

Diuretics in the management of chronic heart failure: when and how

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SUMMARY

Heart failure is an increasingly prevalent condition resulting in recurrent hospitalisations and significant mortality and morbidity.

The management of heart failure has evolved, and multiple drugs have an established mortality benefit in heart failure with reduced ejection fraction.

Although the focus should be on ensuring that patients are treated with the maximum tolerated doses of these guideline-directed therapies, diuretics continue to play a key role in the management of clinical congestion in all forms of heart failure.

Clinicians play a key role in heart failure management. Familiarity with the role of diuretics and their dosing and monitoring is critical.

Introduction

Heart failure affects approximately 2% of the adult Australian population, and the prevalence is increasing.¹ The natural history of the condition is characterised by episodes of acute decompensation, with significant associated mortality.² Heart failure can be classified as heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). HFrEF is characterised by impaired contractility of the left ventricular myocardium with a left ventricular ejection fraction (LVEF) below 50%. HFpEF is characterised by diastolic dysfunction that limits the filling of the left ventricle, although the LVEF remains greater than 50%.

The management of HFrEF has evolved over the last two decades and multiple drug classes have an established mortality benefit, including angiotensin receptor–neprilysin inhibitors, ACE inhibitors, beta blockers, mineralocorticoid receptor antagonists and sodium–glucose co-transporter 2 (SGLT2) inhibitors. The primary aim is to establish patients on the maximum tolerated doses of these guideline-directed medical therapies, all of which reduce heart failure-related mortality. However, patients with hypervolaemia should also be treated with diuretics for symptom relief. When euvolaemia is achieved, diuretic therapy should be reduced or stopped where possible to prioritise these mortality-reducing drugs.

Principles of diuretic therapy

In heart failure, the abnormal cardiac filling and resultant high venous pressures can lead to the typical symptoms and signs of ‘clinical congestion’, including dyspnoea (particularly orthopnoea and paroxysmal

nocturnal dyspnoea), an elevated jugular venous pressure, hepatic enlargement and tenderness, peripheral oedema, pulmonary oedema and the formation of ascites. In patients with heart failure and clinical congestion, diuretics are first-line therapy to improve symptoms. While they may not have an established mortality benefit, diuretics were used as background therapy in most patients in the pivotal trials that showed the survival benefit of the aforementioned heart failure therapies.¹ The aim of using diuretics is to achieve euvolaemia. Once this is achieved, the diuretic dose should be reduced to the lowest effective dose or potentially discontinued.

Loop diuretics are the most frequently used diuretics due to their rapid onset and efficacy.³ Acting on the sodium–potassium–chloride symporter of the ascending limb of the loop of Henle, loop diuretics promote the excretion of sodium and chloride, as well as potassium.² Furosemide (frusemide) is the most commonly used first-line therapy, which is typically started at a dose of 20–40 mg once daily in the outpatient setting. Patients who are furosemide (frusemide)-naïve typically have greater diuresis when the drug is started. If there is no response, the dose should be increased to reach the required threshold of diuresis.⁴ The typical total daily dose for maintenance ranges between 40 mg and 240 mg. In the setting of advanced renal failure, daily doses up to 500 mg may be needed, and liaison with the treating nephrologist is recommended. To optimise the effect, it is recommended to divide the daily dose into morning and midday doses if more than 80 mg is required in a day.

Although furosemide (frusemide) is the only loop diuretic on the Pharmaceutical Benefits Scheme (PBS), there are other drugs in the class with differing pharmacological properties, including bumetanide.

The oral bioavailability of bumetanide is high (approximately 80–90%), while that of furosemide (frusemide) varies. As such, a direct conversion is not consistently reliable, although in general, oral furosemide (frusemide) 40 mg is considered to be equivalent to oral bumetanide 0.5–1 mg.² Some clinicians favour the use of bumetanide for its higher oral bioavailability over furosemide (frusemide) in the setting of significant peripheral oedema, as bowel wall oedema may limit absorption.⁵ A recent systematic review, however, did not show a significant benefit over furosemide (frusemide).⁶ Given that furosemide (frusemide) contains a sulfonamide moiety, it carries a potential risk of cross-reactivity in the setting of sulfonamide allergies.⁷ Etacrynic acid (which does not contain the sulfonamide moiety) is an alternative loop diuretic for patients with sulfonamide allergies.

Refractory congestion and sequential nephron blockade

If congestion persists despite adequate dosing of loop diuretics, clinicians should consider 'sequential nephron blockade', the addition of diuretics that exert their effects at successive components of the nephron. However, it should be noted that sequential nephron blockade is a potent combination. While the combination can be more effective, it carries an increased risk of renal dysfunction and electrolyte imbalance and so should be used cautiously, particularly in elderly patients. This approach includes the concurrent use of thiazide diuretics and mineralocorticoid receptor antagonists. Thiazides act more distally in the nephron, by blocking the sodium–chloride co-transporter in the distal convoluted tubule.² Thiazide-like diuretics, which lack the benzothiadine backbone in their molecular structure, also act on the same transporter but have a longer elimination half-life.⁸ The addition of thiazides may help overcome diuretic resistance, which can arise from prolonged use of a loop diuretic and the resultant nephron remodelling and increased sodium reabsorption.⁹

A readily available thiazide is hydrochlorothiazide, which can be started at 12.5–25 mg per day, and increased up to a total of 50 mg per day. Several thiazide-like diuretics can also be used, including indapamide, metolazone and chlortalidone, without strong evidence for the superiority of one drug.⁴

Some clinicians favour the potent diuretic metolazone in the setting of refractory congestion, although it is a highly specialised drug with restrictions on

prescribing and is generally dispensed from hospitals. While it may be dosed daily in the acute setting, in the non-acute environment, doses of metolazone can be reduced to 2.5–5 mg once weekly.

Monitoring and adverse effects of diuretics

Given the potential for renal dysfunction and electrolyte imbalance (particularly hypokalaemia and hyponatraemia, the latter especially with thiazide diuretics), regular monitoring is required. Monitoring of electrolytes (particularly sodium and potassium), urea and creatinine should be performed 1–2 weeks after starting or adjusting diuretic doses, and eventually every six months in the long term.¹

Abnormal potassium concentrations are associated with increased mortality in heart failure.^{1,3} Diuretics, as well as the other heart failure therapies, can change potassium concentrations. Dietary measures are helpful in addressing both low and high potassium concentrations and should be used. Increasing the dose of mineralocorticoid receptor antagonists can also be used to mitigate the hypokalaemia induced by diuretics, if not already at the maximum tolerated dose. Occasionally, potassium supplementation may be required with close monitoring.

Hyponatraemia is frequent, occurring in up to 20% of patients hospitalised with heart failure, and is also associated with higher mortality in heart failure.^{1,3} The presence of hyponatraemia should prompt an assessment of fluid status. Hyponatraemia is usually dilutional in the setting of hypervolaemia, which may respond to fluid restriction. Occasionally it is due to diuretics, particularly thiazides and thiazide-like diuretics, and if the patient is not hypervolaemic, the clinician should reconsider the need for diuretics.¹

Hyperuricaemia is common among patients with heart failure. Prescribers should be aware of the risk of gout exacerbations associated with diuretics, particularly thiazides.¹

Clinicians must also be aware of the rare complication of ototoxicity with loop diuretics, typically with high-dose intravenous therapy or in the setting of impaired renal function. Concurrent use of other potentially ototoxic drugs, such as aminoglycosides, also increases the risk.¹⁰

Prescribers should also be mindful of the potential for interactions with other heart failure therapy. Diuretic doses may need to be reduced to mitigate the risk of adverse effects of hypotension and hypovolaemia when starting beta blockers, renin–angiotensin system blockade or SGLT2 inhibitors.¹¹

Primary care physicians play a key role in titrating diuretics, particularly following hospitalisation, when

early outpatient follow-up has been shown to reduce readmissions.¹² The doses of diuretics are often increased during admissions for exacerbations of heart failure, and patients are instructed to follow up with their GPs in the week following discharge for further titration. On follow-up, assessments of body weight, fluid status, renal function and electrolytes should be performed to ensure that a patient is euvoelaemic. Once euvoelaemia is established, the goal is to ensure a patient's body weight remains stable at their dry weight, by ensuring compliance with fluid restrictions and gentle adjustments in the dose of diuretics. Should a patient become hypovolaemic, then clinicians should reduce the dose of diuretics until the body weight returns to baseline. While exact dose alterations must be individualised, furosemide (frusemide) doses are often reduced by 40 mg (although the adjustments are greater in the setting of high-dose diuretics). Follow-up at 1–2 weeks following a dose adjustment is crucial.

Clinicians can trial stopping diuretics in patients with heart failure who are stable on optimal therapy, have not been recently hospitalised due to heart failure, and are receiving a dose of up to 80 mg furosemide (frusemide). The dose can gradually be reduced, and patients should be closely monitored for rebound hypervolaemia.¹³

Diuretics in renal dysfunction

Renal impairment often coexists with heart failure and is an independent predictor of mortality.³ However, acute increases in creatinine during diuretic treatment are common and do not necessitate a reduction in the dose, particularly if congestion is present.⁴ Data suggest that these increases in creatinine in response to diuresis are usually transient and do not worsen outcomes. Moreover, in patients with pre-existing renal impairment, a higher dose of diuretics is required to exert the same effect. Diuretics form part of the treatment of cardiorenal syndromes by improving ventricular filling and reducing renal venous pressures, thereby enhancing renal perfusion.¹⁴

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists are one of the proven pillars of therapy for HFrEF. Despite being classed as potassium-sparing diuretics, their benefit occurs through neurohormonal modulation and effects on ventricular remodelling rather than diuresis itself.¹⁵ In the kidneys, aldosterone antagonists modulate the expression and activity of sodium and potassium channels in the distal nephron.² Spironolactone and eplerenone doses are identical.

They should be started at low doses (e.g. 12.5 mg daily), particularly in the setting of diabetes or renal impairment. International guidelines recommend up-titration over 1–2 months to 25–50 mg daily,³ although the risk of hyperkalaemia is higher when the dose of spironolactone or eplerenone is 50 mg and above.

Mineralocorticoid receptor antagonists should be avoided or used cautiously in patients with stage IV–V chronic kidney disease or a potassium concentration above 5 mmol/L. With each dose adjustment, electrolytes and renal function should be checked at 1–2 weeks and then monthly for three months, before eventually stretching out to every six months. If the estimated glomerular filtration rate (eGFR) reduces by more than 30% or potassium concentration rises above 5.5 mmol/L, the mineralocorticoid receptor antagonist should be reduced and may need to be stopped altogether if the potassium concentration rises above 6 mmol/L. Spironolactone can also cause gynaecomastia and, if this occurs, it may be substituted with eplerenone.¹ However, eplerenone is only listed on the PBS for HFrEF, specifically after acute myocardial infarction.

Sodium-glucose co-transporter 2 inhibitors

SGLT2 inhibitors have shown benefits for both HFrEF and HFpEF. Dapagliflozin or empagliflozin are recommended in all patients with HFrEF already receiving optimal treatment with an ACE or angiotensin receptor–neprilysin inhibitor, a beta blocker and a mineralocorticoid receptor antagonist, irrespective of the presence of diabetes.³ Dapagliflozin has recently been included on the PBS for the treatment of HFrEF, improving patient access to the drug.

Although it is not thought to be the primary mechanism responsible for their benefits in terms of cardiovascular death and heart failure-related hospitalisation, SGLT2 inhibitors have diuretic and natriuretic properties, giving them an added benefit of reducing congestion.³ If a patient is euvoelaemic on starting SGLT2 inhibitors, the prescriber can consider reducing the dose of diuretics. A reversible reduction in the eGFR by up to 30% often occurs after starting SGLT2 inhibitors and should not lead to premature discontinuation.³ The evidence in favour of SGLT2 inhibitors in HFpEF is also evolving, and they are currently recommended in HFpEF guidelines.¹⁶

Clinicians should be mindful of the adverse effects of SGLT2 inhibitors. While there are conflicting data about a possible increased urinary tract infection risk, the risk of fungal genital infection is increased

3–5-fold.¹⁷ SGLT2 inhibitors can also result in hypovolaemia and euglycaemic ketoacidosis.¹⁷ Due to their mild diuretic effect, reducing or stopping loop or thiazide diuretics should be considered if a patient is euvolaemic. Patients should also be instructed to withhold their SGLT2 inhibitors perioperatively and during ‘sick days’.¹⁷

Carbonic anhydrase inhibitors

There is renewed interest in the use of acetazolamide for acute decompensated heart failure. Acetazolamide is a carbonic anhydrase inhibitor, which inhibits the reabsorption of sodium and bicarbonate in the proximal tubule. The randomised, placebo-controlled Acetazolamide in Acute Decompensated Heart Failure with Volume Overload trial included hospitalised patients with acute decompensated heart failure who were also receiving intravenous loop diuretics. In this trial, the addition of intravenous acetazolamide resulted in a greater incidence of successful early decongestion, without increasing the rate of adverse events.¹⁸ This promising finding offers another potential drug to assist in the challenge of achieving decongestion in decompensated heart failure, although it should be noted that the use of SGLT2 inhibitors was a contraindication and that the drug was administered intravenously in this trial. Further evidence is required to determine whether there is a role for oral acetazolamide in the primary care setting.

Non-pharmacological fluid management

In patients with congestive heart failure, a 1.5 L fluid restriction can be considered on the basis of biological plausibility, although the supporting evidence is lacking.¹ In patients without clinical congestion, fluid restriction is not recommended.

Self-management is a key component of the management of heart failure, and heart failure action plans should be instituted where possible. Numerous practical clinical resources are available for patients, including the NPS MedicineWise program on heart failure, which was developed in collaboration with the Heart Foundation and provides a succinct outline of the goals in heart failure and how to achieve them. The program also offers a practical guide to assist GPs in the up-titration of heart failure medicines. The Heart Foundation’s ‘Heart Failure Resources for Patients’ also offers a range of practical resources for patients to assist with self-management.

A self-care written strategy encourages weight monitoring, adherence to drugs, fluid management and physical activity, and alerts patients to the early signs and symptoms of congestion. Rapid weight gain (e.g. 2 kg over two days) is likely to be related to hypervolaemia and should prompt patients to consult with their GP or other supervising healthcare professional. In motivated and competent patients, a flexible diuretic plan can enable patients to safely titrate diuretic doses in response to hypervolaemia. For example, a patient is recommended to take 40 mg furosemide (frusemide) if their body weight increases by more than 2 kg over two days.

Exercise programs should be considered for patients with heart failure. There is good-quality evidence supporting the role of exercise in improving physical fitness, quality of life and hospital admissions in the heart failure population.¹ Regular, moderate-intensity exercise has well-demonstrated safety and efficacy and is recommended for all patients with heart failure.

Nurse-led clinics have been shown to improve survival, reduce hospitalisations and reduce the time required to achieve optimal doses of therapy.¹ If oral diuretics are insufficient, intravenous administration may be suitable and can be provided in the outpatient setting, either by the local heart failure service or the treating GP (particularly in the rural setting), thereby avoiding hospital admissions.

Conclusion

While the aim of heart failure management should be the initiation and up-titration of guideline-directed medical therapies with a proven mortality benefit, diuretics still play an important role in the management of symptomatic congestion in all forms of heart failure. When euvolaemia is achieved, diuretics may be stopped or flexibly used in conjunction with a heart failure action plan in selected patients, allowing for further up-titration of the proven guideline-directed therapies. Furosemide (frusemide) is typically the first-line diuretic. Combinations of diuretics can result in significant clinical improvement, although prescribers should be cognisant of possible additive adverse events such as electrolyte abnormalities, renal impairment and hypovolaemia. An understanding of dosing, monitoring and adverse events is critical for GPs managing heart failure. ◀

Conflicts of interest: none declared

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