Pharmacological management of chronic heart failure

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Abstract

Chronic heart failure is a progressive and life-limiting syndrome that is caused by a failure of the heart to pump blood around the body effectively. It frequently leads to a range of distressing symptoms, such as breathlessness, fatigue and fluid retention. Chronic heart failure can be caused by a variety of cardiac diseases, but is commonly linked to coronary heart disease and hypertension. In response to these, the body initiates a series of compensatory mechanisms, which ultimately become maladaptive, and the manipulation of these mechanisms is the cornerstone of pharmacological management of the condition. This article explains the compensatory mechanisms that occur in chronic heart failure and outlines the medicines commonly used in its management.

Introduction

Chronic heart failure is an end-stage condition that causes impaired quality of life (QoL) and often recurrent hospital admission (McDonagh et al, 2021). It typically affects older adults with cardiovascular disease, with the average age at diagnosis being 77 years (National Institute of Health and Care Excellence [NICE], 2018). The condition has a high mortality; in one study, 67% of patients had died within five years of diagnosis (Tsao et al, 2018). Chronic heart failure affects 1-2% of the population of developed countries, and an estimated 64.3 million people worldwide (Groenewegen et al, 2020). Its prevalence has increased worldwide, driven largely by increases in low-to-middle income countries and in older people, and further increases are predicted as the global population ages (Lippi and Sanchis-Gomar 2020). Chronic heart failure is a major burden on healthcare resources; in the UK it accounts for 5% of emergency hospital admissions and 1 million bed days per year (National Institute for Cardiovascular Outcomes Research 2022).

While many treatments are used in chronic heart failure – such as such as cardiac rehabilitation, patient education and psychological support - the cornerstone of its management is pharmacological (McDonagh et al, 2021). Several drugs have been shown to decrease mortality, hospital admissions and symptoms in people with chronic heart failure. Despite this, there is evidence that life-prolonging therapy is under-prescribed and frequently discontinued during acute hospital admissions (Rossignol et al, 2019). There is therefore significant scope to improve the care of this population.

This article describes the first-line medicines used in chronic heart failure, discusses their recommendations in clinical guidelines and identifies important practice points for healthcare practitioners, including nurses. To support medicines optimisation and enhance nurses' understanding of the context in which such medicines are used, this article defines chronic heart failure, outlines its classification and discusses the compensatory mechanisms employed by the body.

Definition of chronic heart failure

Chronic heart failure is a clinical syndrome in which typical signs and symptoms occur in the presence of a functional or structural abnormality in heart function (McDonagh et al, 2021). Common symptoms include breathlessness, fatigue, and exercise intolerance; typical signs are rapid weight gain, ankle swelling and elevated jugular venous pressure (Schwinger, 2021). The most common disorders leading to chronic heart failure are coronary artery disease and hypertension, while other common causes include heart valve disease, arrhythmias and cardiomyopathies (Rossignol et al, 2019).

Regardless of aetiology, impairment of circulatory function in chronic heart failure causes a decrease in cardiac output and/or an increase in intracardiac pressures. This causes fluid congestion and widespread organ dysfunction, meaning that the effects of chronic heart failure are systemic and not confined to the cardiovascular system (Heidenreich et al, 2022).

Classification of chronic heart failure

Various classification systems can be used to categorise and describe heart failure. The two classification systems that are most relevant to clinical practice are left ventricular ejection fraction (LVEF) and New York Heart Association functional classification (McDonagh et al 2021).

Left ventricular ejection fraction

LVEF describes the proportion of blood ejected from the left ventricle during systole. A normal LVEF at rest is 55 to 70% (Marieb & Keller, 2021). The measurement of LVEF using echocardiography is a routine aspect of CHF diagnosis. The result is used to place patients in one of three categories (McDonagh et al, 2021):

- Heart failure with reduced ejection fraction (HFrEF) – a LVEF of ≤40%.
- Heart failure with mildly reduced ejection fraction (HFmrEF) – a LVEF of 41-49%.
- Heart failure with preserved ejection fraction (HFpEF) – a LVEF of ≥50%.

New York Heart Association functional class

The New York Heart Association functional classification is a subjective assessment of heart failure symptom severity. The score ranges from I to IV and is used to gauge the severity of heart failure, response to treatment, and prognosis (McDonagh et al, 2021). It is also used in therapeutic decision making, including when determining patient's eligibility for certain medicines. The New York Heart Association functional classification is shown in table 1.

Functional class	Description of symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results undue breathlessness, fatigue, or palpitations.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Table 1. New York Heart Association functional classification (McDonagh et al, 2021)

Compensatory mechanisms

In an attempt to maintain homeostasis, several compensatory mechanisms in the body are triggered by chronic heart failure. It is important that nurses have knowledge of these mechanisms because this can assist them with symptom recognition, and it underpins the rationales for various pharmacological interventions. These compensatory mechanisms include:

- Increased sympathetic nervous system activity.
- Upregulation of the renin-angiotensin-aldosterone system (RAAS).
- Increased production of natriuretic peptides.

These mechanisms attempt to improve cardiac output but eventually become counterproductive, resulting in fluid overload and deteriorating symptoms. This leads to episodes of 'decompensated' heart failure, which often requires aggressive treatment and hospital admission. Pharmacological therapy targets these compensatory mechanisms and aims to manipulate them to prevent decompensation and improve clinical outcomes.

Increased sympathetic nervous system activity

The sympathetic nervous system plays a major role in regulating cardiac output and blood pressure (Marieb and Keller, 2021). Sympathetic nerve fibres release noradrenaline from their postganglionic neurons. Noradrenaline binds to beta-adrenergic receptors on the heart, increasing heart rate and contractility – both of which increase cardiac output. The release of noradrenaline from sympathetic nervous system fibres that innervate the blood vessels causes vasoconstriction, raising preload, afterload and blood pressure (Marieb & Keller, 2021).

Preload is the degree to which cardiac muscle cells (cardiomyocytes) are stretched at the end of diastole (Osborne 2017). This stretch is caused by blood filling the ventricles before ventricular contraction. In a normal heart, increased preload causes an increase in stroke volume (the amount of blood ejected by the ventricle with each heartbeat). An increase in stroke volume increases cardiac output (the volume of blood ejected by the ventricle in one minute).

In contrast, afterload is the resistance to the ejection of blood from the ventricle during systole (Marieb and Keller 2021). The primary determinant of afterload is resistance in the arterial system;

vasoconstriction of these vessels raises not only blood pressure, but also the resistance to blood flow out of the heart. Therefore, increased afterload reduces cardiac output. Although preload, afterload and cardiac output are usually discussed with reference to the left ventricle, the same factors determine the output of the right ventricle of the heart (Schwinger 2021).

While an increase in sympathetic nervous system activity raises cardiac output and blood pressure in the short term, it also increases the workload of the heart. Myocardial oxygen demand and intracardiac pressures rise, exacerbating any underlying ischaemia and fluid congestion in the veins leading into the heart. Therefore, this response is maladaptive in chronic heart failure; in the short-term cardiac output rises, but in the longer term a deterioration of heart failure occurs.

Upregulation of the renin-angiotensin-aldosterone system

The RAAS assists in regulating sodium and fluid balance, as well as the longer-term control of blood pressure (Marieb and Keller 2021). A decline in cardiac output in patients with chronic heart failure reduces mean arterial pressure and perfusion of the kidney (Easa et al 2021). This fall in perfusion is detected by cells in the juxtaglomerular apparatus of the kidney, which respond by releasing the enzyme renin (Welch 2017). Renin release can also be triggered by a fall in serum sodium, which is detected by macula densa cells in the distal convoluted tubule of the kidney, although this mechanism is less relevant to chronic heart failure.

The release of renin is the first part of a chemical cascade that produces three active hormones; angiotensin II, aldosterone and vasopressin (also known as antidiuretic hormone). Figure 1 shows the RAAS.

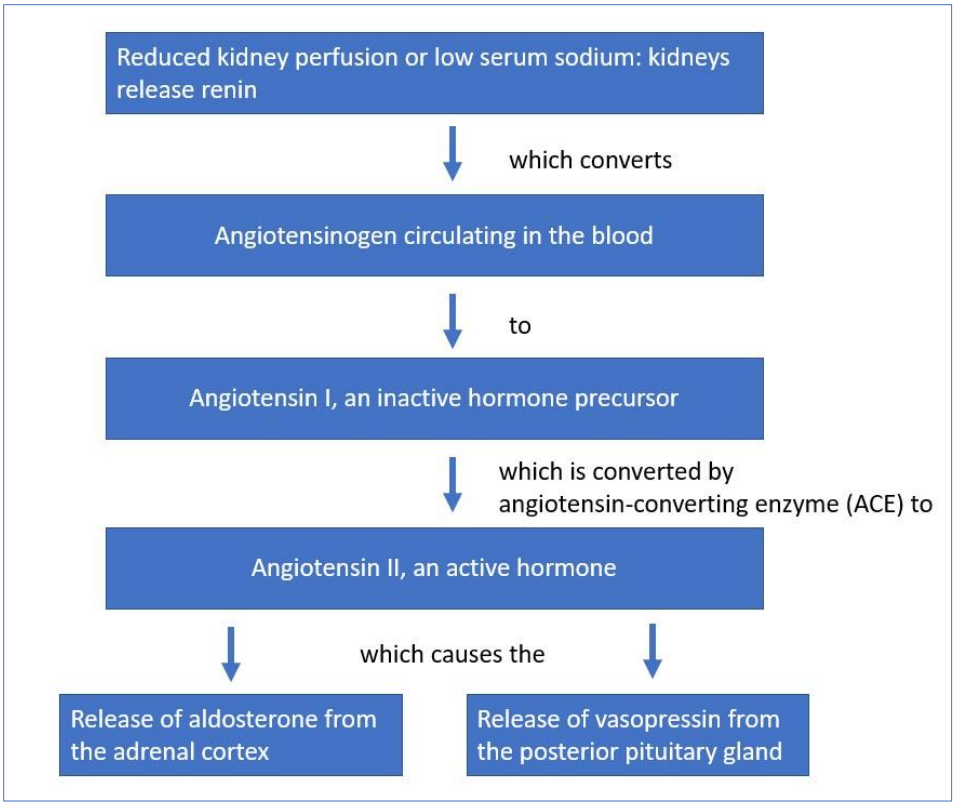

Figure 1. Renin-angiotensin-aldosterone system (based on Fountain & Lappin, 2021)

Angiotensin II, aldosterone and vasopressin hormones all cause vasoconstriction. Aldosterone also acts on the kidney, increasing the reabsorption, from the kidneys into the bloodstream, of sodium and water, while vasopressin increases water reabsorption and triggers the thirst mechanism (Marieb and Keller, 2021). The combined effect of these hormones is to increase intracardiac pressures, cardiac work, and blood pressure. Fluid is retained, which accumulates in the lungs, gut, and peripheral tissues. The resulting organ congestion is responsible for many of the symptoms of chronic heart failure (Schwinger, 2021).

Increased production of natriuretic peptides

Natriuretic peptides are hormones produced by cardiac myocytes in response to increased wall stress, for example when the chamber walls are overstretched (McDonagh et al, 2021). They counter-regulate the effects of the RAAS and sympathetic nervous system by promoting vasodilatation, and the excretion of sodium and fluid, and therefore reduce heart failure symptoms. Unlike the two compensatory mechanisms described previously, the long-term effects of natriuretic peptides in chronic heart failure are beneficial rather than maladaptive. Natriuretic peptides are primarily broken down by neprilysin, an enzyme found mainly in kidney tissue (Jhund & McMurray, 2016).

Pharmacological therapy

The aims of pharmacological therapy in patients with chronic heart failure are to improve functional capacity, prevent hospital admission and reduce mortality (McDonagh et al 2021). Before the 1980s, nitrates, diuretics and digoxin were the medicines commonly used to manage chronic heart failure. While these medicines demonstrated some success in terms of improving patients' functional capacity and preventing hospital admissions, they had no proven effect on mortality (Rossignol et al, 2019). The modern management of CHF began in 1988, with the publication of the landmark CONSENSUS trial (Swedberg et al, 1988). This randomised controlled trial demonstrated a 40% mortality reduction in patients with HFrEF taking enalapril, an angiotensin converting enzyme (ACE) inhibitor. Subsequent trials of beta blockers had similar findings, establishing these two groups of medicines as the cornerstones of therapy (McDonagh et al, 2021).

Several medicines have since been added to clinical guidelines on chronic heart failure such as mineralocorticoid receptor antagonists and ivabradine. In each case, randomised controlled trials demonstrated further reductions in morbidity and mortality when the new medicine was added to standard therapy. However, although the use of these medicines is supported by high-quality evidence, most of the trials were conducted exclusively in patients with HFrEF. As a result, there are extensive evidence-based guidelines for pharmacological therapy in patients with this type of heart failure, but not for patients with HFmrEF or HFpEF. The only medicines recommended across all types of heart failure are diuretics (NICE 2018, McDonagh et al 2021).

Diuretics

While there is no convincing evidence that diuretics reduce mortality, their role in managing the symptoms associated with congestion and fluid overload is well established (Rossignol et al, 2019). Diuretics increase the excretion of fluid and electrolytes by the kidney. Both loop and thiazide-like diuretics can be used in chronic heart failure, although loop diuretics are preferred because they produce a more powerful and short-lived diuresis than thiazide-like diuretics (Felker et al, 2020). In

cases of severe fluid overload or diuretic resistance both types can be used, although this requires considerable care because the risk of adverse events is increased.

The most used loop diuretics in clinical practice are furosemide and bumetanide. These medicines are given intravenously during acute hospital admission and orally as maintenance therapy, while subcutaneous administration can be used during end-of-life care. Thiazide diuretics are typically used as adjuncts to loop diuretics, and common examples include bendroflumethiazide and metolazone (Joint Formulary Committee 2022).

Unlike other medicines used in chronic heart failure, there is no recommended or target dose; instead, diuretics should be titrated to achieve the desired clinical effect (NICE, 2018). Because diuretics are not associated with increased survival and may cause dehydration, electrolyte imbalance and hypotension, the smallest dose needed to maintain euvolaemia (the ideal fluid volume for the specific patient) should be used. Some patients are able to stop diuretics altogether, or use them as required (Rossignol et al, 2019).

Management of heart failure with reduced ejection fraction

In addition to diuretics, four first-line groups of medicines are recommended in patients with HFrEF (McDonagh et al 2021):

- Beta-blockers
- RAAS inhibitors: ACE inhibitors, angiotensin receptor blockers (ARB) and angiotensin receptor-neprilysin inhibitors.
- Mineralocorticoid receptor antagonists.
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors.

Patients are typically prescribed one drug from each group (Heidenreich et al, 2022; McDonagh et al, 2021). Second-line and third-line drugs include ivabradine, digoxin and the combination of nitrates and hydralazine (NICE, 2018); however, discussion of these medicines is beyond the scope of this article.

Beta blockers

Beta-blockers prevent noradrenaline and adrenaline from binding to beta-adrenergic receptors (Rossignol et al, 2019). This counters the maladaptive sympathetic nervous system response seen in chronic heart failure. Therapeutic effects include reductions in heart rate, contractility, preload, and afterload (McDonagh et al, 2021). This reduces the workload of the heart, with good-quality evidence of improvements in symptoms, as well as reductions in hospitalisations and deaths due to heart failure (Joseph et al 2019).

Beta blockers reduce blood pressure and slow electrical activity in the sinus and atrioventricular (AV) nodes, so they should be avoided in patients with hypotension, bradycardia, and second/third degree AV block (Heidenreich et al, 2022). Beta-blockers can also trigger bronchospasm so their initiation in patients with asthma should be undertaken with care or avoided. In the UK, bisoprolol and carvedilol are licensed for use in heart failure; nebivolol has a license for stable mild to moderate heart failure in patients aged 70 years and over (Joint Formulary Committee, 2022).

Beta-blockers should only be commenced in patients who are clinically stable. A low initial dose is titrated in stages, typically every few weeks, until the full or maximum tolerated dose is achieved. For example, bisoprolol is commonly started at 1.25mg daily and increased to 10mg daily if possible. The patient's heart rate, cardiac rhythm and blood pressure should be assessed on initiation and with each dose increase (Rossignol et al, 2019). If symptomatic hypotension develops, it may be possible to continue therapy by revising other aspects of care. Strategies include reducing or stopping non-essential medicines that lower blood pressure, for example diuretics and vasodilators, treating hypovolaemia and staggering the administration of heart failure medicines rather than administering them all at the same time of day.

Renin-angiotensin-aldosterone system inhibitors

Angiotensin-converting enzyme inhibitors

ACE inhibitors block the conversion of angiotensin I to angiotensin II (figure 1), thereby reducing plasma levels of all three active hormones produced by the RAAS. This promotes vasodilatation and reduces sodium and fluid retention.

Like beta-blockers, ACE inhibitors lower BP and should only be commenced in patients who are haemodynamically stable (McDonagh et al, 2021). They reduce perfusion pressure at the kidney, which typically causes a transient reduction in estimated glomerular filtration rate (eGFR) and an increase in serum creatinine (Clark et al 2019). Guidelines suggest that a fall in eGFR of <10% from baseline (provided eGFR is >25mL per minute per 1.73m^2) or a rise in serum creatinine <50% (provided it is <266 micromol/L) is acceptable (McDonagh et al 2021). Falls greater than this should prompt clinical review, and the dose of the ACE inhibitor may be reduced, or the medicine stopped temporarily. If stopped, the aim should be to restart the medicine as soon as possible and to optimise the dose (Rossignol et al, 2019).

ACE inhibitors promote an increase in serum potassium, primarily via their effects on aldosterone levels and this can lead to hyperkalaemia (Rossignol et al, 2019). Hyperkalaemia should not prevent ongoing therapy if it is mild, and the patient is otherwise well. Mild hyperkalaemia is defined as a serum potassium of 5.5mmol/L to 5.9mmol/L; at this level, increased biochemical monitoring is recommended and the dose may need to be reduced (Clarke et al, 2019). Factors that can contribute to hyperkalaemia should be addressed, for example hypovolaemia, potassium supplements, sodium substitutes and non-essential medicines known to promote hyperkalaemia such as non-steroidal anti-inflammatory drugs. Moderate-to-severe hyperkalaemia (serum potassium of ≥6mmol/L), or mild hypokalaemia in a patient who is acutely unwell, should trigger urgent expert review.

Several ACE inhibitors are licensed for heart failure in the UK, with enalapril, lisinopril and ramipril commonly being used (Joint Formulary Committee, 2022). A typical approach would be to start a patient on 1.25mg ramipril daily, then to increase the dose in stages to 10mg daily if tolerated. Careful monitoring of the patient's renal function, electrolytes and blood pressure is required during initiation and uptitration (Heidenreich et al 2022). Some patients develop intolerance of ACE inhibitors, often experiencing a dry cough.

Angiotensin receptor blockers

ARBs block the effects of angiotensin II on target organs (Schwinger, 2021). Despite having a different mechanism, they have similar physiological effects to ACE inhibitors, so they are recommended as an alternative in patients who develop intolerance to ACE inhibitors (NICE, 2018). Examples of ARBs include candesartan cilexetil, irbesartan and valsartan. As with beta-blockers and ACE inhibitors, a low starting dose is gradually uptitrated to achieve the full or maximum tolerated dose. The effects of ARB on blood pressure, renal function and potassium are similar to those of ACE inhibitors, so the same precautions apply during initial treatment and dose increases (Joint Formulary Committee, 2022).

Angiotensin receptor neprilysin inhibitors

Angiotensin receptor neprilysin inhibitors are medicines that combines an ARB with a neprilysin inhibitor. Inhibiting neprilysin prolongs the half-life of natriuretic hormones, promoting vasodilatation, diuresis, and sodium excretion (Jhund & McMurray, 2016). ARBs achieve similar results via a different mechanism, so the effect is additive. At present, there is only one medicine in this class: sacubitril valsartan.

Sacubitril valsartan was compared with enalapril in the PARADIGM trial (McMurray et al, 2014). A 20% reduction in the primary end point (cardiovascular death or hospitalisation) was seen in patients taking sacubitril valsartan. Patients recruited to the trial were already taking an ACE inhibitor or ARB before switching to the trial medicine; this necessity has been incorporated into NICE (2018) guidelines for the use of sacubitril valsartan. NICE (2018) restricts their recommendation to patients with a LVEF of ≤35% and New York Heart Association functional class II-IV who remain symptomatic despite optimal pharmacological therapy. Since the publication of the NICE (2018) guidelines, trials have shown that de novo initiation of sacubitril valsartan is safe and effective, and this approach is approved by subsequent guidelines from professional organisations (Heidenreich et al, 2022; McDonagh et al, 2021).

Sacubitril is typically started at a dose of 49/51mg twice daily, increased to 97/103mg twice daily after 2-4 weeks if possible (McDonagh et al, 2021). A reduced dose of 24/26mg should be considered in patients with a systolic BP less than 110mmHg or renal impairment. There must be a washout period of 36 hours when switching a patient from an ACE inhibitor to sacubitril valsartan because this reduces the risk of angioedema. The risks of hypotension, renal impairment and hyperkalaemia in patients taking sacubitril valsartan are comparable to those for ACE inhibitors, so the monitoring requirements are similar. In addition, monitoring the patient's liver function is recommended, with caution advised if their hepatic transaminases exceed twice the normal upper limit (Joint Formulary Committee, 2022).

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists block receptor sites for aldosterone, and to a lesser degree other steroid hormones, on target organs including the kidneys (Rossignol et al, 2019). Although they also target the RAAS, they improve morbidity and mortality when given in addition to an ACE inhibitor, ARB or angiotensin receptor neprilysin inhibitor (McDonagh et al, 2021).

Two Mineralocorticoid receptor antagonists are available in the UK: eplerenone and spironolactone. These medicines are started at a dose of 25mg daily, then increased to 50mg if possible (Joint National Formulary, 2022). They have similar effects to ACE inhibitors on blood pressure, renal

function and serum potassium, so require the same monitoring during initiation and uptitration (NICE, 2018). Spironolactone can cause gynaecomastia (enlargement of male breast tissue), which may reduce adherence to this medicine. This side effect is seen less often with eplerenone, so this medicine is generally preferred because it is more likely to be tolerated (McDonagh et al 2021).

Sodium-glucose co-transporter 2 inhibitors

SGLT2 inhibitors are hypoglycaemic agents used in the management of diabetes mellitus (Braunwald, 2022). They reduce the reabsorption of glucose in the proximal convoluted tubule of the kidney, thereby lowering blood glucose levels. During safety trials, cardioprotective properties of SGLT2 inhibitors were noted – in particular a reduction in hospitalisations due to chronic heart failure – which led to trials in HFrEF patients with and without diabetes. These trials confirmed there were symptomatic and prognostic cardiovascular benefits when SGLT2 inhibitors were added to optimal pharmacological therapy for HFrEF, regardless of patients' diabetic status (McMurray et al 2019, Packer et al 2020).

Two SGLT2 inhibitors are used in chronic heart failure in the UK: dapagliflozin and empagliflozin. Both of these medicines have been approved by NICE (2021, 2022) for all patients with HFrEF. In chronic heart failure, the recommended dose of both medicines is 10mg once daily, with no dose titration required. A transient drop in eGFR is common on initiation but should not necessitate discontinuation, since over the longer term SGLT2 inhibitors improve renal outcomes and slow the progression of chronic kidney disease (Braunwald 2022). Dapagliflozin and empagliflozin are contraindicated in severe renal impairment (Joint Formulary Committee 2022).

SGLT2 inhibitors cause an osmotic diuresis that may reduce loop diuretic requirements and blood pressure. Before initiating an SGLT2 inhibitor, it is considered effective practice to check the patient's glycated haemoglobin ($HbA1_c$) to identify previously undiagnosed type 2 diabetes (South East London Integrated Medicines Optimisation Committee 2021). Patients with diabetes should be referred to a diabetes specialist so that any interactions with other hypoglycaemic medicines can be managed. SGLT2 inhibitors also increase the risk of genital mycotic infection, urinary tract infection and diabetic ketoacidosis (Braunwald 2022).

Management of heart failure with mildly reduced ejection fraction

HFmREF has much in common with HFrEF in terms of its pathophysiology, and is thought to represent a mild form of HFrEF (McDonagh et al 2021). Although there is limited research evidence to support practice, guidelines suggest that the four groups of medicines recommended in HFrEF – that is, beta-blockers, RAAS inhibitors, mineralocorticoid receptor antagonists and SGLT2 inhibitors – can also be given to patients with HFmREF (McDonagh et al 2021). The rationale is that they are likely to reduce the risk of hospitalisation and death in these individuals. It should be noted that the level of recommendation is relatively weak for their use in HFmREF (class IIb – may be considered) compared to their use in HFrEF (class I – is recommended).

Management of heart failure with preserved ejection fraction

While several studies have attempted to address the evidence deficit in HFpEF, at the time of writing only the EMPORER-Preserved trial had reached its clinical endpoint. This trial demonstrated a 21% reduction in a combined endpoint of heart failure hospitalisation or death in patients with HFpEF who were taking empagliflozin (Anker et al 2021). This reduction suggested a role for SGLT2 inhibitors in the management of HFpEF, however this has yet to translate into clinical guidelines in the UK. Recommendations for patients with HFpEF include diuretics for symptom control, alongside the management of any comorbidities. Managing comorbidities may involve some of the medicines discussed previously; for example, beta-blockers are standard therapy in atrial fibrillation, while ACE inhibitors are first-line medicines for hypertension (McDonagh et al 2021).

Conclusion

Chronic heart failure is a complex condition associated with significant symptoms, increased use of healthcare resources, and a high mortality rate. Pharmacological therapy is central to the management of chronic heart failure, particularly in patients with HFrEF. In this population, the initiation of a beta-blocker, RAAS inhibitor, mineralocorticoid receptor antagonist and SGLT2 inhibitor has the potential to significantly improve patient outcomes. Careful management of these medicines is required to avoid adverse effects and facilitate optimal therapy, in accordance with clinical guidelines.

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