Drugs for systemic hypertension and angina

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Abstract

Drugs used for the treatment of hypertension and for the management of angina are discussed here. Their major mechanisms of action, key pharmacokinetic principles essential for safe use and important adverse effects are explained. Each class of drug is also given context for effective clinical use.

Keywords α-Adrenoceptor blockers; β-adrenoceptor blockers; angina pectoris; calcium channel blockers; hypertension; MRCP; nitrates; sinus node inhibitor; vasodilators

Key points

- Antihypertensive medications target three main mechanisms to lower blood pressure: the renin–angiotensin system, the autonomic nervous system and locally active mediators
- Anti-anginal medications primarily aim to reduce myocardial oxygen demand or improve oxygen supply to the myocardium
- Oxygen demand to the myocardium is typically reduced by direct action on the heart reducing heart rate and contractility, by reducing preload by dilatation of the venous system, or by reducing afterload by decreasing arterial resistance

Drugs for systemic hypertension

Drugs used for the management of hypertension manipulate three systems that control systemic blood pressure: the autonomic nervous system, the renin–angiotensin–aldosterone system and locally acting vascular mediators (Figure 1).

Calcium channel blockers

Mechanisms: calcium channel blockers reduce blood pressure largely by arterial vasodilatation, achieved by blocking the influx of calcium via transmembrane L-type channels in the smooth muscle cells of resistance vessels. These channels are also present in the myocardium, and blockade here causes a reduction in heart rate and contractility, which contributes to the reduction of systemic blood pressure.

Calcium channel blockers can be subdivided into the dihydropyridine group (e.g. nifedipine, amlodipine) and non-dihydropyridines (Table 1), which bind to different sites on L-type calcium channels. The different subunit structures of these channels in vascular and cardiac tissue explain drug selectivity: dihydropyridines act mainly on vascular smooth muscle, whereas verapamil and, to a lesser extent, diltiazem also have important actions on the myocardium.[1]

Pharmacokinetics: most calcium channel blockers have short half-lives, so modified-release formulations are necessary for a prolonged action. Amlodipine has a longer half-life of 1–2 days.

Adverse effects: dihydropyridines produce vasodilator effects, such as flushing, headache, ankle oedema and reflex tachycardia. Many of these (other than oedema) can be reduced by using a modified-release formulation. By contrast, diltiazem and verapamil produce less vasodilatation but can cause bradycardia and heart block, which is a greater risk when they are taken with a β-adrenoceptor blocker. Verapamil and diltiazem can worsen heart failure owing to their negative inotropic effects, but many dihydropyridines also reduce myocardial contractility when left ventricular function is impaired.

β-Adrenoceptor antagonists (β-blockers)

Mechanism: β-adrenoceptor antagonists are competitive antagonists. They reduce blood pressure by decreasing cardiac output and, indirectly, by reducing renin release, which results in vasodilatation and decreased plasma volume. There are many different β-blockers with differing pharmacological effects (Table 2):

- β_1-adrenoceptor selective (cardioselective) drugs (e.g. atenolol, bisoprolol, metoprolol) show selectivity for β_1-adrenoceptors, although this decreases at higher doses.
- Non-selective drugs (e.g. propranolol) are antagonists at both β_1-and β_2-adrenoceptors. Both non-selective and β_1-selective drugs have the same effect on blood pressure.
- Partial agonist activity at β-adrenoceptors (e.g. pindolol) results in less resting bradycardia and some peripheral vasodilatation.
- Vasodilator activity can also be produced by drugs with antagonist action at α-adrenoceptors (e.g. labetalol, carvedilol), or by those promoting endothelial nitric oxide production (e.g. nebivolol). Vasodilatation may be advantageous when treating hypertension.

Pharmacokinetics: lipophilic drugs, such as propranolol and metoprolol, have good gut absorption and extensive liver metabolism that varies greatly among individuals, so individualized dosing is more important to maximize benefit. Their half-lives are generally short, and modified-release formulations are usually preferred.

Hydrophilic drugs, such as atenolol, are less well absorbed orally, but are excreted unchanged in the urine. They usually give more predictable plasma concentrations and generally have longer half-lives.

Adverse effects: β_1-adrenoceptor antagonists can cause acute left ventricular failure when given in large doses to people with impaired left ventricular function. They can also worsen

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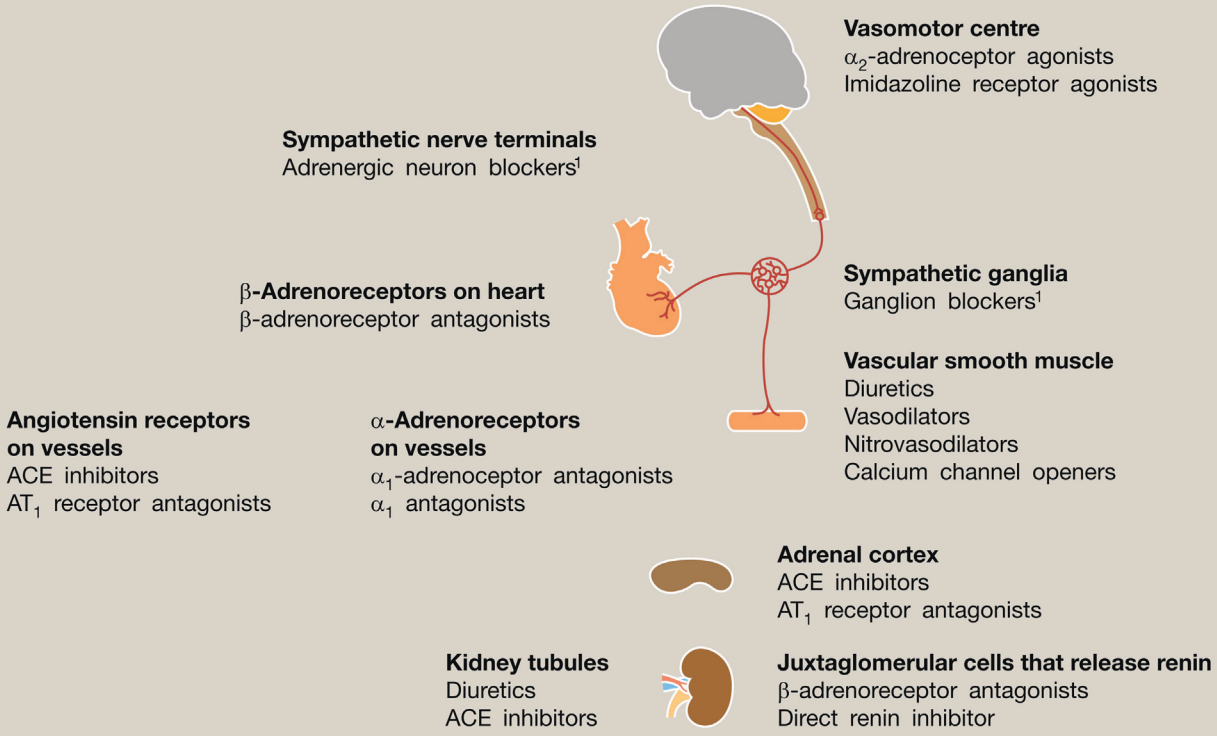
Sites of action of drugs for the treatment of hypertension



[1]Classes of drug that are rarely used now. ACE, angiotensin-converting enzyme; AT, angiotensin II.

Adapted from Waller DG, Renwick AG and Hillier K. *Medical Pharmacology and Therapeutics.* 3rd edition. Philadelphia: Saunders, 2010. With permission from Elsevier.

Figure 1

intermittent claudication and Raynaud's phenomenon, and excessive bradycardia can lead to syncope.

β_2-Adrenoceptor antagonism can produce bronchospasm in individuals with asthma, a potential problem even with cardioselective drugs. This is rarely an issue in chronic obstructive pulmonary disease, where there is little reversibility of the airway narrowing. Gluconeogenesis in the liver is reduced, which in people with insulin-dependent diabetes mellitus can increase the risk of hypoglycaemia while blocking the physiological signs associated with hypoglycaemia.

Most β-blockers alter blood lipids by raising concentrations of triglycerides (triacylglycerols) and decreasing high-density lipoprotein-cholesterol. Central nervous system effects are more prominent with lipophilic drugs that readily cross the blood–brain barrier; these can include sleep disturbance, vivid dreams and hallucinations.

Sudden withdrawal should be avoided, especially in ischaemic heart disease, as upregulation of β-adrenoceptors with chronic use can lead to increased catecholamine sensitivity, with tachycardia and palpitation.

The main interactions of β-blockers are with the calcium channel blockers diltiazem and especially verapamil. Combinations can cause profound bradycardia and hypotension.[1]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists

In hypertension, these drugs produce arterial vasodilatation by limiting the direct effects of angiotensin II on vascular smooth muscle and its ability to increase sympathetic tone. They also decrease the production of aldosterone, which promotes renal salt and water loss. For further details, see the article on drugs for heart failure (see also Drugs for heart failure and arrhythmias in *Medicine* 2022; **50**(8)).

Direct renin inhibitors

Mechanism: aliskiren (Table 3) is a selective renin inhibitor that competitively binds to renin and blocks the generation of angiotensin I (and therefore angiotensin II). Unlike ACE inhibitors and angiotensin receptor antagonists, it does not cause a compensatory rise in plasma renin, and produces a more complete block of the pathway.

Adverse effects: diarrhoea and cough are reported. When used in combination with an ACE inhibitor or angiotensin II receptor antagonist, renal function can deteriorate. Such combinations are contraindicated in patients with renal impairment or diabetes mellitus.[2]

Calcium channel blockers

Drug	$t_{½}$ (hours)	Modified-release	Negative inotropic effect	Vasodilator	Bradycardia	Dose reduction	Pregnancy	Breastfeeding
Dihydropyridines								
Amlodipine	30–60	No	No	+++	No	L	?A (3)	A
Felodipine	12–25	Yes	No	+++	No	L	A	
Isradipine	2–6	No	+	+++	No	L	?A (3)	A
Lacidipine	7–8	No	+	+++	No	L	?A (3)	A
Lercanidipine	3–5	No	+	+++	No	L, R	A	A
Nicardipine	1–12	Yes	+	+++	No	L, R	?A (3)	A
Nifedipine	2–4	Yes	+	+++	No	L	?A (3)	
Non-dihydropyridines								
Diltiazem	2–5	Yes	++	++	Yes	L, R	A	?A
Verapamil	2–5	Yes	+++	+	Yes	L	A	

Modified-release: formulation available to prolong effect.
Negative inotropic effect: when present, avoid in heart failure.
Vasodilator: comparative degree of vasodilator action.
Bradycardia: reduces heart rate at rest and on exercise.
Dose reduction: reduce dose or avoid in liver (L) impairment, or reduce dose in renal (R) impairment.
Pregnancy: avoid (A), or avoid unless essential in third trimester (?A (3)) as it can inhibit labour.
Breastfeeding: manufacturer advises avoid (A) as no information is available, or avoid (?A) unless there is no suitable alternative.
$t_{½}$, plasma half-life.

Table 1

Diuretics

Thiazide diuretics, and less frequently loop and potassium-sparing diuretics, are used to treat hypertension. Their mechanism of action is likely to be 2-fold. First, there is an initial decrease in intravascular volume, although compensatory mechanisms are activated to reduce this over time. Second, their sustained hypotensive action is by direct arterial dilatation, possibly by decreasing calcium entry into smooth muscle cells and by stimulating local vasodilator prostaglandins. Thiazides in particular reduce blood pressure at doses too low to cause effective diuresis.

Thiazide diuretics: in the kidney, thiazides inhibit Na^+/Cl^- co-transporters in the proximal diluting segment of the distal

β-adrenoceptor antagonists

Drug	$t_{½}$ (hours)	Selectivity	Vasodilator activity	Dose reduction	Pregnancy	Breastfeeding
Acebutolol	7	Yes	No	R	A (1, 2)	?A
Atenolol	7	Yes	No	R	A (1, 2)	?A
Bisoprolol	11	Yes	No	L, R	A (1, 2)	
Carvedilol	6	No	Yes	L	A (1, 2)	
Celiprolol	5	Yes	Yes	R	A (1, 2)	?A
Labetalol	3	Yes	Yes	L, R		
Metoprolol	3–10	Yes	No	L	A (1, 2)	
Nadolol	17–24	No	No	L, R	A (1, 2)	?A
Nebivolol	10	Yes	Yes	L, R	A (1, 2)	?A
Oxprenolol	2	No	Yes	L	A (1, 2)	
Pindolol	4	No	Yes	R	A (1, 2)	
Propranolol	4	No	No	L, R	A (1, 2)	
Timolol	2–5	No	No	L, R	A (1, 2)	

Selectivity: β_1-adrenoceptor selective (cardioselective).
Vasodilator activity: vasodilator action in addition to β-adrenoceptor antagonist action.
Dose reduction: avoid or reduce dose in liver (L) or renal (R) impairment.
Pregnancy: avoid (A) in first (1) or second (2) trimester.
Breastfeeding: possibly avoid (?A) as present in breast milk in quantities that can affect the infant.
$t_{½}$, plasma half-life.

Table 2

Other antihypertensive drugs

Drug	$t_{½}$ (hours)	Dose reduction	Pregnancy	Breastfeeding
Vasodilators				
Aliskiren	40	R	A	A
Hydralazine	4	L, R		
Minoxidil	3–4	R	A	
Centrally acting antihypertensives				
Clonidine	20–25			A
Methyldopa	1–2	L, R		
Moxonidine	2–3	L, R	A	A
α-Adrenoceptor antagonists				
Doxazosin	9–12			A
Indoramin	5			
Prazosin	3	L, R		
Terazosin	12			

Dose reduction: reduce dose or avoid in liver (L) or renal (R) impairment.
Pregnancy: avoid (A).
Breastfeeding: avoid (A).
$t_{½}$, plasma half-life.

Table 3

convoluted tubule and early collecting duct. Their diuretic action is less effective in renal impairment.

Adverse effects – hyponatraemia and hypokalaemia can occur, especially in the first 2 weeks of treatment; renal function and electrolytes should be checked within 2 weeks and less frequently thereafter. Hyperuricaemia can occur but does not often cause clinical gout. Prolonged hypokalaemia leads to progressive, reversible impairment of glucose tolerance over several months by inhibiting insulin release. Thiazides adversely affect plasma lipids, and this becomes more likely as the dose increases.

Loop diuretics: these are discussed in more detail in the chapter on drugs for heart failure. Because of their short duration of action, they are not used as first-line therapy for hypertension; however, they can be useful if volume expansion is contributing to the hypertension, as in renal failure or from the use of vasodilator drugs.

Potassium-sparing diuretics: these are discussed in more detail in the chapter on drugs for heart failure. Amiloride and triamterene are weak antihypertensive agents. Spironolactone is most useful to treat hyperaldosteronism or resistant hypertension.

Centrally acting antihypertensives (Table 3)

Selective imidazoline receptor agonist:

Mechanism – moxonidine stimulates imidazoline I1 receptors in the ventrolateral medulla, thereby decreasing sympathetic outflow and lowering blood pressure without reflex tachycardia. It has a long duration of action.

Adverse effects: moxonidine can cause a dry mouth, nausea, fatigue, dizziness and headache.

Centrally acting α_2-adrenoceptor agonists:

Mechanism – methyldopa is a pro-drug that is metabolized in the nerve terminal to a neurotransmitter analogue, while clonidine acts directly on the receptors. Potent agonist activity at presynaptic α_2-adrenoceptors in the brainstem decreases sympathetic outflow and increases vagal activity.

Methyldopa is most often used to treat hypertension in pregnancy, whereas clonidine is rarely used at all.

Adverse effects: decreased sympathetic activity can result in postural or exertional hypotension, which is less troublesome with clonidine. Ejaculatory failure can affect some men. The action of these drugs, particularly methyldopa, on the central nervous system can also cause sedation and drowsiness.

Methyldopa can cause a reversible positive Coombs test, although haemolytic anaemia is rare. Sudden withdrawal of clonidine can cause reflex tachycardia, sweating and anxiety.[1]

α-Adrenoceptor antagonists (α-blockers; Table 3)

Mechanism: α_1-selective antagonists, such as doxazosin and prazosin, act on postsynaptic α_1-adrenoceptors to relax smooth muscles in arterioles and venous capacitance vessels.

Adverse effects: postural hypotension from peripheral venous pooling can be troublesome. Headache, lethargy, dizziness, nausea and urinary frequency or incontinence also occur.

Minoxidil

Mechanism: minoxidil (Table 3) opens adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle, hyperpolarizing the cell membrane and closing voltage-gated calcium channels. This leads to smooth muscle relaxation and vasodilatation.

Adverse effects: hirsutism restricts the use of minoxidil to men. Activation of the renin–angiotensin–aldosterone system encourages salt and water retention with peripheral oedema. Minoxidil is a powerful vasodilator and can cause flushing,

headache and a reflex tachycardia with associated palpitation. Concurrent use of an ACE inhibitor or a β-blocker and a loop diuretic is almost always necessary to minimize adverse effects.

Hydralazine

Mechanism: hydralazine (Table 3) causes arterial vasodilatation by smooth muscle relaxation, possibly by activation of guanylate cyclase raising intracellular cyclic guanosine monophosphate. It is rarely used, except to treat pre-eclampsia.

Adverse effects: hydralazine is extensively metabolized by acetylation in the liver. Slow acetylators have a higher risk of dose-related systemic lupus erythematosus-type syndrome, which can develop over months and slowly resolves on drug withdrawal. Other adverse effects, which are largely caused by vasodilatation, include headaches, dizziness, flushing and hypotension. Tachycardia can result from reflex sympathetic activation.

Drugs for angina

Medications for angina generally aim to decrease myocardial oxygen requirements, or increase blood supply to the myocardium (Figure 2).

Organic nitrates

Mechanism: the metabolites of glyceryl trinitrate (GTN) and isosorbide mononitrate (ISMN) (Table 4) release nitric oxide, which activates enzymes in the vascular endothelium, and reduce the availability of intracellular calcium in vascular smooth muscle. Nitrates dilate venous capacitance vessels, large systemic arteries and coronary arteries, which decreases cardiac preload, decreases afterload and increases blood supply to ischaemic myocardium when there is coronary artery vasoconstriction.

Pharmacokinetics: GTN is rapidly absorbed in the gut but metabolized to an inactive substance by first-pass metabolism. It is well absorbed sublingually, and an aerosol spray is preferred to tablets because of the longer storage time before efficacy is lost. GTN works within a minute or so to relieve angina, and provides prophylaxis for up to 30 minutes. The buccal tablet has a slower release and longer duration, whereas a transdermal patch can deliver the drug via a rate-limiting matrix across the skin to maintain a stable blood concentration. Given by intravenous infusion, it is short acting, which can be useful for titrating the dose against relief of pain when treating unstable angina.

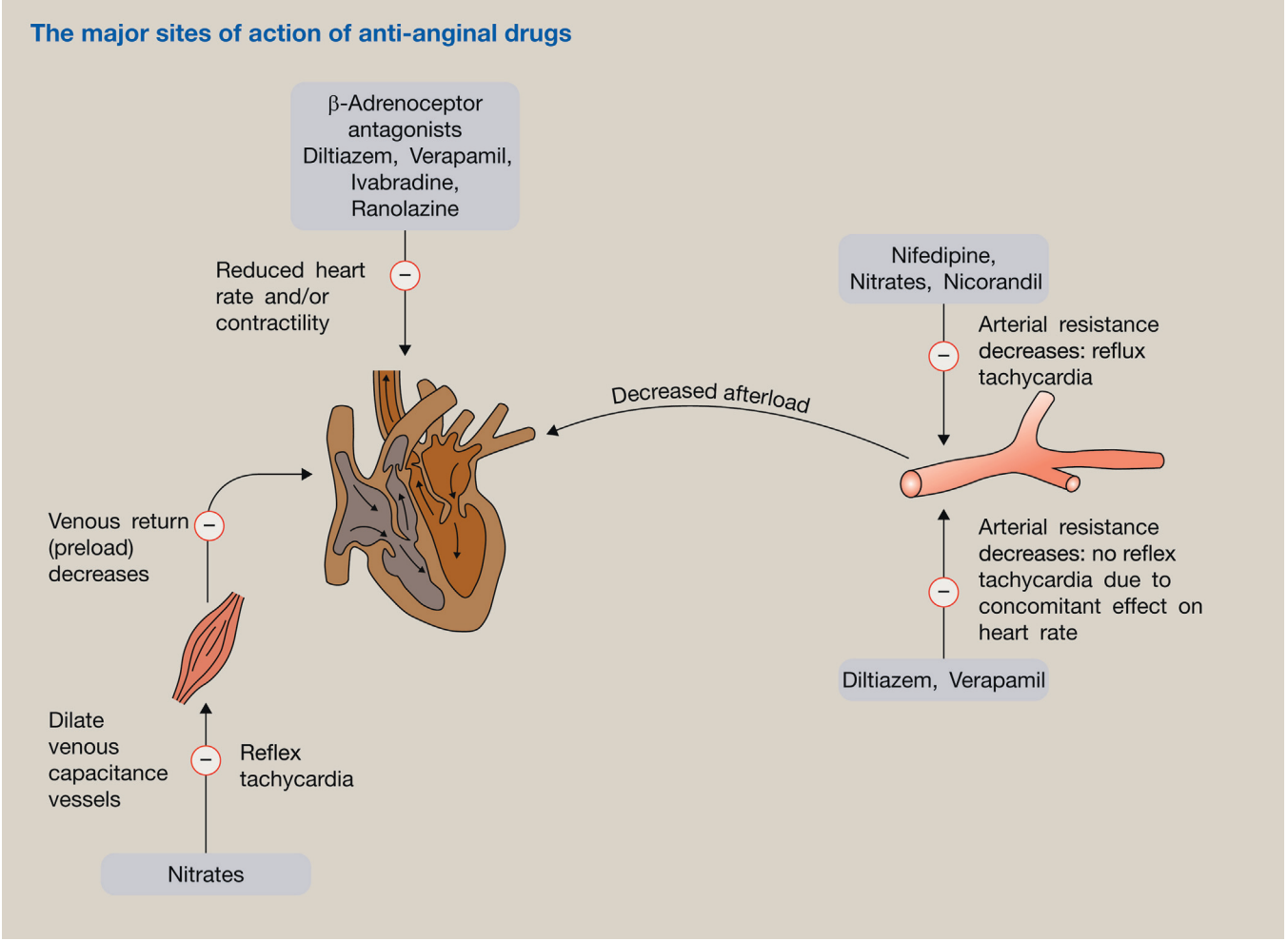


Figure 2 Reproduced from Waller DG, Sampson T. Medical pharmacology and therapeutics, 5th edn. Elsevier Health Sciences, 2017 with permission from Elsevier.

Other anti-anginal drugs

Drugs	$t_{½}$ (hours)	Dose reduction	Pregnancy	Breastfeeding
GTN	1–3 minutes	L, R	C	C
Isosorbide dinitrate	0.5–2	L, R	A	C
Isosorbide mononitrate	3–7	L, R	A	C
Nicorandil	1		A	A
Ivabradine	2	L, R	A	A
Ranolazine	2	L, R	A	A

Dose reduction: use with caution or avoid in severe liver (L) or renal (R) impairment.
Pregnancy: avoid (A) or use only if benefit outweighs risk (C).
Breastfeeding: avoid (A) or use only if benefit outweighs risk (C).
$t_{½}$, plasma half-life; GTN, glyceryl trinitrate.

Table 4

ISMN is completely absorbed orally, does not undergo first-pass metabolism and provides a predictable and prolonged response. A once-daily modified-release formulation is often given.

Adverse effects: venodilatation can cause postural hypotension, dizziness, syncope and reflex tachycardia. The latter can be limited by concurrent use of a β-blocker. Arterial dilatation can cause headache and flushing. Tolerance to the therapeutic effects of nitrates can occur with regular use but can be limited by ensuring a 'nitrate-low' period each day. This is achieved by asymmetrical dosing (morning and lunchtime with the twice-daily formulations) or by using a once-daily modified-release formulation that allows plasma nitrate to fall after a few hours. Transdermal patches should be removed for a few hours each day. Hypotension can be worsened by concurrent treatment with phosphodiesterase drugs used to treat impotence, such as sildenafil.[3,4]

β-Adrenoceptor antagonists (β-blockers)

Mechanism: β-blockers decrease myocardial oxygen demand by reducing heart rate (particularly on exertion), reducing myocardial contractility and lowering blood pressure. Diastole is also lengthened, which gives more time for coronary perfusion and increases myocardial oxygen supply. The additional vasodilator action of some β-blockers makes an uncertain contribution to the anti-anginal action of the drugs. Along with calcium channel blockers they are recommended as first-line treatment for stable angina. Further details are given above.

Calcium channel blockers

Mechanism: all calcium channel blockers produce arterial vasodilatation, which reduces afterload and thus myocardial oxygen demand, and can also relieve coronary artery spasm. The non-dihydropyridine drugs verapamil and diltiazem also decrease exercise heart rate and can be more effective than the dihydropyridines as monotherapy for the treatment of angina by further decreasing oxygen demand. For details of these drugs, see above.[1,3]

Potassium channel opener

Mechanism: nicorandil (Table 4) promotes vasodilatation in systemic and coronary arteries by opening ATP-sensitive potassium channels, increasing potassium efflux from smooth muscle cells. The resultant hyperpolarization of the cell membrane inhibits the opening of voltage-dependent calcium channels and relaxes vascular smooth muscle. This is enhanced by the local production of nitric oxide from a nitrate-like action of nicorandil, which also causes venodilatation.

Adverse effects: an initial headache in 25–50% of patients usually decreases with continued use. Dizziness, mouth and anal ulcers and gastrointestinal disturbance can also occur.[3,4]

Sinus node inhibitor

Mechanism: ivabradine (Table 4) slows the heart rate at the sinoatrial node by inhibiting sodium and potassium influx through the 'funny current' f-channels during diastole, which delays spontaneous depolarization of these cells. Because it binds to the open channel, inhibition is use dependent – the faster the node is firing, the more effective the drug is. Ivabradine has no effect on myocardial contractility. The reduction in heart rate can also be beneficial in heart failure.[5]

Adverse effects: f-channels are also found in the eye; at higher doses, visual symptoms such as flashing lights and blurred vision can therefore occur, which resolve on stopping the drug. Headache, dizziness and ventricular ectopics have been reported. Bradycardia can be problematic, and ivabradine is not recommended if the heart rate is <60 beats per minute.

Late sodium current inhibitor

Mechanism: ranolazine (Table 4) blocks late sodium transit into myocytes during the plateau phase of the action potential, leading to a decrease in intracellular accumulation of calcium. The result is a decrease in diastolic wall tension, which in turn decreases myocardial oxygen demand and improves blood flow in the intramyocardial coronary blood vessels. Because the late sodium current is active in hypoxic tissue, ranolazine is particularly effective in ischaemic myocardium.[5]

Adverse effects: ranolazine also causes gastrointestinal disturbance, lethargy, headaches and dizziness but does not depress myocardial contractility. Lengthening of the QT interval on the electrocardiogram (ECG) can occur, although it has not been associated with an increased incidence of arrhythmia. ECG monitoring is advised, especially if ranolazine is taken with other drugs that also lengthen the QT interval.[5] ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 50-year-old African Caribbean woman presented with a gradual onset of swelling of her lips and the area around her eyes over 2 days. Her breathing was unaffected, and she otherwise felt well. She had a past medical history of hypertension and ischaemic heart disease. She was taking amlodipine, aspirin, atorvastatin, indapamide and ramipril. There had been no recent changes to her medications.

What drug is the most likely cause of her presentation?

A. Amlodipine
B. Aspirin
C. Atorvastatin
D. Indapamide
E. Ramipril

Question 2

A 78-year-old man presented for review. He had severe two-vessel coronary disease that was not suitable for percutaneous intervention and he had declined open heart surgery. He had continuing symptoms of exertional angina. He also had dizziness when standing up. He was taking aspirin, low-dose rivaroxaban, bisoprolol and atorvastatin.

On clinical examination, he looked well. His heart rate was 70 beats/minute, in atrial fibrillation, and seated blood pressure was 90/50 mmHg.

What is the most appropriate addition anti-anginal medication?

A. Amlodipine
B. Isosorbide mononitrate
C. Ivabradine
D. Nicorandil
E. Ranolazine

Question 3

A 68-year-old woman presented for review after the finding of a low potassium of 2.4mmol/litre on routine testing. She was asymptomatic. She had a past medical history of hypertension and ischaemic heart disease. She was taking amlodipine, aspirin, bisoprolol, doxazosin, indapamide and valsartan.

What drug is the most likely culprit?

A. Amlodipine
B. Bisoprolol
C. Doxazosin
D. Indapamide
E. Valsartan