Cardiovascular drugs act on the heart or blood vessels to control the cardiovascular system. They are used to treat a variety of conditions from hypertension to chronic heart failure.

- Hypertension: an increase in blood pressure (typically systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg but decisions to treat are based on overall cardiovascular risk). Hypertension is associated with causing strokes, ischaemic heart disease, chronic heart failure (CHF) and renal damage and therapy aims to reduce these risks.
- Ischaemic heart disease includes angina (where coronary blood flow is impaired) and myocardial infarction.
- CHF is impaired cardiac function where the pump activity of the heart is insufficient for the body’s demands.

**Angiotensin-converting enzyme inhibitors (ACEIs)**

e.g. enalapril, lisinopril, ramipril

**Mechanism of action (Figure 13.1)**

- ACEIs inhibit the conversion of angiotensin I to angiotensin II by inhibiting angiotensin-converting enzyme (ACE), which is predominantly in the lungs.
- Angiotensin II is a vasoconstrictor (directly, and indirectly via enhancing sympathetic activity).
- Angiotensin II increases the release of aldosterone (sodium/fluid-retaining and potassium-losing hormone).

**Figure 13.1** Flow diagram of the renin–angiotensin–aldosterone pathway and the actions of angiotensin-converting enzyme (ACE) inhibitors to reduce the conversion of angiotensin (AI) to angiotensin II (AII).
ACE is also involved in the breakdown of bradykinin (an endogenous vasodilator) and so ACEIs will increase bradykinin levels.

ACEIs reduce angiotensin II-induced vasoconstriction and indirectly aldosterone-induced sodium/fluid retention and so lower blood pressure and fluid overload.

Adverse effects

- A dry cough (10% of patients) may be present due to increased bradykinin levels. This may result in the patient changing to an angiotensin AT$_1$ receptor antagonist (see below).
- Renal damage may occur, especially in patients with renovascular disease, where angiotensin II is elevated to maintain renal blood flow and an ACEI will lead to reduced renal flow (leading to damage) and severe hypotension.
- First-dose hypotension: this is a large drop in blood pressure at the start of therapy – patients are advised to take the first dose when retiring to bed.
- Hyperkalaemia (increased plasma K$^+$), due to inhibition of aldosterone (K$^+$-losing hormone). This is especially a problem when used with potassium-sparing diuretics (see Chapter 14) or with potassium chloride as a salt substitute.
- Occasionally associated with angio-oedema, which leads to swollen lips, tongue and eyelids and can result in airway obstruction.

Clinical context

- Hypertension: in the UK, first choice for hypertension in patients under 55 years of age.
- Diabetic nephropathy: ACEIs reduce the renal damage associated with diabetes. Widely used in patients of any age with hypertension and diabetes.
- CHF: first-choice drug for reducing symptoms and mortality. ACEIs may reverse or prevent the adverse effects of angiotensin II in CHF (which forms part of adverse neurohormonal adaptation).
- Ischaemic heart disease and post myocardial infarction: routinely used to reduce mortality.

Angiotensin (AT$_1$) receptor antagonists

‘sartans’, e.g. losartan

Mechanism of action (Figure 13.2)

- Competitive antagonism of the actions of angiotensin II at the AT$_1$ receptor. Angiotensin II acts at AT$_1$ (vasoconstriction and aldosterone releases) and AT$_2$ receptors (roles are uncertain but may be important in the fetus).
- They have essentially the same consequences as ACEIs but do not affect bradykinin levels.

Adverse effects

- Same as ACEIs but unlikely to cause a cough.
Clinical context
- Used when ACEIs are not tolerated due to cough.
- Sometimes used with ACEIs for dual blockade, but this increases the risk of side-effects.

Renin inhibitors
e.g. aliskiren
- Directly inhibit the renin enzyme and so interfere with the renin–angiotensin system.
- Used in the treatment of hypertension.

Beta-blockers
e.g. atenolol

Mechanism of action
- Competitive antagonists of $\beta_1$- and $\beta_2$-adrenoceptors and so oppose the actions of noradrenaline from sympathetic nerves and circulating adrenaline.
- $\beta$-adrenoceptors: G-protein-coupled receptors which activate adenylyl cyclase and increase cyclic adenosine monophosphate (cAMP; see Chapter 3).
  - $\beta_1$-adrenoceptors: heart, coupled to increases in force of contraction (positive inotropic) and heart rate (positive chronotropic) (see Chapter 12).
  - $\beta_2$-adrenoceptors: lungs, coupled to bronchodilatation (see Chapter 17), and on blood vessels, coupled to vasodilatation.
- $\beta$-blockers act at $\beta_1$- and $\beta_2$-adrenoceptors to varying degrees. Cardioselective ones (e.g. atenolol) are selective (but not specific) for $\beta_1$-adrenoceptors and may have some action at $\beta_2$-adrenoceptors. Older agents (e.g. propranolol) are non-selective.
- Hypertension: the mechanism is uncertain but may decrease cardiac output (blockade of cardiac $\beta_1$-adrenoceptors), may reduce renin release (blockade of $\beta_1$-adrenoceptors)
of β-adrenoceptors on renal juxtaglomerular cells) and may have central actions.

- Angina: reduce heart rate and so cardiac work. The reduction in heart rate increases the time for diastole, during which coronary flow occurs, and so improves coronary blood flow.

### Adverse effects

- Blockade of bronchial β<sub>2</sub>-adrenoceptors can cause bronchoconstriction, even with cardioselective agents, and so β-blockers are avoided in patients with asthma and used with caution in chronic obstructive pulmonary disease.
- Cold peripheries due to blockade of vasodilator β<sub>2</sub>-adrenoceptors.
- Impotence.

### Clinical context

- Angina: reduced cardiac work and improved coronary blood flow mean that β-blockers are first-choice drugs for prevention.
- Post-myocardial infarction: used after a heart attack to reduce mortality.
- Certain cardioselective agents (metoprolol, bisoprolol, carvedilol) are used in CHF as they oppose the adverse effects of noradrenaline in neurohormonal adaptation and are proven to reduce mortality. They are used with caution, starting at a low dose and titrating upwards as β-blockers initially reduce cardiac output and cause a worsening of CHF at the start of treatment.
- Hypertension: in the UK no longer used as first-choice drugs as they are less effective at reducing stroke, heart attack, heart failure and diabetes compared to ACEIs, diuretics and calcium channel blockers.
- Antiarrhythmic: reduce sympathetic drive to heart.
- Commonly used to control atrial fibrillation.
- Anxiety: block the sympathetic component of anxiety.
- Hyperthyroidism: reduce initial symptoms due to increased sympathetic activity.
- Migraine: for prevention.
- Glaucoma: as topical agents which reduce pressure in the eye.

### Diuretics

Although these act on the kidney, they are widely used in cardiovascular disease (CHF and hypertension) to reduce extracellular volume and/or oedema (see Chapter 14).

### Calcium channel inhibitors

1. Dihydropyridines, e.g. amlodipine, nifedipine
2. Rate-limiting, e.g. verapamil.

### Mechanism of action (Figure 13.3)

- Calcium channel inhibitors inhibit calcium channels and so reduce calcium entry to contractile smooth muscle and cardiac muscle.
Cardiovascular drugs

Dihydropyridines are selective for calcium channels on vascular smooth muscle and so cause vasodilatation.

Rate-limiting agents have greater activity on cardiac muscle and so reduce the force of cardiac contraction and heart rate (see Chapter 12). They are also used as class IV antiarrhythmics (Chapter 12). Their ability to control heart rate means that they are beneficial in angina, partly because they prevent the reflex tachycardia which occurs as response to vasodilatation following inhibition of arterial calcium channels.

**Adverse effects**

- Dihydropyridines: arteriolar vasodilatation may lead to increases in fluid leaving the circulation, resulting in ankle oedema.
- Verapamil: inhibition of calcium channels in gastrointestinal smooth muscle can lead to constipation.

**Clinical context**

- Hypertension: in the UK, first-choice drugs for patients over 55 years. Act via vasodilatation and, in the case of the rate-limiting agents, also via reducing cardiac output.
- Angina: due to vasodilatation which reduces cardiac work and coronary vasodilatation which will increase coronary blood flow. Rate-limiting agents also reduce heart rate, reducing cardiac work and increasing time for diastole (and so increasing coronary flow).
- Antiarrhythmic: rate-limiting agents acting via inhibition of cardiac calcium channels.

**Nitrates**

e.g. glycercyl trinitrate, isosorbide mononitrate

**Mechanism of action (Figure 13.3)**

- Release nitric oxide which acts on soluble guanylyl cyclase to increase cyclic guanosine monophosphate (cGMP) to cause vasodilatation.
Vasodilatation is predominantly venous.
Angina: increased venodilatation reduces venous return (return of blood to the heart) and so reduces cardiac work. May also cause coronary vasodilatation.

**Adverse effects**
- Vasodilatation may lead to a throbbing headache which should respond to paracetamol.
- Nitrate tolerance: continued exposure to nitrates (usually oral agents such as mononitrates) can result in them becoming less effective. A nitrate-free period (e.g. overnight) can reduce the risk of tolerance.

**Clinical context**
- Glyceryl trinitrate for sublingual administration (e.g. a spray) causes rapid relief of angina.
- Oral nitrates (e.g. isosorbide mononitrate) may be used for regular prevention in angina.

**Potassium channel activators**

* e.g. nicorandil

**Mechanism of action (Figure 13.3)**
- Potassium channel activators activate adenosine triphosphate (ATP)-sensitive potassium (K\textsubscript{ATP}) channels on vascular smooth muscle (see Chapter 4).
- The opening of these K\textsubscript{ATP} channels causes K\textsuperscript{+} to leave the smooth muscle, resulting in hyperpolarisation, which causes the cells to become less excitable, and this results in vasorelaxation.

**Adverse effects**
- The vasodilatation can result in a reflex increase in heart rate.

**Clinical context**
- Nicorandil is used in angina for its vasodilator actions.

**Pacemaker inhibitors**

* e.g. ivabradine
- This new drug inhibits the I\textsubscript{f} (f for funny) ion channel responsible for sodium and potassium currents in the sinoatrial node which are responsible for pacemaker activity. This leads to a reduction in heart rate and so cardiac work, which is beneficial in angina.
- Ivabradine is used in angina when β-blockers are contraindicated.

**Alpha-blockers**

* e.g. prazosin

Mechanism of action
■ Competitive antagonists of α-adrenoceptors and so block sympathetic-mediated vasoconstriction, leading to vasodilatation.

Adverse effects
■ Numerous, due to blockade of the sympathetic nervous system, and this limits their tolerability and usage.
■ Postural or orthostatic hypotension, due to blockade of sympathetic nervous system, and so the patient is unable to maintain blood pressure when getting up.
■ Reflex tachycardia: hypotensive action provokes a reflex increase in heart rate.

Clinical context
■ Hypertension: α-blockers are added to therapy when other agents have failed to control blood pressure.
■ Prostatic hypertrophy: they are used to reduce symptoms of poor urinary outflow and urgency when the prostate is enlarged, which is common in males over the age of 50 years.

Centrally acting antihypertensives
e.g. α-methyldopa, moxonidine, clonidine

Mechanisms of action
■ Thought to decrease sympathetic drive and/or increase vagal output from central cardiovascular control centres.
■ α-methyldopa: a false substrate resulting in an analogue of noradrenaline acting at central α2-adrenoceptors.
■ Moxonidine: an imidazoline which activates central imidazoline receptors.
■ Clonidine: an α2-adrenoceptor agonist which acts centrally to decrease sympathetic output.

Clinical context
■ Hypertension: these agents are not widely used due to widespread side-effects and no advantages over other antihypertensive agents.
■ Hypertension in pregnancy: α-methyldopa is sometimes used as it appears safe in pregnancy.

Cardiac glycosides

Digoxin
■ Inhibition of the sodium pump (3Na+/2K+ ATPase).
■ Inhibition of sodium pump in cardiac cells leads to Na+ accumulation in the cells (Figure 13.4). This increases intracellular Na+ and so reduces the rate of Ca2+ efflux which is driven via a Na+/Ca2+ exchanger. The reduced Ca2+ efflux leads to increased intracellular Ca2+, leading to an increase in the force of contraction (positive inotrope).
- Acts on the atrioventricular node (AVN) to cause a degree of conduction block which is of benefit in atrial fibrillation.
- Increases vagal activity, which slows the heart and induces a degree of AVN block.

**Figure 13.4** Actions of digoxin on the sodium pump of a cardiac cell leading to increased calcium entry in exchange for sodium.

**Clinical context**
- Digoxin has a narrow therapeutic window and so is predisposed towards toxicity (nausea, anorexia, visual disturbances, cardiac arrhythmias).
- It used to be widely used in CHF for its positive inotropic actions but is now reserved for CHF with atrial fibrillation or when CHF patients are refractory to other treatments.
- The actions of digoxin are enhanced in hypokalaemia when the sodium pump is less active due to reduced levels of potassium.
- Digoxin is largely renally excreted and renal function is measured during treatment to determine the appropriate dose.

**HMG CoA reductase inhibitors (statins)**

* e.g. simvastatin, pravastatin

**Mechanism of action**
The statins inhibit the hepatic enzyme, hydroxyl-methylglutaryl coenzyme A reductase (HMG CoA reductase), which catalyses the first committed step of cholesterol synthesis in the liver. This leads to a reduction in cholesterol synthesis. The reduced synthesis of cholesterol by the liver also promotes the uptake of low-density lipoprotein (LDL) by the liver, which further reduces circulating cholesterol levels.

**Adverse effects**
Very occasionally they may cause muscle damage. In severe cases the muscle may break down, releasing myoglobin, which can lead to renal damage.
Clinical context
- These are cholesterol-lowering drugs given to patients with a high cardiovascular risk (previous heart attack, ischaemic heart disease, hypertension, diabetes) or abnormally high cholesterol levels to reduce overall risk. High-dose statin therapy may stabilise atherosclerotic plaques and even cause regression.
- Simvastatin (at a low dose) is now an over-the-counter medicine.
- Most statins are given at night when cholesterol synthesis is greatest.
- They undergo extensive first-pass metabolism and so they are hepatoselective.
- They have limited effects in hypertriglyceridaemia.

Fibrates
e.g. bezafibrate, fenofibrate

Mechanism of action
- Fibrates are activators of peroxisome proliferator-activated receptor alpha (PPAR-α; see Chapter 2) and lead to alterations in lipoprotein metabolism.
- This results in the induction of many fatty acid-metabolising enzymes, including peripheral lipoprotein lipases, which promote the breakdown of very-low-density lipoprotein (VLDL: with small reductions in LDL and increases in high-density lipoprotein (HDL)) and also lead to reductions in triglycerides.

Adverse effects
Very occasionally they may cause muscle damage and the risk is increased when used with statins.

Clinical context
- Used in hypertriglyceridaemia.

Key Points
- Cardiovascular drugs have a range of clinical uses (from hypertension to heart failure).
- Key targets involve interfering with the sympathetic nervous system (e.g. blockade of adrenoceptors), inhibiting the renin–angiotensin–aldosterone system (ACEIs) and reducing excitability of vascular smooth muscle or cardiac muscle (calcium channel inhibitors).
- Hypertension: ACEIs and calcium channel inhibitors are first-line agents. Thiazide-like diuretics are ‘third-line’ agents. Choice of drugs is also determined by concurrent illnesses.
- Ischaemic heart disease: β-blockers are first-line and calcium channel inhibitors are second-line drugs. Glycerol trinitrate spray is used to relieve attacks.
- CHF: ACE inhibitors, certain β-blockers and diuretics play major roles
- Digoxin is used in CHF with atrial fibrillation or in refractory CHF.
- Statins are effective at reducing cardiovascular risk, even in patients with ‘normal’ cholesterol levels.
Self-assessment

1. Which one of the following is a reason to avoid using an ACEI?
   a. heart failure
   b. hypokalaemia (low plasma potassium)
   c. renovascular disease
   d. asthma

2. Which one of the following is a reason to avoid using a β-blocker?
   a. hypertension
   b. hypokalaemia (low plasma potassium)
   c. renovascular disease
   d. asthma

3. Which one of the following is thought to contribute towards the antianginal effects of β-blockers?
   a. reduced release of noradrenaline
   b. local anaesthetic effects on sensory nerves
   c. reduction in the heart rate with prolongation of diastolic time
   d. direct coronary vasodilatation

4. Which one of the following is unlikely to occur with verapamil?
   a. increase in heart rate
   b. reduced force of cardiac contraction
   c. fall in blood pressure
   d. constipation

5. Which of the following is inhibited by digoxin?
   a. ATP-sensitive potassium channels
   b. proton pump
   c. sodium pump
   d. calcium channels