

Drug therapies in chronic heart failure: a focus on reduced ejection fraction

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ABSTRACT

There are multiple evidence-based drug treatments for chronic heart failure (HF), both disease-modifying agents and those for symptom control. The majority of the evidence base supports drugs used in HF with reduced left ventricular ejection fraction. The mainstay of disease modification involves manipulation of neurohormonal activation that occurs in HF. In addition to established angiotensin-converting enzyme inhibitors, beta blockers and mineralocorticoid receptor antagonists (MRAs), newer agents are now available such as the angiotensin receptor neprilysin inhibitors. Achieving the optimal drug regimen is complex and best performed by a specialist heart failure team. We aim to provide a comprehensive overview of contemporary drug therapies in chronic heart failure, as well as practical guidance for their use. There is a focus on treating patients with challenging comorbidities such as hypotension and chronic kidney disease (CKD), where a thorough understanding of drug therapy is essential. Multiple trials assessing the benefits of new therapies in HF, such as intravenous iron, are also ongoing.

Introduction

Heart failure (HF) is a clinical syndrome with typical signs and symptoms that include dyspnoea, fatigue, peripheral oedema and raised jugular venous pressure. It is caused by many conditions including ischaemic heart disease (IHD), hypertension, valvular heart disease and primary cardiomyopathies all of which result in functional and/or structural cardiac abnormalities. Ischaemic heart disease is the commonest cause in the western world.^{1,2}

Heart failure is common, the Rotterdam Study reported a prevalence of 0.9% in subjects aged 55–64 years, rising to 17.4% in those aged ≥85.³ The lifetime risk for 55-year-olds was 33% for men and 29% for women. Heart failure is responsible for 1–2% of western healthcare systems budgets and inevitably will rise with an ageing population.⁴ The bulk of cost relates to frequent and lengthy hospitalisations. While prognosis has improved, it still

remains poor – recent UK data show in-hospital mortality rates of 8.9%, median length of stay at 9 days and of those surviving to discharge 26.7% die within a year.⁵

The mainstay of treatment for HF is drug therapy. By promptly identifying patients with HF and commencing evidence-based therapies it is possible to markedly improve morbidity and mortality. Patients with HF have typically been grouped into those with preserved or reduced left ventricular (LV) systolic function. Recent guidelines have further divided patients according to LV ejection fraction (EF, LVEF): HF with reduced EF (HFrEF) – EF <40%, HF with preserved EF (HFpEF) – EF ≥50%, and the relatively new term HF with mid-range EF (HFmrEF) – EF 40–49%.⁶ The unifying criteria are the presence of symptoms, with or without signs of HF. Additional characteristics are required to make the diagnosis of HFpEF, including raised natriuretic peptides and relevant structural heart disease (eg left ventricular hypertrophy) and/or markers of diastolic dysfunction. Categorisation of patients with HF according to LVEF is clinically important due to different underlying aetiologies, comorbidities and evidence base for treatment. The evidence that drug therapy improves prognosis (markedly reduced hospitalisation and mortality) is overwhelming for patients with HFrEF. In contrast, there are no clear data to date that drugs improve outcomes for patients with HFpEF (or HFmrEF). The prime focus is of this article is therefore therapies for HFrEF. However, in practice, many of the drugs used in HFrEF are also the mainstay of treatments for HFpEF (and HFmrEF) where they are used to treat symptoms and modify risk factors for HF such as hypertension. The inclusion of HFmrEF is aimed at stimulating research for this group, in order to identify the underlying pathophysiology as well as effective treatment options for this group. However, it may actually create a degree of clinical uncertainty. It is also important to note that in addition to drug therapy all patients with HF are also considered for other evidence based interventions where applicable, such as device therapy (implantable cardioverter defibrillators, cardiac resynchronisation therapy) and cardiac rehabilitation.

Established prognostic therapy in HFrEF

Chronic activation of neurohormonal pathways, in particular the renin-angiotensin-aldosterone axis and sympathetic nervous system, play a central role in the progression of HF.⁷ These activated neurohormonal systems contribute to adverse haemodynamics such as peripheral vasoconstriction with increased afterload and sodium and water retention with subsequent increase in preload. In addition, angiotensin II and

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aldosterone are thought to directly contribute to myocardial and renal fibrosis. The incremental use of neurohormonal antagonists improves survival for patients with HFrEF and are recommended for the treatment of every patient, unless contraindicated or not tolerated. These drugs should be considered as 'disease-modifying', with benefits on mortality, hospitalisation, quality of life (QoL) and markers of left ventricular function. The recommendations are to start at low dose with careful and gradual up-titration.

It is 30 years since the first randomised 'mega trial' (CONSENSUS) established the importance of angiotensin-converting enzyme inhibitors (ACEi) in HFrEF.⁸ Further trials confirmed reductions in mortality and morbidity cementing the place of ACEi as first-line therapy.⁹ These drugs inhibit the activity of angiotensin-converting enzyme and therefore prevent the formation of angiotensin II from angiotensin I. This results in natriuresis and diuresis and a reduction in arterial blood pressure and thereby afterload. The recommended starting and target doses of a number of ACEi with an evidence base in HFrEF are detailed in Table 1.¹⁰ Although it results in an increase in drug burden, a twice-daily ACEi regime (at least for some drugs) may be more effective than once-daily in terms of neurohormonal modification.¹¹ Monitoring of renal function and electrolytes is important (discussed here later).

Angiotensin receptor blockers (ARBs) are considered in patients who are intolerant of ACEis, primarily due to cough; the effect on renal function is similar. They block the action of angiotensin II by preventing it from binding to angiotensin receptors. Candesartan (CHARM study) decreased cardiovascular mortality and morbidity, while valsartan showed a reduction in the combined primary endpoint of mortality and morbidity mainly by reducing HF hospitalisations.^{12,13} The CHARM study suggested additive benefit of ARB to ACEi.¹⁴ However, due to the risk of hypotension, hyperkalaemia and renal dysfunction when combining ACEis and ARBs, and the recommendation for more routine use of mineralocorticoid receptor antagonists (MRAs) this is no longer

advocated.⁶ In contrast, Aliskiren, a direct renin inhibitor, was of no benefit in the ASTRONAUT trial and is not recommended.¹⁵

Despite early scepticism, the beneficial effects of beta blockade in HFrEF are well documented. Beta blockers bind to beta-adrenoceptors and block the binding of adrenaline and noradrenaline to these receptors thereby inhibiting the effects of the sympathetic nervous system. Key studies since the 1990s have shown additive reduction in mortality and morbidity when a beta blocker is given to symptomatic patients with reduced LVEF. This was seen with carvedilol, controlled-release metoprolol (unavailable in UK), bisoprolol and nebivolol, as shown in the COPERNICUS, MERIT-HF, CIBIS-II and SENIORS trials respectively.^{16–19} Data comparing beta blockers are very limited. The COMET trial found carvedilol was superior to (short-acting) metoprolol in reducing all-cause mortality,²⁰ though this may have been affected by low metoprolol dose. In the SENIORS study, nebivolol did not reduce all-cause mortality (secondary endpoint) but, in contrast to other studies, did include patients with HFpEF (36% of subjects).¹⁷ Beta blockers should not be commenced during a heart failure exacerbation (decompensation) because of negative inotropic effects, but should be initiated when the patient is euvoalaemic.²¹ Patient and carer education is crucial; some feel slightly worse after beta blocker initiation but in general this resolves fairly quickly if they persevere. While no study has compared different heart rate targets, the heart rate achieved at day 30 in SHIFT was predictive of outcome – best seen around 60 beats per minute (bpm).²² It is the authors' opinion that optimising beta blocker dose (and ivabradine where required) to achieve a target resting heart rate of around 60bpm in sinus rhythm is appropriate (assuming no adverse symptoms). At least part of the benefit of beta blockade may be explained by heart rate reduction.²³ Following optimisation of ACEi and beta blocker, in patients with HFrEF who remain symptomatic, a MRA (spironolactone or eplerenone) should be added (Fig 1). Mineralocorticoid receptor antagonists antagonise the actions of aldosterone by blocking the mineralocorticoid receptor. While MRAs have diuretic effects and may help achieve optimal fluid balance, key benefits are on reduction of mortality and HF hospitalisations (likely from reducing risk of hypokalaemia and adverse myocardial and renal parenchymal fibrosis from aldosterone excess).^{24–26} Spironolactone was evaluated in patients with severe symptoms and HFrEF,²⁵ while eplerenone showed benefit in patients with severe LV systolic dysfunction and relatively mild symptoms,²⁴ as well as in post myocardial infarction HF.²⁷ Spironolactone can result in painful gynaecomastia and other dose-dependent sexual side effects (due to affinity for progesterone, androgen and glucocorticoid receptors); if these occur it seems intuitive to switch to eplerenone, where these side effects are less common.²⁸ The doses of spironolactone and eplerenone are not interchangeable; in clinical practice a higher dose of eplerenone is often required to achieve a similar effect to 25 mg. This may be due to a lower binding affinity of eplerenone to the mineralocorticoid receptor.²⁹

Newer agents with prognostic benefit

Elevated heart rate has consistently been associated with adverse prognosis in patients with HF.^{30,31} Not all patients with HFrEF tolerate beta blockers or achieve doses high enough to adequately reduce resting heart rate.³² Ivabradine is an I_f ('funny' channel) inhibitor acting on the sinoatrial node to slow heart rate

Table 1. Starting and target doses for commonly used neurohormonal antagonists used in patients with HFrEF¹

Class	Drug name	Starting dose	Target dose
ACEi	Captopril	6.25 mg tds	50 mg tds
	Enalapril	2.5 mg bd	10–20 mg bd
	Lisinopril	2.5–5 mg od	20–35 mg od
	Ramipril	1.25 mg bd	5 mg bd
ARB	Candesartan	4 mg od	32 mg od
	Valsartan	40 mg bd	160 mg bd
Beta blockers	Bisoprolol	1.25 mg od	10 mg od
	Carvedilol	3.125 mg bd	25 mg bd
	Nebivolol	1.25 mg od	10 mg od
MRA	Eplerenone	25 mg od	50 mg od
	Spironolactone	25 mg od	25 mg od

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; bd = twice daily; MRA = mineralocorticoid receptor antagonist; od = once daily; tds = three times a day

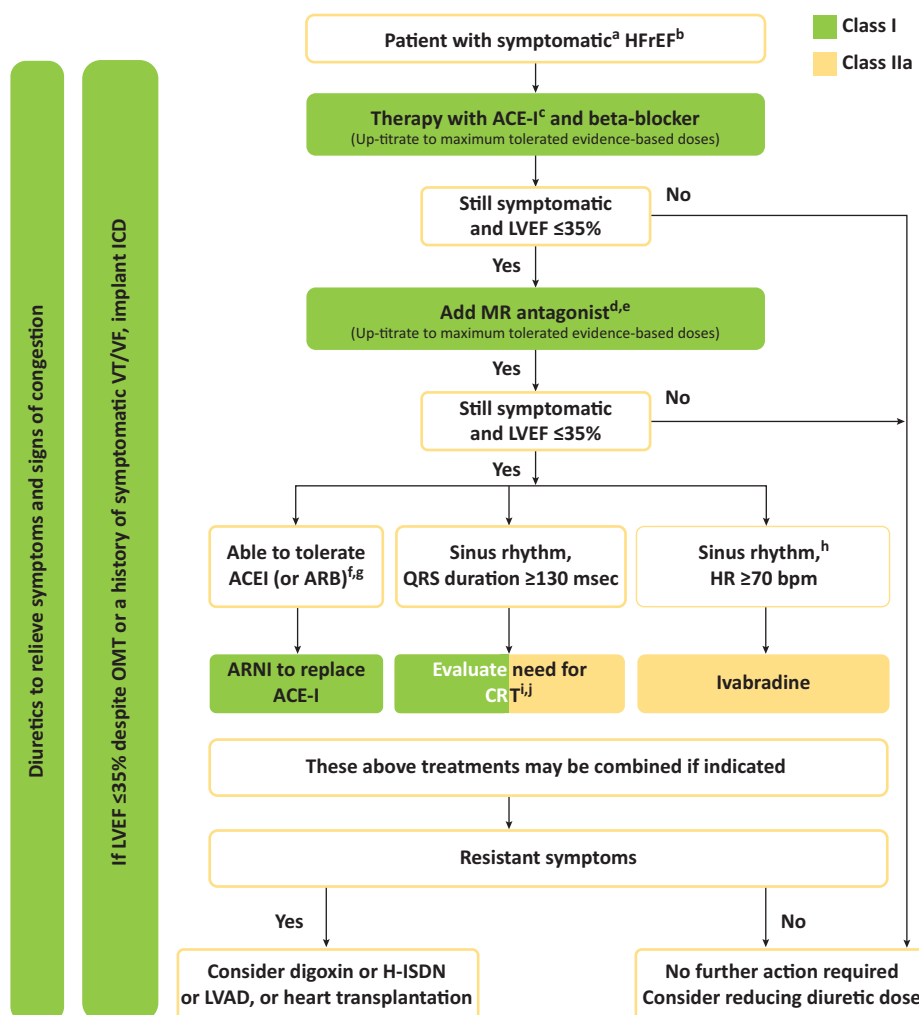


Fig 1. Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction. Reproduced with permission.¹ Green indicates a class I recommendation; yellow indicates a class IIa recommendation. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronisation therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NTproBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia. ^aSymptomatic = NYHA Class II-IV. ^bHFrEF = LVEF <40%. ^cIf ACE inhibitor not tolerated/contraindicated, use ARB. ^dIf MR antagonist not tolerated/contraindicated, use ARB. ^eWith a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP >250 pg/mL or NTproBNP > 500 pg/mL in men and 750 pg/mL in women). ^fWith an elevated plasma natriuretic peptide level (BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalisation within recent 12 months plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL). ^gIn doses equivalent to enalapril 10 mg twice a day. ^hWith a hospital admission for HF within the previous year. ⁱCRT is recommended if QRS ≥130 ms and LBBB (in sinus rhythm). ^jCRT should/may be considered if QRS ≥130 ms with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualised decision).

(therefore only useful in sinus rhythm). The SHIFT study showed benefit on the combined endpoint of cardiovascular death and HF hospitalisation when ivabradine was added to maximum tolerated doses of beta blockers as well as ACEi/ARB and MRA (mainly due to reduction in HF admissions).²² The National Institute for Health and Care Excellence (NICE) approved its use for patients with HFrEF and resting heart rate ≥75 bpm *after* beta blocker optimisation.²⁶ Ivabradine is generally well tolerated, without detrimental effect on blood pressure and is associated with improvements in QoL.³³

Angiotensin receptor neprilysin inhibitors (ARNIs) are a new class of drugs, the first being a combination of valsartan (ARB) and sacubitril (neprilysin inhibitor). The latter augments beneficial counter-regulatory effects of vasodilatory peptides including the natriuretic peptide family. The PARADIGM-HF clinical trial in patients with HFrEF showed sacubitril/valsartan was superior to enalapril at reducing the risk of cardiovascular death and hospitalisation from HF. The trial was stopped early because of significant survival benefit seen with sacubitril/valsartan. The relative risk reduction of cardiovascular death/

hospitalisation from HF was highly significant at 20%.³⁴ Although direct comparisons are not possible, the magnitude of benefit of changing an ACEi to an ARNI was similar to that observed when comparing ACEi to placebo³⁵ or when adding in beta-blocker therapy.¹⁶ Although symptomatic hypotension was more common in those taking sacubitril/valsartan, there was no difference in the rates of discontinuation between groups.

In 2016, NICE published criteria for use of sacubitril/valsartan in HFrEF: New York Heart Association class II–IV, LVEF $\leq 35\%$ established on stable dose of ACEi or ARB.³⁶ The European Society of Cardiology (ESC) guidelines have an IB recommendation for sacubitril/valsartan for patients with HFrEF who remain symptomatic despite treatment with ACEi, beta blocker and MRA.⁶ When ACEi has been standard of care, it must be stopped for at least 36 hours prior to commencing sacubitril/valsartan. Monitoring of renal function is the same as for ACEi and ARB.³⁶

Diuretics

Diuretics are used to reduce symptoms and signs of congestion, and the aim is to render the patient euvoelaemic using the minimum dose. A meta-analysis of randomised controlled trials involving loop or thiazide diuretics showed improvement in exercise capacity, reduction in risk of disease progression and reduction in risk of death, although the latter was based on data from small trials.³⁷ Recently, a retrospective study showed a reduction in hospital and 1-year mortality with more intensive diuretic use (as well as improved use of evidence-based therapies via a multidisciplinary team approach).³⁸ In terms of choice of oral loop diuretics, furosemide has greater variability in absorption, but no study has shown significant difference in outcomes between furosemide and bumetanide.^{39–41}

When patients present with decompensated HF ie with marked fluid excess, a period of intravenous diuretic therapy is generally warranted. Many such patients have chronic kidney disease (CKD) and often the decompensation is associated with worsening renal function or acute kidney injury (AKI). Achievement of euvoelaemia is fundamental and many patients require high dose intravenous loop diuretics and for some additional thiazide diuretics and MRA (progressive nephron blockade). It is important to remember that in general it is congestion per se, as opposed to the diuretics, that has driven the deterioration in renal function.⁴² Data, albeit commonly observational, suggest that adverse prognosis is impacted more by the ongoing presence of oedema as opposed to a deterioration in renal function during hospitalisation.⁴³

Older therapies with some prognostic benefit

The use of a combination of hydralazine and isosorbide dinitrate is given an IIB recommendation in the ESC guidelines for specific situations.⁶ Data on this drug combination are limited to a few small studies in specific patient subgroups, mainly before standard therapy with ACEi and beta blockers was established. There is some evidence of additional benefit when added to standard therapy in black patients with symptomatic HFrEF and dilated LV.⁴⁴ The combination may also be considered in patients who are intolerant of ACEis/ARBs (generally for very severe CKD) but the evidence for this is based on the Veterans Administration

Cooperative Study, involving male patients with HF who were only taking digoxin and diuretics.⁴⁵

Digoxin reduced the rate of hospitalisations in patients with HF in sinus rhythm in the Digitalis Study, but did not reduce mortality.⁴⁶ However, post hoc analysis of the DIG trial showed mortality benefit with low dose digoxin in very high risk groups.⁴⁷ Current guidelines (Fig 1) only advocate the use of digoxin in HFrEF and sinus rhythm in selected cases (in our experience this might include patients with symptomatic hypotension merely tolerating low doses of neurohormonal antagonists).

Drugs with little or no prognostic benefit

The relationship of cholesterol to outcomes in chronic diseases, such as HF, is complex. Large randomised studies have shown no benefit of statins in patients with established HFrEF, irrespective of aetiology.^{48,49} However, in the PROVE IT-TIMI 22 study, intensive statin therapy with atorvastatin 80 mg reduced the risk of hospitalisation for HF following acute coronary syndrome as compared to moderate dose statin (pravastatin 40 mg).⁵⁰

Use of n-3 polyunsaturated fatty acids (n-3 PUFAs) have level IIB recommendation in the ESC guidelines.⁶ The GISSI-HF trial showed a small benefit in decreasing mortality and hospital admissions when n-3 PUFAs were added to standard care.⁵¹ Therefore, while n-3 PUFAs may be considered in symptomatic patients the magnitude of absolute benefit is limited.

Calcium channel blockers do not provide benefit in HFrEF and some may increase the risk of worsening HF and hospitalisations.^{52,53} If a patient with HF requires further antihypertensive or antianginal therapy, a long-acting dihydropyridine, such as amlodipine is considered safe.⁵⁴

Considerations in specific situations

Hypotension

Many prognostically beneficial drugs for HF lower blood pressure. It is vital that all involved in care understand that blood pressure reduction is not the primary reason for their use. The precise blood pressure at which one should reduce drug doses will vary between patients; significant symptomatic hypotension is generally the driving force. When symptomatic hypotension limits drug optimisation, it is generally considered preferable to have patients on some of each of ACEi, beta blocker and MRA, as opposed to a high dose of a single agent.

Renal function

Chronic kidney disease is common in patients with HF and independently associated with adverse prognosis.⁵⁵ Prognostically beneficial drugs in HFrEF such as ACEi, ARB, MRA and ARNIs influence haemodynamics and renal blood flow. However, they are *not* nephrotoxic. During initiation and up-titration it is common to see some increase in serum creatinine or drop in estimated glomerular filtration rate. In general, the risk of stopping or reducing the dose is likely to be of greater detriment to prognosis than a modest increase in serum creatinine.⁵⁶ In contrast, in patients with HFpEF there is no convincing evidence that ACEi, ARB or MRA alter prognosis. As such if renal function deteriorates significantly with their use consider stopping them.

Atrial fibrillation

This is a common comorbidity and a key consideration is whether the patient should receive anticoagulation. In patients where rhythm control is pursued amiodarone is the antiarrhythmic of choice (ideally with beta blockers).⁶ Beta blockers are generally used for rate control, alone or in combination with digoxin. There is controversy as to whether beta blockers are associated with prognostic benefit in HFrEF and atrial fibrillation.⁵⁷ In a patient presenting with decompensated HF and uncontrolled atrial fibrillation, initial rate control with digoxin and offloading is preferential. Once stabilised, beta blockade can be added. Resting target heart rate for patients with atrial fibrillation and HFrEF should be more lenient than for those in sinus rhythm, due at least in part the risk of potential bradycardia-induced arrhythmias.^{58,59} The authors generally look for an apical resting rate of around 70–90 bpm.

Heart failure exacerbation

Diuretic therapy to achieve euvolaemia has been discussed. It is preferential to continue with other drugs such as ACEi or beta blockers at usual dose during the exacerbation if possible.^{60,61} If these drugs are reduced or withheld, this must be considered as a temporary adjustment. Prior to discharge, all drugs should be restarted, with plans in place to reoptimise under outpatient HF services. When a clinician is contemplating stopping a disease modifying drug for HFrEF, it is vital to consider this akin to stopping chemotherapy for cancer. The adverse impact on prognosis may actually be greater in HF and patients should be involved in the final decision making.

Elderly patients

Patients often have multiple comorbidities, and polypharmacy is the norm. For many, QoL is more important than longevity.⁶² Involvement of patients in informed decision making and simplification of drug regimens (including stopping unnecessary drugs) should be standard care. Measuring postural blood pressures and electrocardiogram monitors may be useful to aid in this process. It may be more important to focus on symptoms (for example with diuretics and rate control) rather than on prognostically beneficial medications.

Chronic obstructive pulmonary disease

Beta blockers are not contraindicated in patients with chronic obstructive pulmonary disease.⁶³ Patients with cor pulmonale should be treated according to their LVEF but frequently tolerate drugs poorly due to hypotension and have a poor prognosis.⁶⁴

Systems of care for optimising drug therapy

Outcomes for both inpatients⁵ and outpatients⁶⁵ are improved when patients are managed by a multidisciplinary heart failure team. Although the teams provide multifaceted care a very important role of this team is optimisation of drug therapy.

The future

Iron deficiency is common in HF and associated with worse prognosis.⁶⁶ Several studies have shown that intravenous iron

in patients with HF and iron deficiency results in improved QoL, exercise capacity and symptoms.^{67–69} None were powered to assess mortality or hospitalisation. A number of ongoing studies are addressing this and include the UK based 'The intravenous iron treatment in patients with heart failure and iron deficiency [IRONMAN] study'.⁷⁰

The ongoing GALACTIC-HF trial is assessing whether treatment with omecamtiv mecarbil (a cardiac-specific myosin activator) is superior to placebo in reducing the risk of cardiovascular death or HF events in subjects with chronic HFrEF.⁷¹

Drug therapies in HFpEF/HFmrEF

There are currently no evidence-based treatments available for these groups that significantly affect mortality. Although traditionally HFpEF was thought to be caused solely by left ventricular diastolic dysfunction, it is now understood that there are multiple heterogenic aetiologies such as systemic and pulmonary vascular dysfunction, as well as neurohormonal activation, which makes treatment of this group of patients more challenging.^{72,73} Consequently, the mainstay of management is to alleviate symptoms. Diuretics and exercise training programmes have been shown to improve exercise capacity and QoL.^{74–77}

Many of the drug therapies used in HFrEF have not been shown to be beneficial in HFpEF.^{78–80} New agents are being trialled. There is an ongoing randomised placebo-controlled trial to determine whether vericiguat (a soluble guanylate cyclase stimulator) increases the time to cardiovascular death or HF hospitalisation in patients with HFpEF. It has already been shown to improve QoL.⁸¹ It is hoped future research may yield concrete recommendations for patients with HFmrEF. While specific data are awaited, many clinicians extrapolate trial results from patients with LVEF <40% and use ACEi, beta blockers and MRA in patients with LVEF up to 45%.

Risk factor modification is a crucial consideration in all types of HF, and includes treatment of hypertension and prevention of myocardial ischaemia. As such, many patients with HFpEF/HFmrEF receive ACEi/ARB and beta blockers.

Drug therapies in the prevention of heart failure

By modifying risk factors for HF, the disease can be prevented or the onset delayed. Multiple trials have shown that treating hypertension can prevent HF, especially when diuretics or angiotensin-renin system inhibitors are used.^{82,83} The SPRINT trial assessed the benefits of a lower systolic blood pressure (BP) goal of <120 mmHg vs <140 mmHg, for older and high-risk hypertensive patients. Treating BP to the lower goal resulted in a decrease in cardiovascular disease, death and hospitalisation for HF.⁸⁴ ACEi should also be used in asymptomatic patients with reduced EF, irrespective of comorbid hypertension, as this reduces the risk of developing symptoms of HF and associated hospitalisations.³⁵

The EMPA-REG OUTCOME trial assessed the impact of empagliflozin (an inhibitor of sodium-glucose cotransporter 2) in type 2 diabetics at high risk of cardiovascular disease as compared to placebo. Lower rates of cardiovascular and all-cause mortality, and reduction in HF hospitalisations were seen with empagliflozin.⁸⁵

Conclusion

Heart failure is common and has an adverse prognosis. Evidence-based disease-modifying drug therapy based around neurohormonal modulation and guided by LVEF form the mainstay of therapy. Most HF patients derive symptomatic benefit from these drugs and those with HFrEF derive significant additional prognostic benefits. These therapies continue to evolve and new drugs which have emerged over recent years are being used alongside long-established ones. Contemporary management involves selecting and optimising appropriate drug regimens and, crucially, ongoing modifications to allow for the introduction of newer therapies and changing clinical status. The best outcomes are achieved when specialist teams manage these complex drug regimens, in partnership with patients, throughout the course of the disease. ■

Conflicts of interest

Paul R Kalra has received: research grants from Alere, Pharmacosmos and Servier; speaker fees/advisory boards/meeting support from Alere, Amgen, BMS, Janssen, Novartis, Pfizer, Pharmacosmos, Servier and Vifor.

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