Cardiovascular drugs

Antianginal drugs

The three main types of angina are:

- s*table angina* (angina of effort), where atherosclerosis restricts blood flow in the coronary vessels; attacks are usually caused by exertion and relieved by rest
- *unstable angina* (acute coronary insufficiency), which is considered to be an intermediate stage between stable angina and myocardial infarction
- *Prinzmetal angina* (variant angina), caused by coronary vasospasm, in which attacks occur at rest.

Management depends on the type of angina and may include drug treatment, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

Stable angina

Drugs are used both for the relief of acute pain and for prophylaxis to reduce further attacks; they include organic nitrates, beta-adrenoceptor antagonists (beta-blockers), and calcium-channel blockers.

NITRATES

Organic nitrates have a vasodilating effect; they are sometimes used alone, especially in elderly patients with infrequent symptoms. Tolerance leading to reduced antianginal effect is often seen in patients taking prolonged-action nitrate formulations. Evidence suggests that patients should have a 'nitrate-free' interval to prevent the development of tolerance. Adverse effects such as flushing, headache, and postural hypotension may limit nitrate therapy but tolerance to these effects also soon develops. The short-acting sublingual formulation of **glyceryl trinitrate** is used both for prevention of angina before exercise or other stress and for rapid treatment of chest pain. A sublingual tablet of **isosorbide dinitrate** is more stable in storage than glyceryl trinitrate and is useful in patients who require nitrates infrequently; it has a slower onset of action, but effects persist for several hours.

BETA-BLOCKERS

Beta-adrenoceptor antagonists (beta-blockers), such as **atenolol** , block beta-adrenergic receptors in the heart, and thereby decrease heart rate and myocardial contractility and oxygen consumption, particularly during exercise. Beta-blockers are first-line therapy for patients with effort-induced chronic stable angina; they improve exercise tolerance, relieve symptoms, reduce the severity and frequency of angina attacks, and increase the anginal threshold.

Beta-blockers should be withdrawn gradually to avoid precipitating an anginal attack; they should not be used in patients with underlying coronary vasospasm (Prinzmetal angina).

Beta-blockers may precipitate asthma and should not be used in patients with asthma or a history of obstructive airways disease. Some, including atenolol, have less effect on $beta_2$ (bronchial) receptors and are therefore relatively cardioselective. Although they have less effect on airways resistance they are not free of this effect and should be avoided.

Beta-blockers slow the heart and may induce myocardial depression, rarely precipitating heart failure. They should not be given to patients who have incipient ventricular failure, second- or third-degree atrioventricular block, or peripheral vascular disease.

Beta-blockers should be used with caution in diabetes since they may mask the symptoms of hypoglycaemia, such as rapid heart rate. Beta-blockers enhance the hypoglycaemic effect of insulin and may precipitate hypoglycaemia.

CALCIUM-CHANNEL BLOCKERS

A calcium-channel blocker, such as **verapamil,** is used as an alternative to a beta-blocker to treat stable angina. Calcium-channel blockers interfere with the inward movement of calcium ions through the slow channels in heart and vascular smooth muscle cell membranes, leading to relaxation of vascular smooth muscle. Myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed and coronary or systemic vascular tone may be diminished. Calcium-channel blockers are used to improve exercise tolerance in patients with chronic stable angina due to coronary atherosclerosis or with abnormally small coronary arteries and limited vasodilator reserve.

Calcium-channel blockers can also be used in patients with unstable angina with a vasospastic origin, such as Prinzmetal angina, and in patients in whom alterations in cardiac tone may influence the angina threshold.

Unstable angina

Unstable angina requires prompt aggressive treatment to prevent progression to myocardial infarction.

Initial treatment is with acetylsalicylic acid to inhibit platelet aggregation, followed by heparin. Nitrates and beta-blockers are given to relieve ischaemia; if beta-blockers are contraindicated, verapamil is an alternative, provided left ventricular function is adequate.

Prinzmetal angina

Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

Atenolol

Atenolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives

Tablets , atenolol 50 mg, 100 mg

Injection (Solution for injection), atenolol 500 micrograms/ml, 10-ml ampoule [not included on WHO Model List]

Uses:

angina and myocardial infarction; arrhythmias (section 12.2); hypertension (section 12.3); migraine prophylaxis (section 7.2)

Contraindications:

asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker)

Precautions:

avoid abrupt withdrawal in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment (Appendix 4); diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)); myasthenia gravis; **interactions:** Appendix 1

Dosage:

Angina, *by mouth,* **ADULT** 50 mg once daily, increased if necessary to 50 mg twice daily *or* 100 mg once daily

Myocardial infarction (early intervention within 12 hours), *by intravenous injection* over 5 minutes, **ADULT** 5 mg, then *by mouth* 50 mg after 15 minutes, followed by 50 mg after 12 hours, then 100 mg daily

Adverse effects:

gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal)

Glyceryl trinitrate

Sublingual tablets , glyceryl trinitrate 500 micrograms

Note. Glyceryl trinitrate tablets are unstable. They should therefore be dispensed in glass or stainless steel containers, and closed with a foil-lined cap which contains no wadding. No more than 100 tablets should be dispensed at one time, and any unused tablets should be discarded 8 weeks after opening the container

Uses:

prophylaxis and treatment of angina

Contraindications:

hypersensitivity to nitrates; hypotension; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma

Precautions:

severe hepatic or renal impairment; hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; **interactions:** Appendix 1

Dosage:

Angina, *sublingually,* **ADULT** 0.5–1 mg, repeated as required

Adverse effects:

throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported)

Isosorbide dinitrate

Isosorbide dinitrate is a representative nitrate vasodilator. Various drugs can serve as alternatives

Sublingual tablets , isosorbide dinitrate 5 mg

Sustained-release (prolonged-release) tablets or capsules , isosorbide dinitrate 20 mg, 40 mg [not included on WHO Model List]

Uses:

prophylaxis and treatment of angina; heart failure (section 12.4)

Contraindications:

hypersensitivity to nitrates; hypotension; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma

Precautions:

severe hepatic or renal impairment; hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; **interactions:** Appendix 1

Tolerance. Patients taking isosorbide dinitrate for the long-term management of angina may often develop tolerance to the antianginal effect; this can be avoided by giving the second of 2 daily doses of longer-acting oral presentations after an 8-hour rather than a 12-hour interval, thus ensuring a nitrate-free interval each day

Dosage:

Angina (acute attack), *sublingually,* **ADULT** 5–10 mg, repeated as required

Angina prophylaxis, *by mouth,* **ADULT** 30–120 mg daily in divided doses (see advice on Tolerance above)

Adverse effects:

throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported)

Verapamil hydrochloride

Tablets, verapamil hydrochloride 40 mg, 80 mg

Note. Sustained-release (prolonged-release) tablets are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation

Uses:

angina, including stable, unstable, and Prinzmetal; arrhythmias (section 12.2)

Contraindications:

hypotension, bradycardia, second- and third-degree atrioventricular block, sinoatrial block, sick sinus syndrome; cardiogenic shock; history of heart failure or significantly impaired left ventricular function (even if controlled by therapy); atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome; porphyria

Precautions:

first-degree atrioventricular block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment (Appendix 5); children (specialist advice only); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice; **interactions:** Appendix 1

Dosage:

Angina, *by mouth,* **ADULT** 80–120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal angina)

Adverse effects:

constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; rarely allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; with high doses, hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect)

Antiarrhythmic drugs

Treatment of arrhythmias requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment.

Antiarrhythmic drugs must be used cautiously since most drugs that are effective in treating arrhythmias can provoke them in some circumstances; this arrhythmogenic effect is often enhanced by hypokalaemia. When antiarrhythmic drugs are used in combination, their cumulative negative inotropic effects may be significant, particularly if myocardial function is impaired.

Atrial fibrillation

The increased ventricular rate in atrial fibrillation can be controlled with a **beta-adrenoceptor antagonist** (beta-blocker) or **verapamil** . **Digoxin** is often effective for controlling the rate at rest; it is also appropriate if atrial fibrillation is accompanied by congestive heart failure. Intravenous digoxin is occasionally required if the ventricular rate needs rapid control. If adequate control at rest or during exercise cannot be achieved readily verapamil may be introduced with digoxin, but it should be used with caution if ventricular function is impaired. Anticoagulants are indicated especially in valvular or myocardial disease, and in the elderly. **Warfarin** is preferred to acetylsalicylic acid in preventing emboli. If atrial fibrillation began within the previous 48 hours and there does not appear to be a danger of thromboembolism, antiarrhythmic drugs, such as **procainamide** or **quinidine** , may be used to terminate the fibrillation or to maintain sinus rhythm after cardioversion.

Atrial flutter

Digoxin will sometimes slow the ventricular rate at rest. Reversion to sinus rhythm is best achieved by direct current electrical shock. If the arrhythmia is long-standing, treatment with an anticoagulant should be considered before cardioversion to prevent emboli. Intravenous **verapamil** reduces ventricular fibrillation during paroxysmal (sudden onset and intermittent) attacks of atrial flutter. An initial intravenous dose may be followed by oral treatment; hypotension may occur with high doses. It should not be used for tachyarrhythmias where the QRS complex is wide unless a

supraventricular origin has been established beyond doubt. If the flutter cannot be restored to sinus rhythm, antiarrhythmics such as **quinidine** can be used.

Paroxysmal supraventricular tachycardia

In most patients this remits spontaneously or can revert to sinus rhythm by reflex vagal stimulation. Failing this, intravenous injection of a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective. Verapamil and a beta-blocker should **never** be administered concomitantly because of the risk of hypotension and asystole.

Ventricular tachycardia

Very rapid ventricular fibrillation causes profound circulatory collapse and must be treated immediately with direct current shock. In more stable patients intravenous **lidocaine** or **procainamide** may be used. After sinus rhythm is restored, drug therapy to prevent recurrence of ventricular tachycardia should be considered; a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective.

Torsades de pointes is a special form of ventricular tachycardia associated with prolongation of the QT interval. Initial treatment with intravenous infusion of **magnesium sulfate** (usual dose 2 g over 10–15 minutes, repeated once if necessary) together with temporary pacing is usually effective; alternatively, isoprenaline infusion may be given with extreme caution until pacing can be instituted. **Isoprenaline** is an inotropic sympathomimetic; it increases the heart rate and therefore shortens the QT interval, but given alone it may induce arrhythmias.

Bradyarrhythmias

Sinus bradycardia (less than 50 beats/minute) associated with acute myocardial infarction may be treated with atropine. Temporary pacing may be required in unresponsive patients. Drugs are of limited value for increasing the sinus rate long term in the presence of intrinsic sinus node disease and permanent pacing is usually required.

Cardiac arrest

In cardiac arrest, **epinephrine** (adrenaline) is given by intravenous injection in a dose of 1 mg (10 ml of 1 in 10 000 solution) as part of the procedure for cardiopulmonary resuscitation.

Atenolol

Atenolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives

Tablets , atenolol 50 mg, 100 mg

Uses:

arrhythmias; angina (section 12.1); hypertension (section 12.3); migraine prophylaxis (section 7.2)

Contraindications:

asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker)

Precautions:

avoid abrupt withdrawal especially in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment (Appendix 4); diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)); myasthenia gravis; **interactions:** Appendix 1

Dosage:

Arrhythmias, *by mouth,* **ADULT** 50 mg once daily, increased if necessary to 50 mg twice daily *or* 100 mg once daily

Adverse effects:

gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal)

Digoxin

Tablets , digoxin 62.5 micrograms, 250 micrograms

Oral solution , digoxin 50 micrograms/ml

Injection (Solution for injection), digoxin 250 micrograms/ml, 2-ml ampoule

Uses:

supraventricular arrhythmias, particularly atrial fibrillation; heart failure (section 12.4)

Contraindications:

hypertrophic obstructive cardiomyopathy (unless also atrial fibrillation and heart failure); Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation; intermittent complete heart block; second-degree atrioventricular block

Precautions:

recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; elderly (reduce dose); renal impairment (Appendix 4); avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias); pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Atrial fibrillation, *by mouth* , **ADULT** 1–1.5 mg in divided doses over 24 hours for rapid digitalization *or* 250 micrograms 1–2 times daily if digitalization less urgent; maintenance 62.5–500 micrograms daily (higher dose may be divided), according to renal function and heart rate response; usual range 125–250 micrograms daily (lower dose more appropriate in elderly)

Emergency control of atrial fibrillation, *by intravenous infusion* over at least 2 hours, **ADULT** 0.75–1 mg

Note. Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks

Adverse effects:

usually associated with excessive dosage and include anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias, heart block; rarely rash, intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported

Epinephrine (adrenaline)

Injection (Solution for injection), epinephrine hydrochloride 100 micrograms/ml (1 in 10 000), 10-ml ampoule

Uses:

cardiac arrest; anaphylaxis (section 3.1)

Precautions:

heart disease, hypertension, arrhythmias, cerebrovascular disease; hyperthyroidism, diabetes mellitus; angle-closure glaucoma; second stage of labour; **interactions:** Appendix 1

Dosage:

Caution: different dilutions of epinephrine injection are used for different routes of administration

Cardiac arrest, *by intravenous injection* through a central line using epinephrine injection 1 in 10 000 (100 micrograms/ml), **ADULT** 1 mg (10 ml), repeated at 3-minute intervals if necessary

Note. If central line not in place, same dose is given via peripheral vein, then flushed through with at least 20 ml sodium chloride 0.9% injection (to expedite entry into circulation)

Adverse effects:

anxiety, tremor, tachycardia, headache, cold extremities; nausea, vomiting, sweating, weakness, dizziness, hyperglycaemia also reported; in overdosage arrhythmias, cerebral haemorrhage, pulmonary oedema

Isoprenaline

Isoprenaline is a complementary antiarrhythmic for use in rare disorders or in exceptional circumstances

Injection (Solution for injection), isoprenaline hydrochloride 20 micrograms/ml, 10-ml ampoule

Uses:

severe bradycardia, unresponsive to atropine; short-term emergency treatment of heart block; ventricular arrhythmias secondary to atrioventricular nodal block

Precautions:

ischaemic heart disease, diabetes mellitus or hyperthyroidism; **interactions:** Appendix 1

Dosage:

Cardiac disorders, *by slow intravenous injection,* **ADULT** 20–60 micrograms (1–3 ml of solution containing 20 micrograms/ml); subsequent doses adjusted according to ventricular rate

Bradycardia, *by intravenous infusion,* **ADULT** 1–4 micrograms/minute

Heart block (acute Stokes-Adams attack), *by intravenous infusion,* **ADULT** 4–8 micrograms/minute

Dilution and administration. According to manufacturer's directions

Adverse effects:

arrhythmias, hypotension, sweating, tremor, headache, palpitations, tachycardia, nervousness, excitability, insomnia

Lidocaine hydrochloride

Injection (Solution for injection), lidocaine hydrochloride 20 mg/ml, 5-ml ampoule

Uses:

ventricular arrhythmias (especially after myocardial infarction); local anaesthesia (section 1.2)

Contraindications:

sino-atrial disorder, any grade of atrioventricular block or any other type of conduction disturbances, severe myocardial depression, acute porphyria or hypovolaemia

Precautions:

lower dosage in congestive heart failure, bradycardia, hepatic impairment (Appendix 5), marked hypoxia, severe respiratory depression, following cardiac surgery and in elderly; pregnancy (Appendix 2), breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Ventricular arrhythmias, *by intravenous injection,* **ADULT** , loading dose of 50–100 mg (*or* 1–1.5 mg/kg) at a rate of 25–50 mg/minute, followed immediately by *intravenous infusion* of 1–4 mg/minute, with ECG monitoring of all patients (reduce infusion dose if required for longer than 24 hours)

IMPORTANT. Following intravenous injection lidocaine has a short duration of action (of 15–20 minutes). If it cannot be given *by intravenous infusion* immediately, the initial *intravenous injection* of 50–100 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

Adverse effects:

dizziness, paraesthesia, drowsiness, confusion, apnoea, respiratory depression, coma, seizures, and convulsions, hypotension, arrhythmias, heart block, cardiovascular collapse and bradycardia (may lead to cardiac arrest); nystagmus often an early sign of lidocaine overdosage

Procainamide hydrochloride

Procainamide hydrochloride is a representative antiarrhythmic drug. Various drugs can serve as alternatives

Procainamide hydrochloride is also a complementary drug for use when drugs in the core list are known to be ineffective or inappropriate for a given patient

Tablets , procainamide hydrochloride 250 mg, 500 mg [not included on WHO Model List]

Injection (Solution for injection), procainamide hydrochloride 100 mg/ml, 10-ml ampoule

Uses:

severe ventricular arrhythmias, especially those resistant to lidocaine or those appearing after myocardial infarction; atrial tachycardia, atrial fibrillation; maintenance of sinus rhythm after cardioversion of atrial fibrillation

Contraindications:

asymptomatic ventricular premature contractions, torsades de pointes, systemic lupus erythematosus, heart block, heart failure, hypotension

Precautions:

elderly, renal and hepatic impairment (Appendices 4 and 5), asthma, myasthenia gravis, pregnancy; breastfeeding (Appendix 3); use only under specialist supervision; **interactions:** Appendix 1

Dosage:

Ventricular arrhythmias, *by mouth* , **adult** up to 50 mg/kg daily in divided doses every 3–6 hours, preferably controlled by monitoring plasma-procainamide concentration (therapeutic concentration usually within range 3–10 micrograms/ml)

Atrial arrhythmias, higher doses may be required

Ventricular arrhythmias, *by slow intravenous injection,* **ADULT** 100 mg at rate not exceeding 50 mg/minute, with ECG monitoring; may be repeated at 5-minute intervals until arrhythmia controlled; maximum 1 g

Ventricular arrhythmias, *by intravenous infusion,* **ADULT** 500–600 mg over 25–30 minutes with ECG monitoring, reduced to maintenance dose of 2–6 mg/minute; if further treatment by mouth required, allow interval of 3–4 hours after infusion

Adverse effects:

nausea, vomiting, diarrhoea, anorexia, rashes, pruritus, urticaria, flushing, fever, myocardial depression, heart failure, angioedema, depression, dizziness, psychosis; blood disorders include leukopenia, haemolytic anaemia and agranulocytosis after prolonged treatment; lupus erythematosus-like syndrome; high plasma procainamide concentration may impair cardiac conduction

Quinidine sulfate

Quinidine is a representative antiarrhythmic drug. Various drugs can serve as alternatives

Quinidine sulfate is also a complementary antiarrhythmic drug for use when drugs in the core list cannot be made available

Tablets, quinidine sulfate 200 mg

Note. Quinidine sulfate 200 mg = quinidine bisulfate 250 mg

Uses:

suppression of supraventricular arrhythmias and ventricular arrhythmias; maintenance of sinus rhythm after cardioversion of atrial fibrillation

Contraindications:

complete heart block

Precautions:

partial heart block; extreme care in uncompensated heart failure, myocarditis, severe myocardial damage; myasthenia gravis; acute infections or fever (symptoms may mask hypersensitivity reaction to quinidine); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Initial test dose of 200 mg to detect hypersensitivity to quinidine

Arrhythmias, *by mouth,* **ADULT** 200–400 mg 3–4 times daily; increased if necessary in supraventricular tachycardia to 600 mg every 2–4 hours (maximum 3–4 g daily); frequent ECG monitoring required

Adverse effects:

hypersensitivity reactions, nausea, vomiting, diarrhoea, rashes, anaphylaxis, purpura, pruritus, urticaria, fever, thrombocytopenia, agranulocytosis after prolonged treatment, psychosis, angioedema, hepatotoxicity, respiratory difficulties; cardiac effects include myocardial depression, heart failure, ventricular arrhythmias and hypotension; cinchonism including tinnitus, impaired hearing, vertigo, headache, visual disturbances, abdominal pain, and confusion; lupus erythematosus-like syndrome

Verapamil hydrochloride

Tablets, verapamil hydrochloride 40 mg, 80 mg

Note. Sustained-release (prolonged-release) tablets are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation

Injection (Solution for injection), verapamil hydrochloride 2.5 mg/ml, 2-ml ampoule

Uses:

supraventricular arrhythmias; angina (section 12.1)

Contraindications:

hypotension, bradycardia, second- and third-degree atrioventricular block, sinoatrial block, sick sinus syndrome; cardiogenic shock; history of heart failure or significantly impaired left ventricular function (even if controlled by therapy); atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome; porphyria

Precautions:

first-degree atrioventricular block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment (Appendix 5); children (specialist advice only); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1

Verapamil and beta-blockers. Both verapamil and beta-blockers have cardiodepressant activity, and their use together may lead to bradycardia, heart block and left ventricular failure, particularly in patients with myocardial insufficiency. Treatment with beta-blockers should be discontinued at least 24 hours before intravenous administration of verapamil

Dosage:

Supraventricular arrhythmias, *by mouth,* **ADULT** 40–120 mg 3 times daily

Supraventricular arrhythmias, *by intravenous injection,* **ADULT** 5–10 mg over 2 minutes (preferably with ECG monitoring); **ELDERLY** 5–10 mg over 3 minutes; in paroxysmal tachyarrhythmias, further 5 mg may be given after 5–10 minutes if required

Adverse effects:

constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; rarely allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; with high doses, hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect)

Antihypertensive drugs

Management of hypertension

Treatment of hypertension should be integrated into an overall programme to manage factors that increase the risk of cardiovascular events (such as stroke and myocardial infarction). Treatment is ofttten life-long. Hypertension was formerly classified as mild, moderate or severe, but a grading system is now preferred. Grade 1 hypertension is defined as 140–159 mmHg systolic blood pressure and 90–99 mmHg diastolic blood pressure, Grade 2 hypertension 160–179 mmHg systolic and 100–109 mmHg diastolic and Grade 3 hypertension more than 180 mmHg systolic and more than 110 mmHg diastolic. The goal of treatment is to obtain the maximum tolerated reduction in blood pressure.

Lifestyle changes should be introduced for all patients; they include weight reduction, reduction in alcohol intake, reduction of dietary sodium, stopping tobacco smoking, and reduction in saturated fat intake. The patient should eat a healthy nutritious diet including adequate fruit and vegetables and should exercise regularly. These measures alone may be sufficient in mild hypertension, but patients with moderate to severe hypertension will also require specific antihypertensive therapy.

Drug treatment of hypertension

Three classes of drug are used for first-line treatment of hypertension: thiazide diuretics, beta-adrenoceptor antagonists (beta-blockers), and angiotensin-converting enzyme (ACE) inhibitors. Calcium-channel blockers are considered first-line in specific populations only e.g. Africans or the elderly. Other classes of drugs may be used in certain situations.

Thiazide diuretics, such as **hydrochlorothiazide** (see also section 16.1), have been used as first-line antihypertensive therapy, and are particularly indicated in the elderly. They have few adverse effects in low doses, but in large doses they may cause a variety of unwanted metabolic effects (principally potassium depletion), reduced glucose tolerance, ventricular ectopic beats and impotence; they should be avoided in gout. These effects can be reduced by keeping the dose as low as possible; higher doses do not produce an increased reduction in blood pressure. Thiazides are inexpensive and, when used in combination, can enhance the effectiveness of many other classes of antihypertensive drug.

Beta-adrenoceptor antagonists (beta-blockers) such as **atenolol** are effective in all grades of hypertension, and are particularly useful in angina and following myocardial infarction; they should be avoided in asthma, chronic obstructive pulmonary disease, and heart block.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) such as **enalapril** are effective and well tolerated by most patients. They can be used in heart failure, left ventricular dysfunction and diabetic nephropathy, but should be avoided in renovascular disease and in pregnancy. The most common adverse affect is a dry persistent cough.

Dihydropyridine calcium-channel blockers such as **nifedipine** are useful for isolated systolic hypertension, in populations unresponsive to other antihypertensives (e.g. Africans) and in the elderly when thiazides cannot be used. Short-acting formulations

of nifedipine should be **avoided** as they may evoke reflex tachycardia and cause large variations in blood pressure.

Drugs acting on the central nervous system are also effective antihypertensive drugs. In particular, **methyldopa** is effective in the treatment of hypertension in pregnancy.

A single antihypertensive drug is often not adequate and other antihypertensive drugs are usually added in a stepwise manner until blood pressure is controlled.

Hypertensive emergencies

In situations where immediate reduction of blood pressure is essential and treatment by mouth is not possible, intravenous infusion of **sodium nitroprusside** is effective. Over-rapid reduction in blood pressure is hazardous and can lead to reduced organ perfusion and cerebral infarction.

Hypertension in pregnancy

This is defined as a sustained diastolic blood pressure of 90 mmHg or more. Drug therapy for chronic hypertension during pregnancy remains controversial. If diastolic blood pressure is greater than 95 mmHg, **methyldopa** is the safest drug. Beta-blockers should be used with caution in early pregnancy, since they may retard fetal growth; they are effective and safe in the third trimester. ACE inhibitors are contraindicated in pregnancy since they may damage fetal and neonatal blood pressure control and renal function. Women who are taking these drugs and become pregnant should have their antihypertensive therapy changed immediately.

Pre-eclampsia and eclampsia . If pre-eclampsia or severe hypertension occurs beyond the 36th week of pregnancy, delivery is the treatment of choice. For acute severe hypertension in pre-eclampsia or eclampsia, intravenous **hydralazine** can be used. **Magnesium sulfate** (section 22.1) is the treatment of choice to prevent eclamptic convulsions in eclampsia and severe pre-eclampsia.

Atenolol

Atenolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives

Tablets, atenolol 50 mg, 100 mg

Uses:

hypertension; angina (section 12.1); arrhythmias (section 12.2); migraine prophylaxis (section 7.2)

Contraindications:

asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- or

third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker)

Precautions:

avoid abrupt withdrawal especially in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment (Appendix 4); diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)); myasthenia gravis; **interactions:** Appendix 1

Dosage:

Hypertension, *by mouth,* **ADULT** 50 mg once daily (higher doses rarely necessary)

Adverse effects:

gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal)

Enalapril

Enalapril is a representative angiotensin-converting enzyme inhibitor. Various drugs can serve as alternatives

Tablets, enalapril 2.5 mg

Uses:

hypertension; heart failure (section 12.4)

Contraindications:

hypersensitivity to ACE inhibitors (including angioedema); renovascular disease; pregnancy (Appendix 2)

Precautions:

use with diuretics; hypotension with first doses, especially in patients on diuretics, on a low-sodium diet, on dialysis, if dehydrated, or with heart failure; peripheral vascular disease or generalized atherosclerosis (risk of clinically silent renovascular disease); use with great care in severe or symptomatic aortic stenosis; monitor renal function before and during treatment; renal impairment (reduce dose, see also Appendix 4); liver impairment (Appendix 5); possibly increased risk of agranulocytosis in collagen

vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); breastfeeding (Appendix 3); **interactions:** Appendix 1

Use with diuretics.	Risk of very rapid falls in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. High-dose diuretic therapy (furosemide dose greater than 80 mg) should be discontinued, or dose significantly reduced, at least 24 hours before starting enalapril (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic cannot be stopped, medical supervision advised for at least 2 hours after administration or until blood pressure stable
Anaphylactoid reactions.	Avoid enalapril during dialysis with high-flux polyacrilonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom

Dosage:

Hypertension *by mouth* , initially 5 mg once daily; if used in addition to diuretic, in elderly patients, or in renal impairment, initially 2.5 mg daily; usual maintenance dose 10–20 mg once daily; in severe hypertension may be increased to maximum 40 mg once daily

Adverse effects:

dizziness, headache; less commonly, nausea, diarrhoea, hypotension (severe in rare cases), dry cough, fatigue, asthenia, muscle cramps, rash and renal impairment; rarely, vomiting, dyspepsia, abdominal pain, constipation, glossitis, stomatitis, ileus, anorexia, pancreatitis, liver damage, chest pain, palpitations, arrhythmias, angioedema, bronchospasm, rhinorrhoea, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness or insomnia, pruritus, urticaria, alopecia, sweating, flushing, impotence, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus, taste disturbance, tinnitus, blurred vision; electrolyte disturbances and hypersensitivity-like reactions (including fever, myalgia, arthralgia, eosinophilia, and photosensitivity) reported

Hydralazine hydrochloride

Tablets, hydralazine hydrochloride 25 mg, 50 mg

Injection, (Powder for solution for injection), hydralazine hydrochloride, 20-mg ampoule

Uses:

in combination therapy in moderate to severe hypertension, hypertensive crises; hypertension associated with pregnancy (including pre-eclampsia or eclampsia); heart failure (section 12.4)

Contraindications:

idiopathic systemic lupus erythematosus, severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction, cor pulmonale, dissecting aortic aneurysm, porphyria

Precautions:

hepatic impairment (Appendix 5); renal impairment (reduce dose, Appendix 4); coronary artery disease (may provoke angina, avoid after myocardial infarction until stabilized); cerebrovascular disease; check acetylator status before increasing dose above 100 mg daily; test for antinuclear factor and for proteinuria every 6 months; pregnancy (Appendix 2); breastfeeding (Appendix 3); occasionally over-rapid blood pressure reduction even with low parenteral doses; **interactions:** Appendix 1

Dosage:

Hypertension, *by mouth* , **ADULT** 25 mg twice daily, increased if necessary to maximum 50 mg twice daily

Hypertensive crises (including during pregnancy), *by slow intravenous injection,* **ADULT** 5–10 mg diluted with 10 ml sodium chloride 0.9%; if necessary may be repeated after 20–30 minutes

Hypertensive crises (including during pregnancy), *by intravenous infusion,* **ADULT** initially 200–300 micrograms/minute; maintenance usually 50–150 micrograms/minute

Reconstitution and administration. According to manufacturer's directions

Adverse effects:

tachycardia, palpitations, postural hypotension; fluid retention; gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhoea, rarely constipation; dizziness, flushing, headache; abnormal liver function, jaundice; systemic lupus erythematosus-like syndrome, particularly in women and slow acetylators; nasal congestion, agitation, anxiety, polyneuritis, peripheral neuritis, rash, fever, paraesthesia, arthralgia, myalgia, increased lacrimation, dyspnoea; raised plasma creatinine, proteinuria, haematuria; blood disorders including haemolytic anaemia, leukopenia, thrombocytopenia

Hydrochlorothiazide

Hydrochlorothiazide is a representative thiazide diuretic. Various drugs can serve as alternatives

Tablets, hydrochlorothiazide 25 mg

Uses:

alone in mild hypertension, and in combination with other drugs in moderate to severe hypertension; heart failure (section 12.4); oedema (section 16.1)

Contraindications:

severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease

Precautions:

renal and hepatic impairment (Appendices 4 and 5); pregnancy and breastfeeding (Appendices 2 and 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; **interactions:** Appendix 1

Dosage:

Hypertension, *by mouth* , **ADULT** 12.5–25 mg daily; **ELDERLY** initially 12.5 mg daily

Adverse effects:

fluid and electrolyte imbalance leading to dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias; hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible); blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis; acute renal failure; hypersensitivity reactions (pneumonitis, pulmonary oedema, severe skin reactions)

Methyldopa

Tablets , methyldopa 250 mg

Uses:

hypertension in pregnancy

Contraindications:

depression; active liver disease; phaeochromocytoma, porphyria

Precautions:

history of hepatic impairment (Appendix 5); renal impairment (Appendix 4); blood counts and liver-function tests advised; history of depression; positive direct Coomb test in up to 20% of patients (affects blood cross-matching); interference with laboratory tests; pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

Skilled tasks. May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Hypertension in pregnancy, *by mouth,* **ADULT** initially 250 mg 2–3 times daily; if necessary, gradually increased at intervals of 2 or more days, maximum 3 g daily

Adverse effects:

tend to be transient and reversible, including sedation, dizziness, lightheadedness, postural hypotension, weakness, fatigue, headache, fluid retention and oedema, sexual dysfunction; impaired concentration and memory, depression, mild psychosis, disturbed sleep and nightmares; drug fever, influenza-like syndrome; nausea, vomiting, constipation, diarrhoea, dry mouth, stomatitis, sialadenitis; liver function impairment, hepatitis, jaundice, rarely fatal hepatic necrosis; bone-marrow depression, haemolytic anaemia, leukopenia, thrombocytopenia, eosinophilia; parkinsonism; rash (including toxic epidermal necrolysis); nasal congestion; black or sore tongue; bradycardia, exacerbation of angina; myalgia, arthralgia, paraesthesia, Bell palsy; pancreatitis; hypersensitivity reactions including lupus erythematosus-like syndrome, myocarditis, pericarditis; gynaecomastia, hyperprolactinaemia, amenorrhoea; urine darkens on standing

Nifedipine

Nifedipine is a representative dihydropyridine calcium-channel blocker. Various drugs can serve as alternatives

Sustained-release tablets (Modified-release tablets), nifedipine 10 mg

Note. Sustained-release (prolonged-release) tablets are available for once daily administration. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation

Uses:

hypertension

Contraindications:

cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina; porphyria

Precautions:

stop if ischaemic pain occurs or existing pain worsens shortly after starting treatment; poor cardiac reserve; heart failure or significantly impaired left ventricular function; reduce dose in hepatic impairment (Appendix 5); diabetes mellitus; may inhibit labour; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1

Dosage:

Hypertension, *by mouth* (as sustained-release tablets), **ADULT** usual range 20–100 mg daily in 1–2 divided doses, according to manufacturer's directions

Note. Prescribers should be aware that different formulations of sustained-release tablets may not have the same clinical effect; if possible, the patient should be maintained on the same brand

Short-acting formulations of nifedipine should be avoided in hypertension, particularly in patients who also have angina, since their use may be associated with large variations in blood pressure and reflex tachycardia, possibly leading to myocardial or cerebrovascular ischaemia

Adverse effects:

headache, flushing, dizziness, lethargy; tachycardia, palpitations; gravitational oedema (only partly responsive to diuretics); rash (erythema multiforme reported), pruritus, urticaria; nausea, constipation or diarrhoea; increased frequency of micturition; eye pain, visual disturbances; gum hyperplasia; paraesthesia, myalgia, tremor; impotence, gynaecomastia; depression; telangiectasis; cholestasis, jaundice

Sodium nitroprusside

Sodium nitroprusside is a complementary drug for the treatment of hypertensive crisis

Infusion (Powder for solution for infusion), sodium nitroprusside, 50-mg ampoule

Uses:

hypertensive crisis (when treatment by mouth not possible)

Contraindications:

severe hepatic impairment; compensatory hypertension; severe vitamin B_{12} deficiency; Leber optic atrophy

Precautions:

impaired pulmonary function; hypothyroidism; renal impairment (Appendix 4); ischaemic heart disease, impaired cerebral circulation; hyponatraemia; raised intracranial pressure; elderly; hypothermia; monitor blood pressure and blood-cyanide concentration, also blood-thiocyanate concentration if given for more than 3 days; avoid sudden withdrawal (reduce infusion over 15–30 minutes to avoid rebound effects); pregnancy; breastfeeding; **interactions:** Appendix 1

Dosage:

Hypertensive crisis, *by intravenous infusion* , **ADULT** initially 0.3 micrograms/kg/minute; usual maintenance dose 0.5–6 micrograms/kg/minute; maximum dose 8 micrograms/kg/minute; stop infusion if response unsatisfactory after 10 minutes at maximum dose; lower doses in patients already being treated with antihypertensives

Reconstitution and administration. According to manufacturer's directions

Adverse effects:

severe hypotension; effects associated with over-rapid reduction in blood pressure include headache, dizziness; retching, abdominal pain; perspiration; palpitations, apprehension, retrosternal discomfort; rarely reduced platelet count, acute transient phlebitis

Adverse effects associated with excessive concentration of cyanide metabolite include tachycardia, sweating, hyperventilation, arrhythmias, marked metabolic acidosis (discontinue infusion and give antidote, section 4.2.7)

Drugs used in heart failure

Treatment of heart failure aims to relieve symptoms, improve exercise tolerance, reduce incidence of acute exacerbations, and reduce mortality. Drugs used to treat heart failure due to left ventricular systolic dysfunction include ACE inhibitors, diuretics, cardiac glycosides and vasodilators. In addition, measures such as weight reduction, moderate salt restriction, and appropriate exercise should be introduced.

The primary treatment of heart failure is with angiotensin-converting enzyme inhibitors (ACE inhibitors) such as **enalapril** which can be used in all stages of chronic heart failure to prevent further deterioration and progression of heart disease.

A thiazide diuretic such as **hydrochlorothiazide** is used in the management of mild to moderate heart failure when the patient has mild fluid retention and severe pulmonary oedema is not present; however thiazides are ineffective if renal function is poor. In these patients, and in more severe fluid retention, a loop diuretic such as **furosemide** (section 16.2) is required. In severe fluid retention, intravenous furosemide produces relief of breathlessness and reduces preload sooner than would be expected from the time of onset of diuresis. Hypokalaemia may develop, but is less likely with the shorter-acting loop diuretics than with the thiazides; care is needed to avoid hypotension.

A combination of a thiazide and a loop diuretic may be required to treat refractory oedema. The combination often produces a synergistic effect on solute and water excretion, which relieves symptoms in the diuretic-resistant heart failure patient. However, the combination may produce excessive intravascular volume depletion and electrolyte disturbances including potentially life-threatening hypokalaemia.

The aldosterone antagonist **spironolactone** (section 16.3) may be considered for patients with severe heart failure who are already receiving an ACE inhibitor and a diuretic; a low dose of spironolactone (usually 25 mg daily) reduces symptoms and mortality rate in these patients. Close monitoring of serum creatinine and potassium is necessary with any change in treatment or in the patient's clinical condition.

Digoxin , a cardiac glycoside, increases the strength of cardiac muscle contractions and increases cardiac output. In mild heart failure, digoxin inhibits the sympathetic nervous system and produces arterial vasodilation. It produces symptomatic

improvement, increases exercise tolerance, and reduces hospitalization, but it does not reduce mortality. It is considered for patients with atrial fibrillation and those who remain symptomatic despite treatment with an ACE inhibitor, a diuretic, and a suitable beta-blocker.

Vasodilators are used in heart failure to reduce systemic vascular resistance. **Isosorbide dinitrate** (section 12.1) produces mainly venous dilatation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnoea. Hydralazine (section 12.3) produces mainly arterial vasodilation, which reduces left ventricular afterload, and increases stroke volume and cardiac output. Isosorbide dinitrate and hydralazine can be used in combination when an ACE inhibitor cannot be used.

Dopamine , an inotropic sympathomimetic, may be given for short periods in the treatment of severe heart failure. Dosage is critical; at low doses it stimulates myocardial contractility and increases cardiac output, however, higher doses (more than 5 micrograms/kg per minute) cause vasoconstriction, with a worsening of heart failure.

Enalapril

Enalapril is a representative angiotensin-converting enzyme inhibitor. Various drugs can serve as alternatives

Tablets, enalapril 2.5 mg

Uses:

heart failure (with a diuretic); prevention of symptomatic heart failure and prevention of coronary ischaemic events in patients with left ventricular dysfunction; hypertension (section 12.3)

Contraindications:

hypersensitivity to ACE inhibitors (including angioedema); renovascular disease; pregnancy (Appendix 2)

Precautions:

use with diuretics; hypotension with first doses, especially in patients on diuretics, on a low-sodium diet, on dialysis, if dehydrated, or with heart failure; peripheral vascular disease or generalized atherosclerosis (risk of clinically silent renovascular disease); use with great care in severe or symptomatic aortic stenosis; monitor renal function before and during treatment; renal impairment (reduce dose, see also Appendix 4); liver impairment (Appendix 5); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); breastfeeding (Appendix 3); **interactions:** Appendix 1

Use with diuretics.	Risk of very rapid falls in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. High-dose diuretic therapy (furosemide dose

	greater than 80 mg daily) should be discontinued, or dose significantly reduced, at least 24 hours before starting enalapril (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic cannot be stopped, medical supervision advised for at least 2 hours after administration or until blood pressure stable
Anaphylactoid reactions.	Avoid enalapril during dialysis with high-flux polyacrilonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom

Dosage:

Heart failure, asymptomatic left ventricular dysfunction, *by mouth* , **adult** , initially 2.5 mg daily under close medical supervision; usual maintenance dose 20 mg daily in 1–2 divided doses

Adverse effects:

dizziness, headache; less commonly, nausea, diarrhoea, hypotension (severe in rare cases), dry cough, fatigue, asthenia, muscle cramps, rash and renal impairment; rarely, vomiting, dyspepsia, abdominal pain, constipation, glossitis, stomatitis, ileus, anorexia, pancreatitis, liver damage, chest pain, palpitations, arrhythmias, angioedema, bronchospasm, rhinorrhoea, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness or insomnia, pruritus, urticaria, alopecia, sweating, flushing, impotence, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus, taste disturbance, tinnitus, blurred vision; electrolyte disturbances and hypersensitivity-like reactions (including fever, myalgia, arthralgia, eosinophilia, and photosensitivity) reported

Digoxin

Tablets , digoxin 62.5 micrograms, 250 micrograms

Oral solution , digoxin 50 micrograms/ml

Injection (Solution for injection), digoxin 250 micrograms/ml, 2-ml ampoule

Uses:

heart failure; arrhythmias (section 12.2)

Contraindications:

hypertrophic obstructive cardiomyopathy (unless also severe heart failure); Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation; intermittent complete heart block; second-degree atrioventricular block

Precautions:

recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; elderly (reduce dose); renal impairment (Appendix 4); avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias); pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Heart failure, *by mouth* , **ADULT** 1–1.5 mg in divided doses over 24 hours for rapid digitalization *or* 250 micrograms 1–2 times daily if digitalization less urgent; maintenance 62.5–500 micrograms daily (higher dose may be divided), according to renal function and heart rate response; usual range 125–250 micrograms daily (lower dose more appropriate in elderly)

Emergency loading dose, *by intravenous infusion* over at least 2 hours, **ADULT** 0.75–1 mg

Note. Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks

Adverse effects:

usually associated with excessive dosage and include anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias, heart block; rarely rash, intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported

Dopamine hydrochloride

Dopamine hydrochloride is a complementary drug for inotropic support

Concentrate for infusion (Concentrate for solution for infusion), dopamine hydrochloride 40 mg/ml, 5-ml ampoule

Uses:

cardiogenic shock in myocardial infarction or cardiac surgery

Contraindications:

tachyarrhythmia, ventricular fibrillation; ischaemic heart disease; phaeochromocytoma; hyperthyroidism

Precautions:

correct hypovolaemia before, and maintain blood volume during treatment; correct hypoxia, hypercapnia, and metabolic acidosis before or at same time as starting treatment; low dose in shock due to myocardial infarction; history of peripheral vascular disease (increased risk of ischaemia of extremities); elderly; **interactions:** Appendix 1

Dosage:

Cardiogenic shock, *by intravenous infusion* into large vein, **ADULT** initially 2–5 micrograms/kg/minute; gradually increased by 5–10 micrograms/kg/minute according to blood pressure, cardiac output and urine output; seriously ill patients up to 20–50 micrograms/kg/minute

Dilution and administration. According to manufacturer's directions

Adverse effects:

nausea and vomiting; peripheral vasoconstriction; hypotension with dizziness, fainting, flushing; tachycardia, ectopic beats, palpitations, anginal pain; headache, dyspnoea; hypertension particularly in overdosage

Hydrochlorothiazide

Hydrochlorothiazide is a representative thiazide diuretic. Various drugs can serve as alternatives

Tablets, hydrochlorothiazide 25 mg

Uses:

heart failure; hypertension (section 12.3); oedema (section 16.1)

Contraindications:

severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease

Precautions:

renal and hepatic impairment (Appendices 4 and 5); pregnancy and breastfeeding (Appendices 2 and 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; **interactions:** Appendix 1

Dosage:

Heart failure, *by mouth* , **ADULT** initially 25 mg daily on rising, increasing to 50 mg daily if necessary; **ELDERLY** initially 12.5 mg daily

Adverse effects:

fluid and electrolyte imbalance leading to dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias; hypokalaemia, hypomagnesaemia, hyponatraemia,

hypochloraemic alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, gout; rashes, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible); blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis; acute renal failure; hypersensitivity reactions (pneumonitis, pulmonary oedema, severe skin reactions)

Antithrombotic drugs and myocardial infarction

Anticoagulants prevent thrombus formation or the extension of an existing thrombus. For further details see section 10.2 (drugs affecting coagulation).

Antiplatelet drugs also help to inhibit thrombus formation by decreasing platelet aggregation.

Thrombolytics (fibrinolytics) such as **streptokinase** are used to break up thrombi; they are used to treat acute myocardial infarction, extensive deep vein thrombosis, major pulmonary embolism and acute arterial occlusion.

Myocardial infarction

Management of myocardial infarction includes two phases:

- initial management of the acute attack
- long-term management, including prevention of further attacks

Initial management

Oxygen (section 1.1.3) should be given to all patients, except those with severe chronic obstructive pulmonary disease.

Pain and anxiety are relieved by slow intravenous injection of an opioid analgesic such as **morphine** (section 2.2). **Metoclopramide** (section 17.2) may also be given by intramuscular injection to prevent and treat nausea and vomiting caused by morphine.

Acetylsalicylic acid 150–300 mg by mouth (preferably chewed or dispersed in water) is given immediately for its antiplatelet effect.

Thrombolytic drugs such as **streptokinase** help to restore perfusion and thus relieve myocardial ischaemia; they should ideally be given within 1 hour of infarction (use after 12 hours requires specialist advice).

Nitrates (section 12.1) may also be given to relieve ischaemic pain.

Early administration of beta-blockers such as **atenolol** (section 12.1) have been shown to reduce both early mortality and the recurrence rate of myocardial infarction; initial intravenous administration is followed by long-term oral treatment (unless the patient has contraindications).

ACE inhibitors (section 12.4) have also been shown to be beneficial in initial management (unless patient has contraindications) when given within 24 hours, and if possible continued for 5–6 weeks.

If arrhythmias occur, they should be treated aggressively, but the likelihood decreases rapidly over the first 24 hours after infarction. Ventricular fibrillation should be treated immediately with a defibrillator; if this is ineffective alone, the antiarrhythmic drug **lidocaine** (section 12.2) should be given.

All patients should be closely monitored for hyperglycaemia; those with diabetes mellitus or raised blood-glucose concentration should receive **insulin** .

Long-term management

Acetylsalicylic acid should be given to all patients in a dose of 75–150 mg daily by mouth, unless it is contraindicated. The prolonged antiplatelet effect has been shown to reduce the rate of reinfarction.

Treatment with **beta-blockers** should be continued for at least 1 year, and possibly for up to 3 years.

ACE inhibitors such as **enalapril** (section 12.4) should also be used since they reduce mortality, particularly in patients with left ventricular dysfunction.

Nitrates (section 12.1) may be required for patients with angina.

The use of **statins** (section 12.6) may also be considered in patients with high risk of recurrence.

Stroke

Stroke (cerebrovascular accident) may be ischaemic or haemorrhagic; precise diagnosis is essential, as management for the two types of stroke is quite different.

Primary prevention of both types of stroke includes reduction of high blood pressure, stopping smoking, weight reduction, and cholesterol reduction. Atrial fibrillation, acute myocardial infarction, and valvular disease may produce embolism and ischaemic stroke. Prophylaxis in patients at risk of ischaemic stroke includes oral anticoagulants such as warfarin (section 10.2) and antiplatelet drugs such as acetylsalicylic acid. Treatment of acute ischaemic stroke includes use of **acetylsalicylic acid** , anticoagulants such as heparin, and of thrombolytics, such as streptokinase. Streptokinase must be used with extreme caution due to risk of bleeding. Long-term therapy with acetylsalicylic acid reduces the risk of having another stroke.

Antiplatelet and thrombolytic drugs are **not** used in the management of haemorrhagic stroke, as they may exacerbate bleeding. The main treatment is to normalize blood pressure.

Acetylsalicylic acid is normally given for at least one year after coronary artery bypass surgery. It is also given to patients with prosthetic heart valves who have had cerebral embolism despite warfarin treatment.

Acetylsalicylic acid

Tablets , acetylsalicylic acid 100 mg

Dispersible tablets (Soluble tablets), acetylsalicylic acid 75 mg [not included on WHO Model List]

Uses:

prophylaxis of cerebrovascular disease or myocardial infarction; pyrexia, pain, inflammation (section 2.1.1); migraine (section 7.1)

Contraindications:

hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (Reye syndrome, see section 2.1.1); active peptic ulceration; haemophilia and other bleeding disorders

Precautions:

asthma; uncontrolled hypertension; pregnancy (Appendix 2); breastfeeding (Appendix 3); see also section 2.1.1; **interactions:** Appendix 1

Dosage:

Prophylaxis of cerebrovascular disease or myocardial infarction, *by mouth* , **ADULT** 75–100 mg daily

Adverse effects:

bronchospasm; gastrointestinal haemorrhage (rarely major), also other haemorrhage (for example subconjunctival); see also section 2.1.1

Streptokinase

Streptokinase is a complementary drug; it is used in the management of myocardial infarction and thromboembolism

Injection (Powder for solution for injection), streptokinase 1.5 million-unit vial

Uses:

life-threatening deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism; thrombosed arteriovenous shunts; acute myocardial infarction

Contraindications:

recent haemorrhage, surgery (including dental), parturition, trauma; heavy vaginal bleeding; haemorrhagic stroke, history of cerebrovascular disease (especially recent or if residual disability); coma; severe hypertension; coagulation defects; bleeding diatheses, aortic dissection; risk of gastrointestinal bleeding such as recent history of peptic ulcer, oesophageal varices, ulcerative colitis; acute pancreatitis; sever liver disease; acute pulmonary disease with cavitation; previous allergic reactions

Precautions:

risk of bleeding from any invasive procedure, including injection; external chest compression; pregnancy (Appendix 2); abdominal aneurysm or where thrombolysis may give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolization); diabetic retinopathy (small risk of retinal haemorrhage); recent or concurrent anticoagulant treatment

Dosage:

Thrombosis, *by intravenous infusion,* **ADULT** 250 000 units over 30 minutes, followed by 100 000 units every hour for 12–72 hours according to condition with monitoring of clotting parameters

Myocardial infarction, *by intravenous infusion,* **ADULT** 1 500 000 units over 60 minutes

Thrombosed arteriovenous shunts, consult manufacturer's literature

Adverse effects:

nausea and vomiting; bleeding, usually limited to site of injection but internal bleeding including intracranial haemorrhage may occur (if serious bleeding occurs, discontinue infusion—coagulation factors may be required); hypotension, arrhythmias (particularly in myocardial infarction); allergic reactions including rash, flushing, uveitis, anaphylaxis; fever, chills, back or abdominal pain; Guillain-Barré syndrome reported rarely

Lipid-regulating drugs

The primary aim of therapy is to reduce progression of atherosclerosis and to improve survival in patients with established cardiovascular disease, to reduce premature cardiac morbidity and mortality in people at high risk of cardiovascular events and to prevent pancreatitis due to hypertriglyceridaemia. Before starting drug therapy dietary measures, reduction of blood pressure and cessation of smoking should be tried. The WHO Expert Committee on the Selection and Use of Essential Medicines recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia. Beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG Co A) reductase inhibitors, often referred to as 'statins', are potent and effective lipid-lowering drugs with a good tolerability profile. Several of these drugs have been shown to reduce the incidence of fatal and non-fatal myocardial infarction, stroke and mortality (all causes), as well as the need for coronary bypass surgery. All remain

very costly, but may be cost-effective for secondary prevention of cardiovascular disease as well as for primary prevention in some very high-risk patients. Since no single drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the WHO Model List; the choice of drug for use in patients at highest risk should be decided at national level.