Ischaemic heart disease

Clinical manifestations of myocardial ischaemia

Stable angina

Acute coronary syndromes (unstable angina, myocardial infarction and sudden death)

Drug treatment of angina

Management of stable angina

Management of acute coronary syndromes

Management of acute coronary syndromes without ST-segment elevation

Management of ST-segment elevation myocardial infarction

The heart receives about 5% of the cardiac output at rest via the coronary arteries, and extracts about 75% of the oxygen from the blood perfusing the coronary vasculature. When the metabolic demand from the myocardium becomes greater (for example with exercise), coronary artery blood flow increases by up to three- to fourfold, to supply the necessary oxygen; there is no increase in the percentage of oxygen extracted from the blood passing through the myocardium. Myocardial perfusion occurs largely during diastole, when the muscle of the heart is relaxed and not compressing the intramyocardial vessels. Therefore, unlike for other organs, cardiac perfusion is reliant on the diastolic blood pressure.

Ischaemic heart disease most frequently arises as a result of restriction of blood flow to cardiac muscle by atheroma in the large epicardial coronary arteries. Atheromatous plaques tend to form in areas of flow disturbance, such as bends in the vessels or near branching vessels. A brief overview of the mechanisms involved in atheroma formation and plaque rupture is given in Figure 5.1. The plaques are often confined to a small segment of the coronary artery, but atheroma can diffusely involve a long segment of the vessel. Localised plaques frequently involve only part of the circumference of the arterial wall, leaving the rest free of significant disease and still able to respond to vasoconstrictor and vasodilator influences. Flow disturbances, and the consequent changes in shear stress, at the site of an atheromatous plaque impair endothelial function and reduce local generation of vasodilator substances such as nitric oxide (see organic nitrates below). Therefore, diseased segments of an artery are particularly prone to vasospasm, which produces dynamic flow limitation superimposed on the fixed atheromatous narrowing. If the coronary artery disease is longstanding, then collateral vessels can develop around the atheromatous narrowing, and improve perfusion distal to the diseased segment of the artery.

The major risk factors for coronary artery disease (in common with atheroma in other parts of the vascular tree) are male gender, smoking, hypertension, hypercholesterolaemia and diabetes mellitus. The effects of these risk factors are additive, and when several are present coronary atheroma occurs more extensively and at a younger age. There are two morphological types of atheromatous plaque. Some have a lipid-rich core, with a substantial infiltration of inflammatory cells and a thin fibrous cap. Such plaques are relatively unstable (‘vulnerable’ plaques) and are more prone to plaque disruption by ulceration or rupture of the cap, leading to thrombus formation (see below). Other plaques have a fibrotic core, with a thick fibrous cap, and are more stable. The reasons why both stable and unstable plaques can coexist in the coronary circulation is not well understood.

Myocardial ischaemia can sometimes occur in the presence of structurally normal epicardial coronary arteries. In this situation, it arises either from abnormal regulation of the microvascular circulation within the myocardium, or from intense vasoconstriction of an epicardial artery (coronary vasospasm).

CLINICAL MANIFESTATIONS OF MYOCARDIAL ISCHAEMIA

STABLE ANGINA

Angina pectoris is pain arising from heart muscle after it switches to anaerobic metabolism, and is a symptom of reversible myocardial ischaemia. Ischaemia is the consequence of an imbalance between oxygen supply and oxygen demand in a part of the myocardium (Fig. 5.2). This results from an inability to increase coronary blood flow sufficiently to meet the metabolic demands of the heart, usually because of a fixed atheromatous narrowing of an epicardial coronary artery. Early atheromatous plaques enlarge by stretching the medial smooth muscle (remodeling) and do not narrow the lumen of the vessel until 40–50% of the cross-sectional area of the vessel is diseased. Once luminal narrowing occurs, symptoms arise when 75% of the cross-sectional area of the vessel lumen is occluded.

Stable angina is most frequently experienced as chest pain on exertion or with emotional stress and is relieved by rest. Reversible myocardial ischaemia can also present with shortness of breath (due to diastolic stiffening of the left ventricle when a reduced cellular energy supply impairs the uptake of Ca^{2+} by the sarcoplasmic reticulum [see also diastolic heart failure Ch. 7]), or it can occur without symptoms (silent ischaemia). Stable angina is an indication that there is a significant coronary artery narrowing (usually as a consequence of an atheromatous plaque) but there is no
Acute coronary syndromes have a common pathophysiological origin, arising from disruption of an unstable atheromatous plaque in a coronary artery. This can be precipitated by sudden stresses on the cap produced by pulsatile blood flow. Plaque disruption. Vasospasm at the site of an atheromatous plaque accentuates the reduction in flow produced by a fixed atheromatous obstruction, and when it is present angina occurs at a lower work load.

People with stable angina have an increased risk of subsequent myocardial infarction or sudden cardiac death, due to rupture of an atheromatous plaque (see below). On average, the annual rate of such events is about 2%.

**Fig. 5.1** Aspects of inflammatory processes that contribute to coronary heart disease. Multifactorial processes contribute to coronary heart disease; endothelium is damaged and activated; platelets adhere and promote leukocyte infiltration and thrombus formation; low-density lipoprotein (LDL) is oxidised and is taken up into macrophages, subsequently forming foam cells. Dysfunctional expression of a host of cytokines, free radicals and metalloproteinases occurs. Overall there is exacerbation of inflammation, endothelial damage, atheroma formation, plaque rupture and thrombus formation. These processes are influenced by risk factors such as smoking, heredity, hypercholesterolaemia, hypertension, obesity, diabetes, age and gender. IFN-γ, interferon-gamma; IL-10, interleukin-10; MMPs, metalloproteinases; TGF-β, tumour growth factor beta; Th, T helper cell; VCAM-1, vascular cell adhesion molecule 1.

**ACUTE CORONARY SYNDROMES (UNSTABLE ANGINA, MYOCARDIAL INFARCTION AND SUDDEN DEATH)**

Acute coronary syndromes have a common pathophysiological origin, arising from disruption of an unstable atheromatous plaque in a coronary artery. This can be precipitated by sudden stresses on the cap produced by pulsatile blood flow.
flow across the plaque, by elastic recoil of the vessel in diastole or by vasospasm. As a consequence of these stresses, the thin cap over the plaque fissures or ulcerates, leading to plaque rupture and exposure of the core of the plaque to circulating blood. This promotes platelet aggregation (Ch. 11), thrombus formation and local vasospasm and therefore a sudden reduction in blood flow. Platelet–thrombin microemboli can break off from the thrombus and impact in small distal vessels downstream from the thrombus.

**Unstable angina**

If there is incomplete occlusion of the coronary artery following plaque rupture, angina may occur on minimal exertion; if the vessel is almost completely occluded, then angina occurs at rest. A sudden change in severity of ischaemic symptoms is known as unstable angina. Unlike myocardial infarction, symptoms of unstable angina are usually relieved by glyceryl trinitrate (see below), or resolve spontaneously within 30 min.

Unstable angina is distinguished pathologically from other acute coronary syndromes because perfusion of the ischaemic tissue remains sufficient to prevent necrosis of myocytes. More complete coronary artery occlusion leads to myocardial infarction. Following an episode of unstable angina, the thrombus may become incorporated into the plaque or bleeding may occur into the plaque. After healing, the plaque is substantially larger, leading to greater long-term luminal narrowing.

**Myocardial infarction and sudden cardiac death**

Myocardial infarction is usually associated with intense, prolonged chest pain and sympathetic nervous stimulation which increases cardiac work. However, about 15% of infarctions do not present with pain, and may go unrecognised (silent infarction). Myocardial infarction most commonly arises from complete coronary artery occlusion following disruption of an unstable atheromatous plaque (see unstable angina above). Occlusion often occurs at the site of an atheromatous lesion that previously was only producing mild or moderate stenosis of the artery and may not have caused symptoms prior to disruption. Muscle necrosis begins if the occlusion lasts for longer than 20–30 min. The diagnosis of acute myocardial infarction requires a rise in the plasma concentrations of sensitive cardiac markers, such as troponin I or troponin T, that are released from necrotic myocytes. Cell death begins in the subendocardial muscle which is furthest from the epicardial blood supply (the endocardium receives its oxygen from the ventricular cavity), and, unless perfusion is restored, it extends across the full thickness of the myocardium (transmurally) over the next few hours. Activation of endogenous fibrinolysis (Ch. 11) and the presence of a good collateral circulation are factors that favour reperfusion of the ischaemic area and naturally limit the size of the infarct. If very early reperfusion occurs, the damage is usually confined to the subendocardial myocardium.

Prolonged occlusion of a major coronary artery usually produces a full-thickness (or transmural) myocardial infarction. This often produces characteristic changes on the electrocardiograph (ECG), with early ST-segment elevation and eventually pathological Q waves. The resulting infarction is referred to as an ST-elevation myocardial infarction (STEMI). A subendocardial infarction often presents without diagnostic ECG changes. In these cases the ECG may show ST-segment depression or T-wave inversion (consistent with myocardial ischaemia), or even be normal. The resulting infarction is classified as a non-ST-segment elevation infarction (NSTEMI), because of the absence of the characteristic ST-segment changes found with more extensive myocardial damage.

Myocardial infarction principally affects left ventricular muscle, and the amount of muscle lost correlates well with both early and late survival. Infarction of the anterior muscle of the left ventricle (usually resulting from an occlusion in the left coronary artery system) causes greater myocardial loss than does inferior infarction of the ventricle (usually from right coronary artery occlusion). The amount of muscle loss also determines the extent of left ventricular remodeling (a geometrical change in the left ventricle that begins with healing of the infarct) which determines the risk of subsequent heart failure. Sudden cardiac death results when fatal ventricular arrhythmias arise from ischaemic tissue.

**DRUG TREATMENT OF ANGINA**

Drug treatment for angina is directed either:

- to reduce oxygen demand by decreasing cardiac work, and/or
- to increase oxygen supply by improving coronary blood flow.

Drugs can be taken to relieve the ischaemia rapidly during an acute attack or as regular prophylaxis to reduce the risk
of subsequent episodes. Several classes of drug are used to treat angina.

**Organic nitrates**

**Examples**

glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate

**Mechanism of action and effects**

The organic nitrates are vasodilators that relax vascular smooth muscle by mimicking the effects of endogenous nitric oxide. Enzymatic degradation of the nitrate releases nitric oxide, which combines with thiol groups in vascular endothelium to form nitrosothiols. Nitrosothiols activate guanylyl cyclase, which generates the second messenger cyclic guanosine monophosphate (cGMP, Fig. 5.3). cGMP activates protein kinase G, which decreases the availability of intracellular Ca²⁺ to the contractile mechanism of vascular smooth muscle, causing relaxation and vasodilation. Vasodilation is produced in three main vascular beds.

- **Venous capacitance vessels**, leading to peripheral pooling of blood and reduced venous return to the heart. This lowers left ventricular filling pressure (preload), which decreases ventricular wall tension and therefore reduces myocardial oxygen demand. Venous dilation is produced at moderate plasma nitrate concentrations, and tolerance to this action occurs rapidly during continued treatment.
- **Arterial resistance vessels**, leading to reduced resistance to left ventricular emptying (afterload). This lowers blood pressure, decreases cardiac work and contributes to a reduced myocardial oxygen demand. Arterial dilation requires higher plasma nitrate concentrations than does venodilation, but tolerance occurs less readily during long-term treatment.
- **Coronary arteries**: nitrates have little effect on total coronary blood flow in angina; indeed, flow may be reduced because of a decrease in perfusion pressure. However, blood flow through collateral vessels may be improved, and nitrates also relieve coronary artery vasospasm. The net effect is increased blood supply to ischaemic areas of the myocardium. Coronary artery dilation occurs at low plasma nitrate concentrations, and tolerance is slow to develop.

**Pharmacokinetics**

Glyceryl trinitrate is the most widely used organic nitrate. It is well absorbed from the gut but undergoes extensive first-pass metabolism in the liver to inactive metabolites. To increase its bioavailability, glyceryl trinitrate is given by one of four routes that avoid first-pass metabolism.

- **Sublingual**: the tablet is placed under the tongue and is absorbed rapidly across the buccal mucosa. The very short half-life of glyceryl trinitrate (less than 5 min) limits the duration of action to approximately 30 min. Tablets

---

**Fig 5.3 Actions of endogenous and exogenous nitric oxide (NO).** Endogenous NO from endothelial cells relaxes smooth muscle by the following steps: NO activates guanylyl cyclase with subsequent formation of cGMP, which activates protein kinase G, which decreases Ca²⁺ influx into the cell and increases Ca²⁺ storage in the sarcoplasmic reticulum and increases myosin light-chain dephosphorylation. Exogenous agents such as organic nitrates react with tissue thiols, generating NO or nitrosothiols, which then activate guanylyl cyclase and increase cGMP (see also Fig. 6.4).
lose their potency with prolonged storage, and a metered-dose aerosol spray is a more stable delivery mechanism.

- **Buccal**: a tablet containing glyceryl trinitrate in an inert polymer matrix is held between the upper lip and gum, which permits slow release of drug to prolong the duration of action.

- **Transdermal**: glyceryl trinitrate is absorbed well through the skin and can be delivered from an adhesive patch via a rate-limiting membrane or matrix. Steady release of the drug maintains a stable blood concentration for at least 24 h after application of the patch.

- **Intravenous**: the short duration of action of glyceryl trinitrate is an advantage for intravenous dose titration.

Isosorbide dinitrate is well absorbed orally and is biologically active, but this is limited by its short half-life (0.5–2 h) and extensive first-pass metabolism. Variable amounts of a major active metabolite, isosorbide 5-mononitrate, are formed. Isosorbide mononitrate has a longer half-life than dinitrate (3–7 h) and is responsible for the majority of the sustained clinical effect. Modified-release formulations are often used to prolong the duration of action of isosorbide dinitrate. Isosorbide dinitrate is also used via an aerosol spray for a rapid onset of action, or can be given by intravenous infusion (although the longer half-life makes dose titration less easy than with glyceryl trinitrate).

Isosorbide 5-mononitrate is not subject to first-pass metabolism and can be used orally as an alternative to isosorbide dinitrate, since it gives a more predictable clinical response.

**Unwanted effects**

- Venodilation can produce postural hypotension, dizziness, syncope and reflex tachycardia. Tachycardia can be reduced by concurrent use of a β-adrenoceptor antagonist.

- Arterial dilation causes throbbing headaches and flushing, but tolerance to these effects is common during treatment with long-acting nitrates.

- Tolerance to the therapeutic effects of nitrates develops rapidly if there is a sustained high plasma nitrate concentration. Tolerance is therefore a particular problem with delivery of glyceryl trinitrate via transdermal patches or with the long-acting nitrates. The cause is incompletely understood, but an important mechanism may be production of oxygen free radicals (superoxides, generated in response to the excess NO production) which degrade NO. There is limited evidence that co-administration of an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor antagonist or hydralazine (Ch. 6) may reduce nitrate tolerance by impairing superoxide formation. Activation of the sympathetic nervous system and the renin–angiotensin system in response to hypotension may also counteract the vasodilator actions of the nitrates. Tolerance can be avoided by a ‘nitrate-low’ period of several hours in each 24 h. This is preferable to a ‘nitrate-free’ period, which carries a risk of rebound angina. A nitrate-low period is achieved by asymmetric dosing with conventional formulations of isosorbide mononitrate or dinitrate (e.g. twice daily at 8 a.m., 1 p.m.) or by using a once-daily formulation of isosorbide mononitrate that allows plasma nitrate concentrations to fall overnight. Transdermal nitrate patches must be removed for part of each 24 h (e.g. overnight) to prevent tolerance, thereby creating a nitrate-free period.

- Drug interactions are most troublesome with phosphodiesterase inhibitors, such as sildenafil, used in the treatment of erectile dysfunction. These inhibit cGMP metabolism (Ch. 16) and co-administration can result in marked hypotension.

**Beta-adrenoceptor antagonists (β-blockers)**

**Examples**

- atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nebivolol, pindolol, propranolol

**Mechanism of action and effects in angina**

All β-adrenoceptor antagonists (often simply referred to as β-blockers) act as competitive antagonists of catecholamines at β-adrenoceptors. They achieve their therapeutic effect in angina by blockade of the cardiac β1-adrenoceptor with reduced generation of intracellular cAMP. As a result they:

- decrease heart rate (by inhibition of the cardiac β1 pacemaker current in the sinoatrial node; see Ch. 8); this is most marked during exercise, when the rate of rise in heart rate is blunted
- reduce the force of cardiac contraction (see Ch. 7)
- lower blood pressure by reducing cardiac output (a consequence of both the decreased heart rate and force of myocardial contraction).

The overall effect is to reduce myocardial oxygen demand. The slower heart rate also lengthens diastole and gives more time for coronary perfusion, which effectively improves myocardial oxygen supply.

Certain β-adrenoceptor antagonists have additional properties, which might reduce the incidence of unwanted effects or enhance their blood pressure-lowering actions (see below and also Chs 6 and 8):

- **Cardioselectivity.** Some β-adrenoceptor antagonists, for example atenolol, bisoprolol and metoprolol, are selective antagonists at the β1-adrenoceptor. They are usually called cardioselective drugs since the most important site of action on β1-adrenoceptors is the heart. Other β1-adrenoceptor antagonists, for example propranolol, have equal or greater antagonist activity at β1-adrenoceptors; these drugs are referred to as ‘non-selective’ β1-adrenoceptor antagonists. The cardioselectivity of all β1-adrenoceptor antagonists is dose-related, and they produce progressively more β1-adrenoceptor blockade at higher doses (Ch. 1).

- **Partial agonist activity (PAA) or intrinsic sympathomimetic activity (ISA).** Certain β1-adrenoceptor antagonists, such as pindolol, have ISA and therefore act as partial agonists. For example, pindolol is a non-selective β1-adrenoceptor antagonist that also has weak
agonist properties, mainly at $\beta_1$-adrenoceptor (Ch. 1 and Fig. 6.7). If the drug is a partial agonist at the $\beta_1$-adrenoceptor, it will produce vasodilation in some vascular beds (see Fig. 6.7). However, drugs with PAA at the $\beta_1$-adrenoceptor have less inhibitory effect on heart rate and force of contraction and may be less effective than full antagonists in the treatment of severe angina. In contrast they are less likely to cause a resting bradycardia. Beta-adrenoceptor antagonists with PAA are not widely used.

**Vasodilator activity.** Pure $\beta_1$-adrenoceptor antagonists do not cause vasodilation. Indeed, the reflex response to $\beta_1$-adrenoceptor blockade is vasoconstriction, mediated in part by the sympathetic nervous system stimulation of $\alpha_1$-adrenoceptors in response to the fall in cardiac output. However, some $\beta_1$-adrenoceptor antagonists have additional properties that produce arterial vasodilation. Mechanisms of vasodilation include $\beta_2$-adrenoceptor partial agonist activity (e.g. pindolol), $\alpha_1$-adrenoceptor blockade (e.g. carvedilol, labetalol), or an increase in endothelial nitric oxide synthesis (e.g. nebivolol) (Fig. 6.7). Nebivolol (like sotalol [Ch. 8] and propranolol) is a racemic mixture; the $\alpha$-isomer of nebivolol is responsible for both $\beta_1$-adrenoceptor blockade and vasodilation, but the $\beta$-isomer has only vasodilator properties. Vasodilation does not have any proven advantage for the treatment of angina, but may be useful when $\beta_1$-adrenoceptor antagonists are given for the treatment of hypertension (Ch. 6).

**Pharmacokinetics**

Highly lipophilic $\beta_1$-adrenoceptor antagonists, such as propranolol and metoprolol, are well absorbed from the gut but undergo extensive first-pass metabolism in the liver, with considerable variability among individuals. Reduction in heart rate during exercise is closely related to the plasma concentration of a $\beta_1$-adrenoceptor antagonist. Consequently, dose titration of lipophilic $\beta_1$-adrenoceptor antagonists is usually necessary to achieve an optimal clinical response. Most lipophilic $\beta_1$-adrenoceptor antagonists have short half-lives (see compendium), and are often available in modified-release formulations to prolong their duration of action.

Water-soluble (hydrophilic) $\beta_1$-adrenoceptor antagonists, such as, pindolol, and celiprolol, are incompletely absorbed from the gut. They are subject to limited or negligible first-pass metabolism and are eliminated unchanged in the urine. The dose range to maintain effective plasma concentrations is narrower than for those drugs that undergo metabolism. The half-lives of hydrophilic $\beta_1$-adrenoceptor antagonists are usually longer than those of lipophilic drugs (see compendium).

**Unwanted effects**

- **Blockade of $\beta_2$-adrenoceptors.** Beta-adrenoceptor antagonists can precipitate acute heart failure if there is pre-existing poor left ventricular function, when high sympathetic nervous activity is necessary to maintain cardiac output. However, there is a paradox that when used at low doses with gradual dose titration they are part of the core therapy of heart failure (Ch. 7). The reduction in cardiac output can also impair blood supply to peripheral tissues, which can be detrimental in critical leg ischaemia (Ch. 10) or can provoke Raynaud’s phenomenon (Ch. 10). Excessive bradycardia occasionally occurs, and $\beta_2$-adrenoceptor antagonists should be used with caution or avoided in the presence of advanced atrioventricular conduction defect (heart block). Drugs with partial agonist activity are less likely to cause bradycardia or to reduce cardiac output.

- **Blockade of $\beta_2$-adrenoceptors.**
  - *Bronchospasm* can be precipitated in people with asthma and in some people with chronic obstructive pulmonary disease; even cardioselective drugs are not completely safe.
  - *Hypoglycaemia* may be prolonged by non-selective $\beta_1$-adrenoceptor antagonists in people with diabetes who are treated with insulin (Ch. 40). Gluconeogenesis, a component of the metabolic response to hypoglycaemia, is dependent upon $\beta_2$-adrenoceptor stimulation in the liver. Beta-adrenoceptor antagonists also blunt the autonomic response that alerts the diabetic person to the onset of hypoglycaemia.

- **Effects on blood lipid levels.** Most $\beta_1$-adrenoceptor antagonists raise the plasma concentration of triglycerides and lower the concentration of high-density lipoprotein cholesterol (Ch. 48). These changes are modest, but are potentially atherogenic. They are most marked with non-selective $\beta_1$-adrenoceptor antagonists, and do not occur if the drug has partial agonist activity.

- **Central nervous system effects.** These include sleep disturbance, vivid dreams and hallucinations, and are more common with lipophilic drugs, which readily cross the blood–brain barrier. Fatigue and more subtle psychomotor effects, for example lack of concentration and sexual dysfunction, are less frequent.

- **Sudden withdrawal syndrome.** Upregulation of $\beta_1$-adrenoceptors (Ch. 1) during long-term treatment makes the heart more sensitive to catecholamines. Beta-adrenoceptor antagonists should be stopped gradually in people with ischaemic heart disease, to avoid precipitating unstable angina or myocardial infarction.

- **Drug interactions.** The calcium channel blockers verapamil and, to a lesser extent, diltiazem (see below) have potentially hazardous additive effects with $\beta_1$-adrenoceptor antagonists, since both reduce the force of cardiac contraction and slow heart rate.

**Calcium channel blockers (calcium antagonists)**

**Examples**

- amlodipine, diltiazem, nifedipine, verapamil

**Mechanism of action and effects**

Calcium is essential for excitation–contraction coupling in muscle cells. The following controls of intracellular free Ca$^{2+}$ levels are important pharmacologically (Figs 5.4 and 5.5):

- Ca$^{2+}$ can enter cells through transmembrane voltage-gated or ligand-gated channels (Figs 5.4 and 5.5).
Ischaemic heart disease

Calcium channel blockers (often referred to as calcium antagonists) have widely different chemical structures, but act principally by reducing Ca\(^{2+}\) influx through voltage-operated L-type Ca\(^{2+}\) channels. None of the currently available calcium channel blockers affect T-type channels to any important extent, or influence receptor (ligand)-mediated Ca\(^{2+}\) channels (which are involved in neurotransmitter release and respond to endogenous agonists such as noradrenaline [Fig. 5.5]).

There are clinically important differences among the calcium channel blockers, which bind to discrete receptors on the L-type Ca\(^{2+}\) channel. The receptor for verapamil is intracellular, while diltiazem and the dihydropyridines (such as nifedipine) have extracellular binding sites; however, the receptor domains for verapamil and diltiazem overlap. The various classes of calcium channel antagonists have different binding properties with their receptors: verapamil and diltiazem exhibit frequency-dependent receptor binding and gain access to the Ca\(^{2+}\) channel when it is in the open state (Ch. 1); in contrast, the dihydropyridines (e.g. nifedipine, amlodipine) preferentially bind to the channel in its inactivated state (Ch. 1). More Ca\(^{2+}\) channels are inactive in relaxed smooth muscle and dihydropyridines show relative selectivity for binding to

---

**Fig. 5.4 Aspects of the control of calcium regulation and actions of potassium channel openers in cardiac myocytes and blood vessels.** Cation regulation in cardiac cells and in vascular smooth muscle is under the control of a number of different mechanisms. Calcium entry through voltage-gated L-type Ca\(^{2+}\) channels can further amplify free Ca\(^{2+}\) (Ca\(^{2+}\)-induced release of Ca\(^{2+}\)) by stimulating diverse ryanodine receptors in the sarcoplasmic reticulum, releasing stored Ca\(^{2+}\). Intracellular Ca\(^{2+}\) can also be regulated by exchange with Na\(^+\) via the Na\(^+\)/Ca\(^{2+}\) exchangers (NCX). Hyperpolarisation of the cell by drugs which open K\(^+\) channels acts to close voltage-gated L-type Ca\(^{2+}\) channels.

- A rise in intracellular free Ca\(^{2+}\) promotes release of Ca\(^{2+}\) from the sarcoplasmic reticulum through actions at ryanodine receptors (Figs 5.4 and 5.5).
- Ligand-gated channels, linked to G-protein-coupled receptors, release Ca\(^{2+}\) from intracellular stores in the sarcoplasmic reticulum.
- Ca\(^{2+}\) can exit cells in exchange for Na\(^+\) via the Na\(^+\)/Ca\(^{2+}\) exchanger (Fig. 5.4).

There are at least five different types of Ca\(^{2+}\) channel, two of which are found in cardiovascular tissues.

- **Voltage-operated L-type (long-acting, high-threshold-activated, slowly inactivated) Ca\(^{2+}\) channels**: these are important therapeutically and are found in the cell membranes of a large number of excitable cells, including cardiac and vascular smooth muscle. Ca\(^{2+}\) enters the cell through these channels when the cell membrane is depolarised. The cardiac and vascular L-type Ca\(^{2+}\) channels have different subunit structures.
- **Voltage-operated T-type (transient, low-threshold-activated, fast inactivated) Ca\(^{2+}\) channels**: these are found in pacemaker cells of the sinoatrial and atrioventricular nodes, and are also present in vascular smooth muscle.

Calcium channel blockers (often referred to as calcium antagonists) have widely different chemical structures, but act principally by reducing Ca\(^{2+}\) influx through voltage-operated L-type Ca\(^{2+}\) channels. None of the currently available calcium channel blockers affect T-type channels to any important extent, or influence receptor (ligand)-mediated Ca\(^{2+}\) channels (which are involved in neurotransmitter release and respond to endogenous agonists such as noradrenaline [Fig. 5.5]).

There are clinically important differences among the calcium channel blockers, which bind to discrete receptors on the L-type Ca\(^{2+}\) channel. The receptor for verapamil is intracellular, while diltiazem and the dihydropyridines (such as nifedipine) have extracellular binding sites; however, the receptor domains for verapamil and diltiazem overlap. The various classes of calcium channel antagonists have different binding properties with their receptors: verapamil and diltiazem exhibit frequency-dependent receptor binding and gain access to the Ca\(^{2+}\) channel when it is in the open state (Ch. 1); in contrast, the dihydropyridines (e.g. nifedipine, amlodipine) preferentially bind to the channel in its inactivated state (Ch. 1). More Ca\(^{2+}\) channels are inactive in relaxed smooth muscle and dihydropyridines show relative selectivity for binding to
Negative chronotropic effect. Verapamil and diltiazem (but not the dihydropyridines) slow the rate of firing of the sinoatrial node and slow conduction of the impulse through the atrioventricular node (see also Ch. 8). Thus, reflex tachycardia is not seen with these drugs and they also slow the rate of rise in heart rate during exercise.

Reduced cardiac contractility. Most calcium channel blockers (but particularly verapamil) have a negative inotropic effect. Amlodipine does not impair myocardial contractility. Other mechanisms exist (not shown). For example, stimulation of α-adrenoceptors stimulates PLC, which, via IP3 and DAG generation, can release Ca2+ and phosphorylate L-type Ca2+ channels. DAG, diacylglycerol; IP3, inositol 1,4,5 triphosphate; PKA, protein kinase A; PLC, phospholipase C; SR, sarcoplasmic reticulum; RyR, ryanodine receptor; +, stimulates activity; −, inhibits activity.

A comparison of the cardiovascular uses of the different calcium channel blockers is shown in the drug compendium table at the end of this chapter.

Pharmacokinetics

Most calcium channel blockers are lipophilic compounds with similar pharmacokinetic properties. They are almost completely absorbed from the gut lumen, and undergo variable first-pass metabolism. Nifedipine is inactivated by metabolism, while verapamil and diltiazem have active, although less potent, metabolites. Their half-lives are mostly in the range of 2 to 12 h, and modified-release formulations are widely used to prolong their duration of action. Nifedipine is also available in a liquid-containing capsule formula.
Ischaemic heart disease

- Altered gut motility: constipation is most common with verapamil, less so with diltiazem. Nifedipine and related dihydropyridine drugs can cause nausea and heartburn.
- Gum hyperplasia.
- Drug interactions: verapamil and diltiazem can slow the heart rate excessively if they are used in combination with other drugs that have similar effects on atrioventricular nodal conduction, for example digoxin (Ch. 8) or β-adrenoceptor antagonists. Metabolism of many calcium channel blockers can be inhibited or accelerated by drugs that affect the liver P450 cytochrome enzymes.

Potassium channel openers

- Altered gut motility: constipation is most common with verapamil, less so with diltiazem. Nifedipine and related dihydropyridine drugs can cause nausea and heartburn.
- Gum hyperplasia.
- Drug interactions: verapamil and diltiazem can slow the heart rate excessively if they are used in combination with other drugs that have similar effects on atrioventricular nodal conduction, for example digoxin (Ch. 8) or β-adrenoceptor antagonists. Metabolism of many calcium channel blockers can be inhibited or accelerated by drugs that affect the liver P450 cytochrome enzymes.

Mechanism of action

There are many different K+ channels in cell membranes (Ch. 8, Table 8.1). They impact on several aspects of cellular function in health and disease. The K_{ATP} channels exist in...
different tissues in a variety of configurations of subunits, making tissue specificity of drug action on the channels possible. The vascular adenosine triphosphate (ATP)-sensitive channel provides an inward rectifying current, and, when opened, K$^+$ exits the cell and results in hyperpolarisation. The channel is inhibited by ATP. Nicorandil opens the ATP-sensitive channel (Fig. 5.4). The hyperpolarisation produced in vascular smooth muscle cells inhibits opening of the voltage-dependent L-type Ca$^{2+}$ channels, leading to vasodilatation in systemic and coronary arteries (Fig. 5.4). In addition, enhanced K$^+$ channel function may provide protection of myocardial cells against ischaemic injury.

Nicorandil also carries a nitrate moiety, and part of its vasodilator action is via generation of nitric oxide in vascular smooth muscle (see organic nitrates above). This may account for the venodilation produced by the drug.

**Pharmacokinetics**

Nicorandil is rapidly and almost completely absorbed from the gut. It is eliminated by hepatic metabolism and has a short half-life of 1 h. However, the tissue effects correlate poorly with the plasma concentration and the biological effect lasts up to 12 h.

**Unwanted effects**

- Arterial dilation causes headache in 25–50% of people, but tolerance usually occurs with continued use. Palpitations (caused by reflex activation of the sympathetic nervous system) and flushing are less common than headache (Fig. 5.6).
- Dizziness
- Nausea, vomiting.

**Specific sinus node inhibitors**

**Example**

ivabradine

**Mechanism of action**

In cardiac pacemaker cells (such as the sinoatrial node) the pacemaker $I_f$ current is responsible for diastolic depolarisation (Ch. 8). This is an inward current produced by the opening of channels permeable to both Na$^+$ and K$^+$ that are opened by the negative intracellular potential occurring in diastole. Ivabradine is a specific inhibitor of this current, and its major effect is to slow heart rate. The degree of channel inhibition is use-dependent, since ivabradine binds to the open channel from the internal side of the cell membrane. As a result, the efficacy of ivabradine increases with the frequency of channel opening and is greatest at higher heart rates. Unlike $\beta$-adrenoceptor antagonists, ivabradine has no effect on myocardial contractility.

**Pharmacokinetics**

Ivabradine is well absorbed from the gut, and undergoes extensive first-pass metabolism in the gut wall and liver. It is oxidised by CYP3A4 to a metabolite that retains activity. It has a half-life of 2 h.

**Unwanted effects**

- Bradycardia, first-degree heart block. It is recommended that the resting heart rate should not be allowed to fall below 50 beats min$^{-1}$.
- Headache, dizziness.
- Dose-related ocular symptoms, including phosphenes (flashes of light), photopsia, stroboscopic effects and blurred vision from inhibition of the $I_f$ in the eye.

**Late sodium current inhibitors**

**Example**

ranolazine

**Mechanism of action**

Transmembrane Na$^+$ channels are activated during the initial electrical excitation of myocardial cells, and are mainly inactivated during the plateau phase of the action potential. However, a small proportion of the Na$^+$ channels remain open, giving rise to the late Na$^+$ current. This current is increased in the presence of hypoxia, with a consequent increase in the intracellular Na$^+$ concentration. The rise in intracellular Na$^+$ activates the reverse mode of the Na$^+$/Ca$^{2+}$ exchanger in the cell membrane, leading to removal of Na$^+$ from the cell, intracellular Ca$^{2+}$ accumulation and increased diastolic myocardial tension (Fig. 5.4). Ranolazine attenuates the late transcellular Na$^+$ current in ischaemic myocardial cells, and reduces Ca$^{2+}$ accumulation. There are two potentially beneficial consequences of this effect. The lower wall tension in the ventricles should reduce myocardial oxygen demand, and will also reduce compression of small intramyocardial coronary vessels, thus improving myocardial perfusion.

**Pharmacokinetics**

Ranolazine is partially absorbed from the gut, and extensively metabolised in the liver by CYP3A and to a limited extent CYP2D6. It has a short elimination half-life of about 2 h and a modified-release formulation is available.

**Unwanted effects**

- Nausea, dyspepsia, constipation
- Headache, dizziness, lethargy
- Prolongation of the QT interval on the ECG (Ch. 8), with the potential to provoke cardiac arrhythmias if used with other drugs that have the same effect.

**MANAGEMENT OF STABLE ANGINA**

The principal aims of treatment for stable angina are to relieve symptoms and to improve prognosis. Angina has a pronounced circadian rhythm and occurs most frequently in the hours after waking, so a drug given for prevention of symptoms should ideally be effective at this time. However, there is no convincing evidence that control of symptoms
will affect either survival or the risk of a subsequent myocardial infarction. Improvement in prognosis is achieved mainly by using drugs that do not directly affect symptoms. There are several important principles of management.

- **Lifestyle changes:** stopping smoking reduces coronary vasospasm, and may improve symptoms, but importantly reduces the risk of developing an acute coronary syndrome by up to 50%. Weight loss in people with obesity will reduce cardiac work, and regular exercise will improve fitness and attenuate the rise in heart rate on exercise.

- **Reduction of high blood pressure to reduce cardiac work** and to reduce progression of atheroma, and control of diabetes to reduce progression of atheroma.

- **Reduction or elimination of provoking or exacerbating factors, such as anaemia, arrhythmias or thyrotoxicosis.**

- **Sublingual glyceryl trinitrate** remains the treatment of choice for an acute anginal attack. It relieves symptoms within minutes, but gives only short-lived protection (20–30 min). Glyceryl trinitrate can also be taken for short-term prophylaxis before an activity that is likely to produce angina. For people who cannot tolerate a nitrate, a capsule of rapid-release nifedipine can be bitten and the contents swallowed to achieve a rapid effect.

- **If anginal attacks are frequent, a longer-acting prophylactic antianginal drug should be used.** A rise in heart rate is one of the main precipitating factors for angina, and a drug that lowers heart rate, such as a β-adrenoceptor antagonist, verapamil or diltiazem, may be most effective for first-line treatment. Nitrates are less suitable as first-line prophylactic agents because of the risk of tolerance. If symptoms are not controlled by optimal doses of a single drug, then a combination of a β-adrenoceptor antagonist with a calcium channel blocker (not verapamil), or either a β-adrenoceptor antagonist or calcium channel blocker with a long-acting nitrate, can be used. ‘Triple therapy’ (e.g. β-adrenoceptor antagonist, calcium channel blocker and a nitrate) has not been shown convincingly to be better than two agents, but the combination may sometimes give further symptomatic benefit. Nicorandil is generally used in combination therapy. The roles of ivabradine and ranolazine are less certain, particularly as their efficacy in combination with other antianginal drugs is unclear.

- **Low-dose aspirin reduces the risk of subsequent myocardial infarction by about 35%** (see Ch. 11).

- **Lowering the total plasma cholesterol to <4.0 mmol L⁻¹ by diet and by drugs (especially statins) (Ch. 48) reduces the risk of subsequent non-fatal myocardial infarction, cardiac death and the need for a coronary artery revascularisation procedure by more than 30%.**

- **ACE inhibitors** (Ch. 6) have no antianginal action, but reduce the risk of subsequent myocardial infarction, especially in people at high risk of an event.

- **Coronary artery bypass grafting (CABG)** improves long-term prognosis compared with medical treatment in people with a left mainstem coronary artery stenosis, and in those with ‘triple vessel disease’ (significant stenoses of the left anterior descending, left circumflex and right coronary arteries) who have impaired left ventricular function. In less severe disease, it is used for symptom relief.

- **Percutaneous coronary intervention (PCI; angioplasty, usually with insertion of a stent to maintain patency)** is currently used for symptom relief only. Angioplasty alone is followed by a restenosis rate of about 40% at 6 months. This is reduced to about 20% by the use of a bare-metal stent, but with no difference in the risk of myocardial infarction or sudden death. Drug-eluting stents are coated with a polymer matrix containing an antiproliferative drug such as sirolimus or tacrolimus (Ch. 38). Their use has further reduced the risk of restenosis at 6 months to about 8%, but some have been associated with an increased risk of myocardial infarction. Insertion of a coronary artery stent requires intensive antiplatelet therapy with a combination of aspirin and clopidogrel to minimise early in-stent thrombosis. Short-term use of a glycoprotein IIb/IIIa antagonist such as abciximab (Ch. 11) further improves outcome for high-risk procedures.

Symptoms, and their response to treatment, are a poor guide to the severity of coronary artery disease, and exercise stress testing is a more accurate predictor. A poor performance during exercise testing, or failure to respond to two prophylactic drugs in adequate dosages, should lead to consideration of coronary angiography, with a view to CABG or PCI.

### MANAGEMENT OF ACUTE CORONARY SYNDROMES

### MANAGEMENT OF ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

Acute coronary syndromes require urgent treatment even if there is no initial evidence of myocardial infarction, since there is about a 10% risk of progression from unstable angina to myocardial infarction or death. A rise in the plasma concentrations of a sensitive marker of myocardial damage, such as troponin I or troponin T, is used to differentiate unstable angina from myocardial infarction, and to identify those at highest risk of a subsequent myocardial infarction or death. The management of an acute coronary syndrome is initially determined by the ECG. In the absence of ST-segment elevation on the ECG, management is intensive until a plasma troponin is obtained about 12 h after the onset of pain. If this is not raised and the ECG does not show ischaemic changes, then the risk of a subsequent cardiac event is much lower and treatment is then less intensive.

- **Initial treatment is with sublingual glyceryl trinitrate and supplementary oxygen. Analgesia with an intravenous opioid such as morphine (Ch. 19), together with an antiemetic, is used for prolonged pain that does not settle with a nitrate.**

- **A loading dose of aspirin, followed by low-dose aspirin for maintenance** (Ch. 11), should be given. Full anticoagulation with intravenous heparin or, more commonly, subcutaneous low-molecular-weight heparin (enoxaparin; Ch. 11) produces additive benefit. The risk of myocardial infarction or death within 14 days is reduced by about 60% using combined treatment with aspirin and heparin. Fondaparinux (Ch. 11) given subcutane-
Mannitol is as effective as low-molecular-weight heparin, and with a lower risk of bleeding. Dual platelet inhibition with clopidogrel and aspirin for at least a month and up to 1 year reduces the risk of myocardial infarction by a further 20% in non-ST-segment elevation myocardial infarction (NSTEMI) compared to aspirin alone, but is of no benefit in unstable angina. In people with NSTEMI who undergo percutaneous coronary intervention (PCI), the direct thrombin inhibitor bivalirudin (Ch. 11) further reduces the risk of ischaemic events during and after the procedure in combination with clopidogrel and aspirin. Heparin and a glycoprotein IIb/IIIa antagonist such as tirofiban (Ch. 11) can be used instead of bivalirudin, but there is a higher risk of bleeding.

- A β-adrenoceptor antagonist is the first-choice antiangiinal treatment, although a heart rate-limiting calcium channel blocker, such as verapamil or diltiazem, can be used if a β-adrenoceptor antagonist is contraindicated or not tolerated. A β-adrenoceptor antagonist reduces the risk of myocardial infarction by about 15% compared with no antiangiinal treatment. If the symptoms do not settle, then a dihydropyridine calcium channel blocker such as nifedipine, or nicorandil or a nitrate via a buccal tablet or by intravenous infusion can be used with a β-adrenoceptor antagonist. While these drugs often relieve symptoms, there is no evidence that they improve prognosis in acute coronary syndromes.

- In the acute phase of an acute coronary syndrome, angiography (followed when appropriate by CABG or PCI) is carried out for the 10% of people who are refractory to full medical treatment. If the unstable symptoms settle, those who had evidence of myocardial damage during the acute episode (an increase in the plasma concentration of troponin I or troponin T), or those who develop symptoms or ECG changes at an early stage during a standardised exercise test, should also be investigated by angiography.

- Cholesterol reduction to <4.0 mmol L⁻¹ should be initiated by diet and a statin at the time of the event (Ch. 48). This reduces the long-term risk of myocardial infarction or cardiac death by 25–30%.

**MANAGEMENT OF ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION**

The presence of ST-segment elevation on the ECG usually heralds a more extensive myocardial infarction, and, in contrast to non-ST-segment elevation myocardial infarction, assisted early opening of the occluded artery to reperfuse the myocardium limits the extent of myocardial damage and improves long-term outcomes.

- For pain relief, an intravenous opioid analgesic such as morphine (Ch. 19) is given, together with an antiemetic. Intramuscular injection should be avoided, since a low cardiac output and poor tissue perfusion often delay absorption. A nitrate (sublingual or intravenous) can also reduce pain by relief of coronary artery vasospasm at the site of the arterial occlusion, with restoration of some blood flow. An intravenous β-adrenoceptor antagonist can be given to reduce cardiac work, especially if there is hypertension, but should be avoided if there are signs of heart failure.

- Natural fibrinolysis can be enhanced by intravenous fibrinolytic therapy (Ch. 11) to rapidly reperfuse the occluded artery and limit the size of the infarct. Fibrinolysis is used only if there are clear ECG changes of ST-segment elevation acute myocardial infarction (characteristic ST-segment elevation in two or more contiguous leads) or left bundle branch block on the ECG and a good history of acute myocardial infarction. In the latter situation, an acute myocardial infarction cannot be easily diagnosed from the ECG but mortality is high. The greatest reduction in mortality is achieved in people at highest risk of death (i.e. anterior infarcts rather than inferior), the elderly (>65 years of age) and those with a presenting systolic blood pressure below 100 mmHg. Of the available agents, alteplase (rt-PA) produces more rapid reperfusion and opens a greater percentage of occluded vessels than does streptokinase, with better myocardial salvage and a consequent reduction in mortality. The synthetic rt-PA analogues such as tenecteplase achieve a similar outcome to alteplase, but are easier to administer and are increasingly used. Streptokinase is less commonly used now, since it produces symptomatic hypotension during about 10% of administrations. Alteplase and related drugs are less likely to lower blood pressure. Streptokinase should not be given if it has previously been used, since high titres of streptokinase-neutralising antibodies often persist for several years and may make repeat administration ineffective (Ch. 11). Alteplase and related compounds are relatively short-acting, and anti-coagulation with heparin (preferably low-molecular-weight heparin) for 48 h after their use reduces reocclusion of the artery. As an alternative, fondaparinux (Ch. 11) for 8 days may further reduce mortality and reinfarction by up to 25% compared with heparin. Anticoagulation is not usually given after streptokinase because of its longer duration of action. Fibrinolytic therapy significantly reduces mortality if given within 12 h of the onset of pain, but the survival advantage is greater the earlier treatment is given. Treatment within 6 h of the onset of pain saves 30 lives per 1000 people treated, whereas only 20 lives per 1000 are saved if treatment is delayed to 6–12 h after the onset of pain.

- Percutaneous coronary intervention (PCI: coronary angioplasty, usually with insertion of a stent) can reduce mortality more than a fibrinolytic drug. It is the treatment of choice for reperfusion in ST-segment elevation myocardial infarction (‘primary’ PCI) if it can be started within 120 min of presentation, or if there are contraindications to fibrinolysis. ‘Rescue’ PCI can be considered if fibrinolysis has failed to reperfuse the infarct-related vessel.

In addition to the management discussed above, complications of myocardial infarction may need specific treatment (Box 5.1).

**Secondary prophylaxis after myocardial infarction**

Secondary prophylaxis to reduce late mortality after myocardial infarction can be achieved with several approaches.
Beta-adrenoceptor antagonists, started orally soon after
Low-dose aspirin (Ch. 11) inhibits platelet aggregation
An ACE inhibitor (Ch. 6) is of greatest benefit if there is
Box 5.1 Complications after myocardial infarction
Heart failure
Cardiogenic shock
Cardiac rupture
Free wall rupture
Ventricular septal defect
Arrhythmias
Ventricular fibrillation
Ventricular tachycardia
Supraventricular tachycardias
Sinus bradycardia and heart block
Pericarditis
Intracardiac thrombus

■ Stopping smoking is of major benefit, since it reduces
the mortality after a myocardial infarction by up to 50%. Rehabilitation
programmes, which include exercise, also
reduce mortality by up to 25% and improve psychologi-
cal recovery.

■ Low-dose aspirin (Ch. 11) inhibits platelet aggregation
and reduces mortality in the first few weeks when started
within 24 h of the onset of pain, and reduces later mor-
tality by up to 25%. Concurrent use of clopidogrel with
aspirin for up to 1 year after the infarction reduces rein-
farction after both ST- and non-ST-segment elevation
myocardial infarction, compared with aspirin alone.

■ Beta-adrenoceptor antagonists, started orally soon after
the infarct, reduce both death and reinfarction by about
25%, although the mechanism is unknown. Greatest
benefit is seen in those at highest risk, for example fol-
lowing anterior infarction and in those who have had
serious post-infarct arrhythmias or post-infarct angina or
heart failure. Heart failure should be controlled before a
β-adrenoceptor antagonist is given (Ch. 7).

■ An ACE inhibitor (Ch. 6) is of greatest benefit if there is
clinical or radiological evidence of heart failure after
myocardial infarction, with a reduction in mortality of
about 25% over the subsequent year. There is a smaller
survival advantage if there is significant left ventricular
dysfunction after the infarction (an ejection fraction of
40% or less) but no clinical evidence of heart failure. In
this group, a 20% reduction in mortality over 3–5 years
after the event is accompanied by a significant reduction
in non-fatal reinfarction (although the mechanism of this
effect is unknown). ACE inhibitors also reduce both non-
fatal reinfarction and death when there is well-preserved
left ventricular function, although the absolute benefits
are smaller. The effects of an ACE inhibitor are greatest
with high doses, and are additional to those of a
β-adrenoceptor antagonist. An angiotensin receptor
antagonist (Ch. 6) has similar efficacy following myocar-
dial infarction, and should be considered if an ACE
inhibitor is poorly tolerated.

■ Verapamil and diltiazem produce a small reduction in
reinfarction, but do not reduce mortality. They may be
detrimental if there have been symptoms or signs of
heart failure. These drugs should be considered as an
option only for those at high risk who cannot tolerate a
β-adrenoceptor antagonist and who do not have signifi-
cant left ventricular dysfunction. Nifedipine and similar
calcium channel blockers do not improve prognosis after
myocardial infarction.

■ Long-term anticoagulation with warfarin (Ch. 11) reduces
mortality and reinfarction to a similar extent to low-dose
aspirin. In combination with aspirin, warfarin produces a
further reduction in both fatal and non-fatal events but
with an increased risk of bleeding.

■ Cholesterol reduction to <4.0 mmol l⁻¹ should be
attempted by diet and usually cholesterol-lowering
drugs, especially the statins (Ch. 48). Statins reduce
reinfarction and cardiac death by 25–30%. Fibrates are
less effective, but may be useful if the total cholesterol
is not greatly raised but the high-density lipoprotein cho-
lesterol is low.

■ A Mediterranean diet reduces mortality after myocardial
infarction. A further reduction in mortality can be
achieved with supplementary omega-3 fatty acids. An
antiarrhythmic effect may be responsible for these ben-
efits (Ch. 48).

FURTHER READING

General
Hansson GK (2003) Inflammation, atherosclerosis and coronary heart
channels: from pharmacology to function. Biochim Biophys Acta
1757, 715–720
cardiac potassium channels. Cardiovasc Res 62, 9–33
Van der Hayden MAG, Wijnhoven TJM, Opthof T (2005) Molecular
aspects of adrenergic modulation of cardiac L-type Ca²⁺ channels.
Cardiovasc Res 65, 28–39
Stable angina
2533
Bales AC (2004) Medical management of chronic ischemic heart
disease. Selecting specific drug therapies, modifying risk factors.
Postgrad Med 115, 39–46
874
Borer JS (2004) Drug insight: β inhibitors as specific heart-rate-
and the links with endothelial dysfunction and oxidative stress. Br J
Clin Pharmacol 56, 620–628
Feher MD (2003) Lipid lowering to delay the progression of coronary
artery disease. Heart 89, 451–458
Heidenreich PA, McDonald KM, Hasle T et al (1999) Meta-analysis of
trials comparing β-blockers, calcium antagonists and nitrates for
stable angina. JAMA 281, 1927–1936
Knight CJ (2003) Antiplatelet treatment in stable coronary artery
disease. Heart 89, 1273–1278
Ko DT, Hebert PR, Coffey CS et al (2002) β-blocker therapy and
symptoms of depression, fatigue, and sexual dysfunction. JAMA
288, 351–357
Lancet 372, 1335–1341

BMJ 334, 946–949

Lancet 367, 69–78

Pharmacol Ther 100, 215–234

Arch Intern Med 162, 2197–2202

Unstable angina and non-ST-segment elevation myocardial infarction

Bavry AA, Kumbhani DJ, Quiroz R et al (2004) Invasive therapy along with myocardial infarction
Unstable angina and non-ST-segment elevation


Ong HT (2007)

Arch Intern Med 168, 933–941

Am Heart J 153, 830–835

Lancet 355, 1936–1942

Arch Intern Med 163, 1145–1153

Am J Cardiol 92, 651–655

BMJ 334, 1256–1259

Arch Intern Med 165, 241–250

Arch Intern Med 161, 1484–1491

ST-segment elevation myocardial infarction

Lancet 361, 847–858

Heart 90, 581–588

COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group (2005) Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. 
Lancet 366, 1607–1621

BMJ 328, 693–697

Gersh BJ, Antman EM (2006) Selection of the optimal reperfusion strategy for STEMI: does time matter? 
Eur Heart J 27, 761–763

N Engl J Med 356, 47–54

Am J Med 116(5A), 47s–63s

Ann Intern Med 141, 693–704

Int J Cardiol 114, 291–299

Arch Intern Med 165(5), S17–S23

Ann Intern Med 145, 610–617

Lancet 372, 570–584

e. Recombinant tissue-type plasminogen activator (rt-PA) is a genetically engineered copy of an endogenous fibrinolytic agent. rt-PA inhibits the formation of plasmin.

2. From the following statements about angina and myocardial infarction, choose the one incorrect statement.
A. Isosorbide 5-mononitrate is an active metabolite of isosorbide dinitrate and has the advantage that it does not undergo first-pass metabolism.
B. Verapamil can reduce arterial blood pressure without causing reflex tachycardia.
C. Platelet inhibitors such as the glycoprotein Iib/IIa antagonist tirofiban can reduce the risk of myocardial infarction in high-risk individuals with unstable angina.
D. Cholesterol reduction is of little benefit in reducing the risk of recurrence of myocardial infarction.
E. Nifedipine does not improve prognosis after myocardial infarction.

3. Tolerance can develop when using isosorbide dinitrate. Which one of the following changes to the treatment regimen would reduce the likelihood of tolerance developing?
TK, a 65-year-old man who was a landscape gardener, had been having episodes of chest pain that he likened to indigestion. They were brought on by moderately strenuous exercise and relieved by rest but were not relieved by antacids. The symptoms had been present for approximately 1 year, but recently the frequency and intensity of the pains had become worse and they were now occurring several times a week. He was overweight. He drank about 10 units of alcohol a week. He had a good exercise tolerance during a diagnostic exercise test but his ECG showed anterolateral ST-segment depression at peak exercise. There was no evidence of heart failure. A diagnosis of angina was made, and medical treatment started.

Despite continuing medication, 6 months later TK awoke with severe chest pains and dyspnœa that was not relieved by glyceryl trinitrate. Examination, biochemical tests and ECG recordings all led to the diagnosis of an acute ST-segment elevation myocardial infarction.

a. How could his acute attacks of angina have been treated?

b. The frequency of his attacks required prophylactic treatment. What options were available to reduce the frequency of anginal attacks?

c. What other drugs could have been useful to improve his prognosis?

d. Would lifestyle changes help Mr TK?

e. In unstable angina, which drug treatments would have been likely to reduce the progression of the episodes to myocardial infarction or sudden death?

f. What was the likely cause of the myocardial infarction?

g. Why was it important to give fibrinolytic therapy as quickly as possible?

h. TK was given the fibrinolytic agent recombinant tissue-type plasminogen activator (rt-PA; alteplase) because of fears that he would get an allergic response to streptokinase. Was this justified?

i. He was given 150 mg aspirin orally, after an initial loading dose. Would this have any added benefit if fibrinolytic therapy was also given?

j. The normal therapeutic dose of aspirin for headache is about 650 mg. Why was the dose given to TK so small?

k. Consideration was given to administering intravenous heparin to TK, but this was considered unnecessary because he had been given rt-PA. Was this decision correct?

I. Following his myocardial infarction, long-term prophylactic treatment of his condition was considered. Which of the following drugs would have been likely to be of benefit: low-dose aspirin, a β-adrenoceptor antagonist, an ACE inhibitor, verapamil, diltiazem or warfarin?

ANSWERS

1. a. False. Nitric oxide increases cGMP synthesis to bring about reduced intracellular free Ca²⁺ and vasodilation.

b. True. Glyceryl trinitrate undergoes extensive first-pass metabolism after oral dosing, since initial entry into the systemic circulation is via the portal circulation and the liver. Transdermal patches or sublingual administration avoids the portal circulation and the drug gains direct access to the systemic circulation.

c. False. Glyceryl trinitrate does not increase total coronary blood flow. It can, however, treat angina by increasing flow to the ischaemic areas by dilating collateral blood vessels or reducing coronary vasospasm.

d. False. A major component of the benefit of glyceryl trinitrate is its peripheral vasodilator action, reducing preload and, to a lesser extent, peripheral vascular resistance, and afterload. These reduce workload on the heart. The reflex tachycardia that occurs through a fall in peripheral resistance can be reduced by concomitant treatment with a β-adrenoceptor antagonist.

e. False. rt-PA cleaves plasminogen to increase the formation of plasmin, which results in the degradation of the fibrin that forms the framework of the thrombus (see Ch. 11).

2. Answer D.

A. Correct – and can therefore give a more predictable response of greater duration.

B. Correct. Unlike the dihydropyridines, verapamil also acts on the heart and reflex tachycardia does not occur. Modified-release formulations of dihydropyridines or the long-acting dihydropyridine amlodipine also reduce the incidence of reflex tachycardia.

C. Correct. Platelet inhibition with an intravenous glycoprotein IIb/IIIa antagonist such as tirofiban reduces the risk of myocardial infarction or death in those at
high risk (see also Ch. 11). These agents are most effective when there is a raised plasma concentration of the markers of myocardial damage, troponin I or troponin T.

D. Incorrect. Cholesterol reduction to <4.0 mmol L\(^{-1}\) should be attempted. Statins reduce reinfarction and cardiac death by 25–30%. Fibrates are less effective, but may be useful if the total cholesterol is normal or only modestly increased but the high-density lipoprotein cholesterol is low.

E. Correct. Nifedipine and similar dihydropyridine calcium channel antagonists do not improve prognosis after myocardial infarction. Verapamil and diltiazem produce a small reduction in reinfarction, but do not reduce mortality. They may be detrimental if there are signs of heart failure. These drugs should only be considered as an option for those at high risk who cannot tolerate a \(\beta\)-adrenoceptor antagonist and who do not have significant left ventricular dysfunction.

3. Answer B.

The only way to reduce tolerance is to allow periods with low plasma organic nitrate. Tolerance will develop to all the organic nitrates independent of the route given if plasma concentrations remain high continuously. A \(\beta\)-adrenoceptor antagonist will reduce reflex tachycardia but not the development of tolerance.

4. Answer B.

Verapamil and atenolol both have a negative inotropic effect and this could be problematic, particularly if there are signs of heart failure. They also have a negative chronotropic effect and the combination can cause severe bradycardia and heart block. It is possible that amlodipine and atenolol could cause excessive hypotension, but this is less likely. The other combinations are frequently given together:

A. atenolol prevents reflex tachycardia caused by the nitrate
B. diltiazem does not have any direct effect on the heart
E. aspirin will reduce the likelihood of development of myocardial infarction.

5. Case history answers

a. For acute attacks, sublingual glyceryl trinitrate is the first-choice drug to give rapid relief, although protection is only short-lived.

b. For prophylaxis, a \(\beta\)-adrenoceptor antagonist is often the treatment of first choice, or a calcium channel blocker if this is contraindicated. A combination of both, or addition of a long-acting nitrate (but tolerance is a problem), could be used if symptoms are not well controlled with a single agent, but the benefit of triple therapy is not convincing. For example, atenolol and diltiazem given together significantly decrease the number of angina attacks compared with either used alone. These drugs will also lower blood pressure and heart rate, which are precipitating factors for angina. Their use together should be carefully monitored, however, because of the dangers of compounded bradycardia or heart failure.

c. Additional therapy to improve prognosis includes low-dose aspirin (75–150 mg), which has been shown to reduce the risk of subsequent myocardial infarction. Lowering plasma cholesterol concentration by diet or by drugs such as simvastatin can also reduce the risk of subsequent myocardial infarction.

d. Smoking, lack of exercise and obesity are all risk factors for coronary heart disease. TK is exposed to these increased risks and should address these by lifestyle changes.

e. The most consistent evidence is for combined use of heparin and aspirin in unstable angina. Addition of a \(\beta\)-adrenoceptor antagonist produces a small additional benefit.

f. Coronary artery occlusion at the site of an atheroma, causing myocardial necrosis.

g. The benefit of fibrinolytic therapy is strongly dependent upon the delay between symptoms and administration. The benefit is particularly great if fibrinolytic therapy can be administered within 6 h from the onset of pain, but there is good evidence for benefit until at least 12 h.

h. Allergic reactions to streptokinase are extremely rare. TK had not had a previous myocardial infarction and had not previously been administered streptokinase, so would be unlikely to have high titres of streptokinase-neutralising antibodies. It would, therefore, be safe to give TK streptokinase unless he had severe symptomatic hypotension. However, alteplase or a derivative is usually preferred.

i. Aspirin and fibrinolytic therapy have been shown to have additive benefit for treating acute myocardial infarction, reducing subsequent reinfarction or death.

j. Low doses of aspirin reduce the production of the platelet-aggregating agent thromboxane \(A_2\) by platelets, while having less effect on the production of the platelet-disaggregating agent prostaglandin \(I_2\) from endothelial cells. Large doses of aspirin do not produce any additional benefit, and the risk of gastric irritation or ulceration is increased.

k. This is incorrect. Streptokinase has a longer duration of action than rt-PA and it is generally unnecessary to administer heparin when streptokinase has been given. However, it is necessary after the short-acting rt-PA, when it improves the long-term patency of the artery.

l. Low-dose aspirin, \(\beta\)-adrenoceptor antagonists and ACE inhibitors all reduce mortality and the risk of reinfarction. The \(\beta\)-adrenoceptor antagonist will need to be given under close observation, since it carries a risk of worsening heart failure. In people who have signs of heart failure, verapamil and diltiazem may also be detrimental. Warfarin reduces mortality and reinfarction to a similar extent as low-dose aspirin, so is not required unless aspirin is poorly tolerated.
### Drugs used to treat ischaemic heart disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h) and kinetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-adrenoceptor antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All drugs are given orally unless otherwise indicated. Beta-adrenoceptor antagonists are used in a wide variety of indications in addition to ischaemic heart disease, including hypertension and arrhythmias. For completeness, all oral or parenteral β-adrenoceptor antagonists are listed in this chapter, irrespective of their specific licensed clinical uses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>7 [M + R] Oral bioavailability is 50–70%; active acetylated metabolite</td>
<td>β₁-Adrenoceptor selective; 10% β₁-adrenoceptor selective PAA; drug-induced lupus reported</td>
</tr>
<tr>
<td>Atenolol</td>
<td>7 [R] Eliminated by glomerular filtration</td>
<td>β₁-Adrenoceptor selective; given orally, or by injection or intravenous infusion</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>13–24 [M + R] High oral bioavailability (80–90%); oxidised in liver and metabolites eliminated in urine</td>
<td>Also used topically for glaucoma; β₁-adrenoceptor selective</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>11 [M + R] Oral bioavailability is 90%; eliminated equally by glomerular filtration and secretion, and by metabolism in the liver</td>
<td>β₁-Adrenoceptor selective (less than atenolol)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>6 [M] Oral bioavailability is 20–30% owing to first-pass metabolism; metabolites eliminated in bile and urine</td>
<td>β-Adrenoceptor non-selective; vasodilator action from α₁-adrenoceptor blockade</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>5 [R + some bile] Polar compound that has an oral bioavailability of 30–70% because of poor absorption</td>
<td>β₁-Adrenoceptor-selective; vasodilator action because of β₁-adrenoceptor PAA</td>
</tr>
<tr>
<td>Esmolol</td>
<td>0.15 [M] Rapidly hydrolysed in erythrocytes</td>
<td>β₁-Adrenoceptor selective; given by intravenous infusion</td>
</tr>
<tr>
<td>Labetalol</td>
<td>3 [M] Oral bioavailability is variable (10–90%) owing to first-pass metabolism; metabolised by glucuronidation</td>
<td>β₁-Adrenoceptor selective; vasodilator action through α-adrenoceptor blockade; α₁/β₁ selectivity is 1:2 orally and 1:7 intravenously; given orally, or by intravenous injection or intravenous infusion</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>3–10 [M + R] Oral bioavailability is about 50%; wide variability in metabolism by CYP2D6</td>
<td>β₁-Adrenoceptor selective (less than atenolol); given orally, or by injection or intravenous infusion</td>
</tr>
<tr>
<td>Nadolol</td>
<td>17–24 [R + bile] Poor absorption (30%)</td>
<td>β₁-Adrenoceptor non-selective</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>10 [M] Metabolised by oxidation</td>
<td>β₁-Adrenoceptor selective; vasodilator from generation of NO</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>2 [M] Oral bioavailability is 20–80% owing to first-pass metabolism; hydroxy metabolite also active</td>
<td>β₁-Adrenoceptor non-selective; 18% β₁-adrenoceptor non-selective PAA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>4 [M + R] High oral bioavailability (&gt;90%); approximately equal elimination in urine and by metabolism</td>
<td>β₁-Adrenoceptor non-selective; vasodilator because of 35% β₁-adrenoceptor non-selective PAA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4 [M] Oral bioavailability is 10–50% owing to first-pass metabolism; oxidised by P450 and conjugated with glucuronic acid (17%)</td>
<td>β₁-Adrenoceptor non-selective; given orally or by intravenous injection</td>
</tr>
<tr>
<td>Sotalol</td>
<td>7–18 [R]</td>
<td>See under class III drugs (Ch. 8); uses restricted to life-threatening arrhythmias</td>
</tr>
<tr>
<td>Timolol</td>
<td>2–5 [M + some R] Oral bioavailability is 30–60%; eliminated by metabolism and renal excretion (20%)</td>
<td>Also used topically for glaucoma; β₁-adrenoceptor non-selective</td>
</tr>
</tbody>
</table>
### Drugs used to treat ischaemic heart disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h) and kinetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All are given orally unless stated otherwise; indications include angina, hypertension, Raynaud’s phenomenon, arrhythmias and subarachnoid haemorrhage (see Chs 6 and 8–10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dihydropyridines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolites are generally inactive; modified-release formulations are available for many of these drugs and are preferred for the treatment of angina and hypertension as they reduce fluctuations in blood pressure and reflex tachycardia. They have no antiarrhythmic activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>30–60 [M] Oral bioavailability is 60–80%; oxidised in liver</td>
<td>No detrimental effect in heart failure; used once daily</td>
</tr>
<tr>
<td>Felodipine</td>
<td>12–25 [M] Oral bioavailability is about 15% owing to first-pass metabolism; oxidised by CYP3A4</td>
<td>No detrimental effect in heart failure; used once daily</td>
</tr>
<tr>
<td>Isradipine</td>
<td>2–6 [M] Oral bioavailability is 20% owing to first-pass metabolism</td>
<td></td>
</tr>
<tr>
<td>Lacidipine</td>
<td>7–8 [M] Low and variable oral bioavailability (4–52%) (common to many dihydropyridines owing to variable intestinal and hepatic CYP3A4 activity)</td>
<td></td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>3–5 [M] Oral bioavailability is 44% and is increased by a fatty meal; eliminated by CYP3A4-mediated oxidation to inactive metabolites</td>
<td>Long duration of action (24 h), by an undefined mechanism; used once daily</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>1–12 [M] Oral bioavailability is dose-dependent owing to first-pass metabolism (5–10% at low doses and 30–45% at high doses); metabolised in liver</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>2–4 [M] Oral bioavailability is about 40% owing to first-pass metabolism by CYP3A4 in gut wall and liver</td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>8–9 [M] Oral bioavailability is 5–10%; eliminated by oxidation in the liver</td>
<td>Selective for cerebral arteries; use is confined to the prevention and treatment of ischaemic neurological deficits following subarachnoid haemorrhage; given orally or by intravenous infusion</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>2–4 [M] Oral bioavailability is low (5–10%) and variable owing to intestinal and hepatic CYP3A4 metabolism; numerous metabolites</td>
<td></td>
</tr>
<tr>
<td><strong>Non-dihydropyridines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In contrast to dihydropyridines, these drugs are also used for treatment and prevention of supraventricular arrhythmias, but are less effective for Raynaud’s phenomenon. Modified-release formulations are available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>2–5 [M] Oral bioavailability is about 50% owing to first-pass metabolism; a number of metabolites, mostly inactive</td>
<td>Reduces heart rate; some negative inotropic effect and should be avoided in heart failure</td>
</tr>
<tr>
<td>Verapamil</td>
<td>2–5 [M] Oral bioavailability is about 20% owing to first-pass metabolism; oxidised by CYP3A4; metabolites retain activity but are rapidly eliminated by conjugation; half-life is longer after chronic dosing (5–12 h)</td>
<td>Reduces heart rate; marked negative inotropic effect and should be avoided in heart failure; given orally or by slow intravenous injection (over 2 min)</td>
</tr>
<tr>
<td>Drug</td>
<td>Half-life (h) and kinetics</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>1–3 min [M]</td>
<td>Essentially complete first-pass metabolism if swallowed; the dinitrate metabolites have 10% of the activity but half-lives of about 40 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given sublingually, buccally, topically or as an intravenous infusion</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>0.5–2 [M]</td>
<td>Low bioavailability from sublingual (30–60%) and topical (10–30%) administration; the active mononitrate metabolite inhibits clearance of the dinitrate during chronic treatment; high first-pass metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given sublingually, orally (as normal or modified-release tablets), topically or by intravenous infusion</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>3–7 [M]</td>
<td>Oral bioavailability approaches 100%; metabolised by denitration and glucuronide conjugation; low first-pass metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given orally</td>
</tr>
<tr>
<td><strong>Potassium channel activators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicorandil</td>
<td>1 [M]</td>
<td>Essentially complete oral bioavailability; oxidised and denitrated in the liver; biological effect much longer than predicted by half-life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Used for angina; given orally</td>
</tr>
<tr>
<td><strong>Specific sinus node inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>2 [M + R]</td>
<td>Has an active N-dealkylated metabolite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Used for angina; given orally</td>
</tr>
<tr>
<td><strong>Late sodium current inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine</td>
<td>1.4–1.9 [M + 5%R]</td>
<td>Oral bioavailability is about 35–50%; metabolised largely by CYP3A4 and to a limited extent by CYP2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approved for treatment of stable angina (in combination with amlodipine, β-adrenoceptor antagonists or nitrates) in those who have not achieved an adequate response or are intolerant of other antianginal agents</td>
</tr>
</tbody>
</table>

[M], metabolism; [R], renal excretion; PAA, partial agonist activity.