within 3 months and at 12 months of starting treatment.

Statins can cause hyperglycaemia, therefore patients at high risk of diabetes should have blood sugar levels checked before starting statin treatment, and then repeated after 3 months.

10 STABLE ANGINA

Acute attacks of stable angina should be managed with sublingual glyceryl trinitrate; sublingual glyceryl trinitrate can be taken immediately before performing activities known to bring on an attack. If attacks occur more than twice a week, regular drug therapy is required.

Patients with stable angina should be given a beta-blocker or a calcium-channel blocker. Addition of a long-acting nitrate, ivabradine, nicorandil, or ranolazine can be considered.

11 ACUTE CORONARY SYNDROMES (ACS)

11.1 INITIAL MANAGEMENT OF UNSTABLE ANGINA, NSTEMI AND STEMI

Unstable angina and NSTEMI are caused by partial blockage of a blood vessel. Patients with unstable angina have no evidence of myocardial necrosis, whereas in NSTEMI, myocardial necrosis (less significant than with STEMI) will be evident.

STEMI is caused by complete blockage of a blood vessel; this causes irreversible necrosis of the heart muscle leading to complications.

- Aspirin – to limit clot size and allow blood flow
- Morphine – relieve pain and anxiety
- Metoclopramide – to relieve nausea from morphine
- Oxygen – to ease laboured breathing
- Nitrate – vasodilator to ease blood flow

- LMWH – anticoagulant to prevent clot growth

11.1.1 Additional acute management of unstable angina, NSTEMI

Glycoprotein inhibitors – prevent coronary clot

11.1.2 Additional acute management of STEMI

Coronary interventions with PCI or CABG

1. Percutaneous Intervention: Angioplasty plus stent
2. Coronary artery bypass graft: replacing damaged vessel with one from another part of the body

Fibrinolytics are an alternative to PCI; they stimulate plasmin production which breaks down clot.

11.2 LONG-TERM MANAGEMENT ACS

Most patients will require standard angina treatment to prevent recurrence of symptoms.

MI patients should be discharged with the following:

- Dual-antiplatelet for up to 12 months (Aspirin PLUS clopidogrel, or prasugrel, or ticagrelor); thereafter aspirin indefinitely
- Beta-blocker, reviewed after 12 months
- ACE inhibitor; continued indefinitely
- Statin; secondary prevention of CV event

11.3 NITRATES

Potent coronary vasodilators, useful in angina.

Tolerance

Developing tolerance reduces therapeutic effects of nitrates. A nitrate free period of 4 to 12 hours each day usually maintains effectiveness. Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily unless small doses are used; modified-release formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance.

11.4 FIBRINOLYTICS

Fibrinolytics are an alternative to PCI; they stimulate plasmin production degrades thrombi ('clot-busters')

Bleeding

Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (e.g. tranexamic acid); rarely further embolism occurs.

Hypotension

Hypotension can also occur and can usually be controlled by elevating the patient's legs, or by

reducing the rate of infusion or stopping it temporarily.

12 OEDEMA

Loop, thiazide and potassium sparing diuretics (aldosterone antagonists) have a role in relieving oedema due to chronic heart failure. Loop diuretics are also used in pulmonary oedema due to left ventricular failure. Thiazides are also used in lower doses to reduce blood pressure.

12.1 ELDERLY

Initiate on low dose to minimise the risk of adverse effects, then adjust according to renal function. Diuretics should not be used long-term for simple gravitational oedema (this usually responds to increased movement, and support stockings).

12.2 POTASSIUM LOSS

Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia is greater with thiazides than with loop diuretics.

Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides. The use of potassium-sparing diuretics avoids the need to take potassium supplements.

In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy; diuretics can also increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias. Spironolactone, a potassium-sparing diuretic, is chosen for oedema arising from cirrhosis of the liver.

Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension.

12.3 URINARY RETENTION

If there is an enlarged prostate, urinary retention can occur; adequate urinary output should be established before initiating treatment

12.4 DIABETES AND GOUT

Loop and thiazide-related diuretics can exacerbate diabetes and gout.

12.5 DIURETICS (HIGH RISK)

12.5.1 Warning signs

(report immediately to GP)

- Heaviness in the centre of chest
- Water retention
- Depression
- Extreme tiredness, thirst or excessive urination
- Irregular heartbeat, muscle weakness, nausea
- Gout
- Persistent light-headedness and dizziness

12.5.2 Monitoring

- Blood pressure
- Serum electrolytes (Na⁺, K⁺)
- Weight (as a measure of water loss)

12.5.3 Other points

- Prevent postural hypotension in the morning by sitting and standing up slowly
- Drink adequate volume of fluid daily
- Avoid potassium supplements and preparations when taking potassium sparing diuretics (aldosterone antagonists)

12.5.4 Interactions

- Enhanced hypotensive effect when diuretics given with ACE inhibitors, alpha-blockers, angiotensin-II receptor antagonists
- Increased risk of severe hyperkalaemia when potassium-sparing diuretics or aldosterone antagonists given with ACE inhibitors, angiotensin-II receptor antagonists, ciclosporin, potassium salts, tacrolimus
- Hypokalaemia caused by acetazolamide, loop diuretics, thiazides or thiazide-related diuretics increases risk of ventricular arrhythmias with amisulpride, atomoxetine, pimozide, sotalol
- Hypokalaemia caused by diuretics increases the risk of cardiac toxicity with cardiac glycosides
- Plasma concentration of eplerenone increased by clarithromycin (avoid), itraconazole
- Plasma concentration of eplerenone reduced by carbamazepine, phenobarbital, phenytoin, rifampicin (avoid), St. John's Wort
- Increased risk of ototoxicity when loop diuretics given with aminoglycosides, polymyxins, vancomycin