Drugs for heart failure and arrhythmias

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Abstract

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

Keywords ACE inhibitors; angiotensin receptor antagonists; anti-arrhythmic drugs; arrhythmias; beta-blockers; diuretics; drugs; heart failure

What's new?

- Eplerenone is an aldosterone receptor antagonist that is as effective as spironolactone, but does not cause gynaecomastia. It is licensed for the treatment of heart failure following myocardial infarction
- Ivabradine has been shown to reduce morbidity and mortality in the treatment of symptomatic systolic heart failure in sinus rhythm with a ventricular rate greater than 70 bpm
- Although no drug therapies have currently been shown to have a mortality benefit in the treatment of heart failure with preserved ejection fraction, there is increasing evidence supporting the role of spironolactone and large trials looking at this are ongoing

Drugs for heart failure

Medications for heart failure have three main targets:

- to decrease fluid retention in order to reduce circulating blood volume
- to produce arterial and venous dilatation in order to decrease preload and afterload
- to increase myocardial contractility

Further long-term benefits of some medicines are reduction in cardiac remodelling, heart rate reduction or an anti-arrhythmic action that improves long-term prognosis.[1,2]

Diuretics

Two classes of diuretics (loop diuretics and potassium-sparing diuretics) are usually used in heart failure. A third class (thiazide diuretics) is occasionally used in mild disease or in combination with a loop diuretic for resistant oedema.

Loop diuretics

Mechanism — furosemide and bumetanide are most commonly used; they relieve symptoms but do not affect prognosis.[3,4] They bind to the $Na^+/K^+/2Cl^+$ co-transporter in the thick ascending limb of the loop of Henle and inhibit chloride reabsorption, which decreases the electrochemical gradient across the cell so that less sodium is reabsorbed. There is loss of the osmotic gradient required to concentrate urine in the collecting ducts and therefore free water is also lost in the urine.

Up to 25% of filtered sodium can be excreted, and loop diuretics can produce a profound natriuresis and diuresis. Whereas small increases in dosage often give a large increase in effect, the maximum effective dose varies greatly. Higher doses are often needed in renal failure to allow sufficient drug to be secreted into the renal tubule and to reach the site of action.

When given intravenously, loop diuretics produce venous dilatation by stimulating renal release of prostaglandins. The consequent venous pooling can rapidly relieve breathlessness in acute pulmonary oedema before any diuretic effect occurs.

Pharmacokinetics — furosemide has variable gut absorption, particularly if the mucosa is oedematous as a result of right heart failure, whereas bumetanide is more consistently absorbed. When either of these agents is given orally, diuresis begins after 30 minutes and lasts 6 hours, whereas after intravenous dosing it begins within minutes and lasts 2—3 hours.

Adverse effects — renal impairment and postural hypotension can occur as circulating blood volume falls. Dilutional hyponatraemia may arise if free water clearance is less than the natriuresis, and can lead to diuretic resistance. Hypokalaemia can result from hypovolaemia and delivery of more sodium to the distal tubule, both of which stimulate renin and consequently aldosterone secretion. Reversible ototoxicity causing deafness and vertigo is possible with high doses, particularly in renal failure and when intravenous doses are given too rapidly (doses >80 mg should be given by IV infusion no faster than 4 mg/min).

Potassium-sparing diuretics

Mechanism — spironolactone and eplerenone compete with aldosterone for receptor binding in the distal convoluted tubule and collecting duct. This reduces the number of Na^+/K^+ exchange channels, promoting sodium and water loss with potassium retention. The overall diuresis is modest unless there is secondary hyperaldosteronism. Both drugs have been shown to improve prognosis in cardiac failure.[5,6]

Amiloride and triamterene are weak diuretics that block the sodium channel independently of aldosterone. They afford little benefit in heart failure.

Pharmacokinetics — all are given orally. The onset of action of spironolactone is slow, owing to production of an active metabolite (canrenone), starting at 1 day and reaching maximum effect at 3—4 days, while eplerenone has a more rapid onset.

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Adverse effects – hyperkalaemia can be a problem, particularly in renal impairment or when these drugs are used with others that block the renin–angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists. Spironolactone binds to oestrogen receptors, which can result in male impotence and gynaecomastia, or female menstrual irregularities. These effects are not seen with eplerenone.

β-Adrenoceptor antagonists

Bisoprolol, carvedilol and nebivolol are licensed in the UK to treat systolic left ventricular dysfunction, starting with a low dosage followed by slow titration. Other β-blockers do not have data to support their use, and therefore should not be given. They should be initiated only once the heart failure has been stabilized, as in acute failure their negative inotropic effect can cause decompensation. They improve exercise capacity, and also improve prognosis probably by limiting cardiac remodelling and preventing serious arrhythmias.[7,8] More information is given in the Part 2 of this Chapter (*MEDICINE* 2014; **42**(9)), which deals with drugs for hypertension.

Angiotensin-converting enzyme (ACE) inhibitors

All patients with systolic left ventricular dysfunction should take a drug that blocks the renin–angiotensin system, usually an ACE inhibitor. Examples include ramipril, perindopril, and lisinopril (Table 1). They decrease the production of angiotensin II and subsequently aldosterone, which results in arterial and venous dilatation, reduced cardiac and vascular cell proliferation, reduced sympathetic stimulation, and decreased salt and water retention. ACE inhibitors improve survival, probably by reversing ventricular remodelling, and they reduce the risk of myocardial infarction in heart failure caused by ischaemic heart disease.[9] High target doses are most effective, and the dose can usually be titrated rapidly over a couple of weeks.

Adverse effects: a dry, unproductive cough is a class effect that occurs in 10–30% of people, is not dose-related and can begin after many months of use. Postural hypotension, which occurs particularly after the first dose, can be less troublesome if the first dose is given at night. ACE inhibitors can cause renal impairment, particularly in the presence of bilateral renal artery stenosis. Renal function should be monitored closely at initiation, and lower starting doses used in those with pre-existing renal impairment. However, renal function in heart failure often improves after initiation of ACE inhibitor therapy, probably as a result of improved cardiac output. Angio-oedema is more common in people of Afro-Caribbean origin. Taste disturbance may also occur, and can be permanent.

Angiotensin II receptor antagonists

Mechanism: drugs such as candesartan, losartan and valsartan act at AT1 receptor subtypes and inhibit the action of angiotensin II (Table 2). Their efficacy in heart failure is similar to that of ACE inhibitors. This class of drug should therefore be used in the place of ACE inhibitors when the latter cause unacceptable adverse effects (e.g. cough).

Adverse effects: include headache, dizziness, arthralgia, myalgia and fatigue. In contrast to ACE inhibitors, they rarely cause cough and less often angio-oedema.

Ivabradine

The I*f* receptor antagonist ivabradine is licensed for use in symptomatic chronic systolic heart failure if there is sinus rhythm with a rate greater than 75 bpm. It reduces both hospitalization and mortality.[10] Further information on ivabradine is available in Part 2 of this Chapter, which deals with drugs for angina.

Digitalis glycosides

Mechanism: digoxin binds to and partially inhibits Na^+/K^+-ATPase pumps in the cardiac myocyte membrane. This causes a rise in intracellular sodium, which in turn leads to a rise in intracellular calcium by slowing sodium/calcium exchange. The intracellular calcium is stored in the sarcoplasmic reticulum during diastole and is released during systole, increasing myocardial contractility.

ACE inhibitors

Drug	$T_{1/2}$ (h)	Heart failure	Dose reduction	Pregnancy	Breastfeeding
Captopril	2	Yes	R	A	A
Cilazapril	30	Yes	?L, R	A	A
Enalapril	35	Yes	?L, R	A	A
Fosinopril	12	Yes	?L, ?R	A	A
Imidapril	8	No	?L, R	A	A
Lisinopril	12	Yes	R	A	A
Moexipril	10	No	?L, R	A	A
Perindopril	29	Yes	?L, R	A	A
Quinapril	2	Yes	?L, R	A	A
Ramipril	1–5	Yes	?L, R	A	A
Trandolapril	16–24	Yes	?L, R	A	A

$T_{1/2}$: plasma half-life (h), Heart failure: licensed dosage for heart failure, Dose reduction: monitor effect closely in liver (?L) or renal (?R) impairment or reduce dose in renal (R) impairment, Pregnancy avoid (A), Breastfeeding avoid (A) at least for first few weeks, Risk of neonatal hypotension.

Table 1

Angiotensin II receptor antagonists

Drug	$T_{1/2}$ (h)	Heart failure	Dose reduction	Pregnancy	Breastfeeding
Candesartan	9–12	Yes	L, R	A	A
Eprosartan	5–9	No	L, R	A	A
Irbesartan	11–15	No		A	A
Losartan	2	Yes	L	A	A
Olmesartan	13	No	L, R	A	A
Telmisartan	16–23	No	L, R	A	A
Valsartan	5–7	Yes	L, R	A	A

$T_{1/2}$: plasma half-life (h), Heart failure: licensed dosage for heart failure, Dose reduction: reduce dose or avoid in liver (L) impairment, or reduce dose in renal (R) impairment, Pregnancy avoid (A), Breastfeeding avoid (A).

Table 2