Treating comorbidities in heart failure

Tackling the hidden burden

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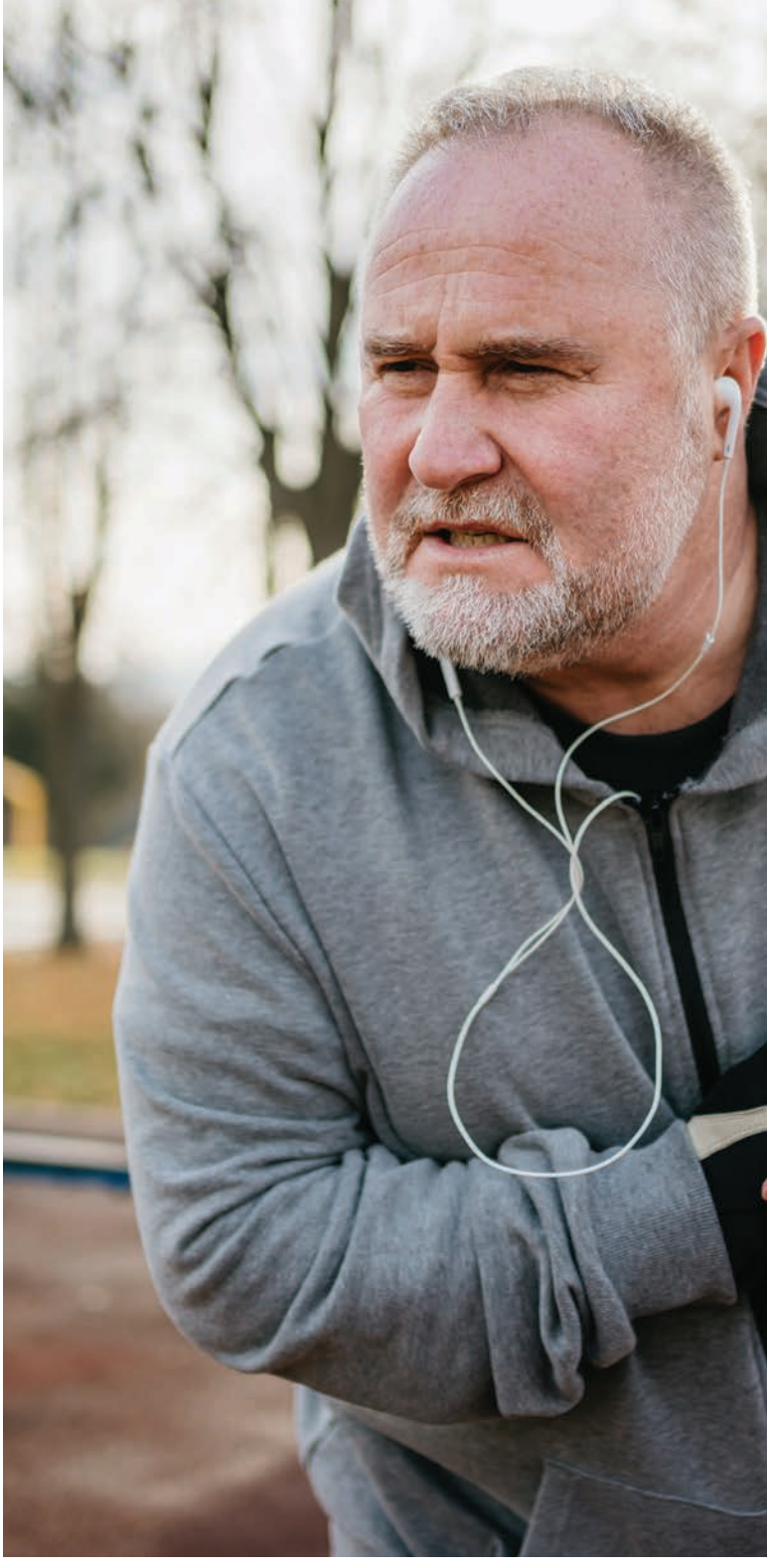
Most patients with heart failure also have comorbidities that require clinical attention. Comprehensive care should optimise guideline-directed medical therapy while addressing these comorbidities. Recent advances in management include sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, finerenone, intravenous iron and vaccinations. GPs are well placed to deliver holistic, patient-centred care to patients with heart failure.



Heart failure (HF) is common in Australia, affecting more than 500,000 individuals (about 2% of the population).[1] Acute HF has a poor prognosis, with one-year all-cause mortality after a hospital admission with HF in Australia estimated at 25% (75% one-year survival).[2] Chronic HF, by contrast, has an 87% one-year survival and 60% at five years.[3] There is no significant difference in survival for HF with reduced ejection fraction (HFrEF) compared with HF with preserved ejection fraction (HFpEF); however, patients with HFpEF are typically older at diagnosis, and increased age at diagnosis is a key factor associated with a poor prognosis.[3]

In an Australian study of HF in general practice, patients with HF were a mean age of 69.8 years and saw their GP 14 times a year,[4,5] which places the GP at the centre of care. Most patients with HF present with comorbidities (Figure 1), and more than 85% of patients are managing an additional two chronic conditions.[6] Comorbidities are associated with worse outcomes, lower use of guideline-directed medical therapy (GDMT) and greater exposure to potentially harmful

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medications.[7] HF is increasingly recognised as part of a cardiovascular–kidney–metabolic syndrome, in which HF and its comorbidities share common metabolic and inflammatory pathways, providing a mechanistic link between these conditions and a number of common therapeutic targets.[8,9] Evidence for managing the comorbidities associated with HF comes from studies in patients with HFrEF, HFpEF or HF across all ejection fractions.[10,11] This article discusses the treatment of common comorbidities in people with HF, focussing on recent changes to the evidence and new listings on the PBS.

Key points

- **Comorbidities are common in patients with heart failure (HF), and are associated with worse outcomes. GPs play a central role in care by addressing comorbidities while optimising guideline-directed medical therapies.**
- **HF is part of a cardiovascular–kidney–metabolic syndrome, in which HF and its comorbidities share common metabolic and inflammatory pathways, and have common therapeutic targets.**
- **Hypertension represents an opportunity to optimise HF therapies to lower blood pressure.**
- **Obesity is strongly linked with HF with preserved ejection fraction, and glucagon-like peptide-1 receptor agonists are emerging as a therapy in this population.**
- **Obstructive sleep apnoea may improve with glucagon-like peptide-1 receptor agonists, which are now recommended in HF management guidelines.**
- **In patients with type 2 diabetes and HF, sodium-glucose cotransporter-2 inhibitors are essential and metformin remains first-line therapy.**
- **HF therapies that delay progression of chronic kidney disease should be used in people with both conditions.**
- **Regular screening for iron deficiency is important, and intravenous iron should be given to people with HF with reduced ejection fraction who are iron deficient, irrespective of anaemia status.**
- **Vaccination against respiratory tract infections reduces morbidity and complications in patients with HF.**
- **Polypharmacy should be addressed in line with patient goals and priorities.**
- **Palliative care can improve symptoms such as dyspnoea and support end-of-life planning.**

Hypertension

Hypertension is the most common comorbidity in patients with HF, and is linked to both its development and worsening.[12] In HFrEF, high blood pressure presents an opportunity to ensure that GDMT is titrated to the maximal tolerated dose. The four pillars of GDMT in HFrEF are an HF-specific beta blocker, ACE inhibitor or angiotensin receptor-neprilysin inhibitor (or angiotensin II receptor blocker if intolerant), mineralocorticoid receptor antagonist (MRA) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, all of which reduce mortality and should be used at the highest doses tolerated.[13,14] These four therapies should be started at low doses, in quick succession, then titrated individually to maximally tolerated doses.[14] No trials have assessed the impact of blood pressure reductions on outcomes in patients with HFrEF and hypertension, and the optimal blood pressure is not known. Diuretics should be reduced to the lowest effective dose, and other antihypertensives reduced or ceased to prioritise higher doses of GDMT. If hypertension persists despite maximal doses of GDMT, amlodipine and hydralazine are safe to use, but diltiazem, verapamil and moxonidine may worsen HF and should be avoided.[13,15-21]

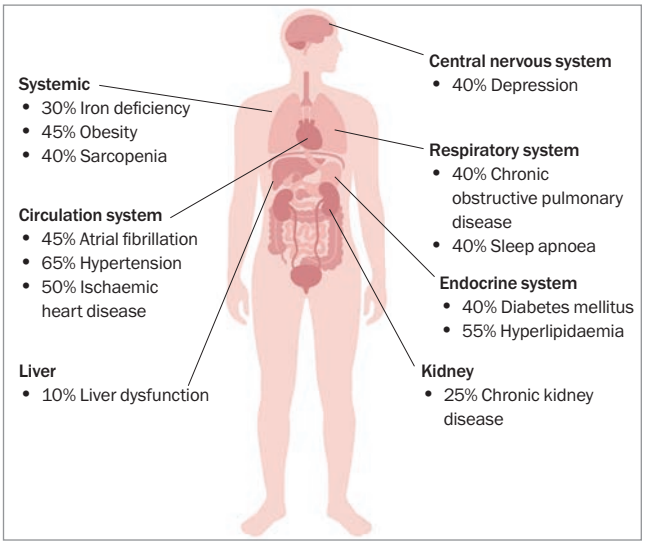

Figure 1. Estimated prevalence of heart failure comorbidities.[8]

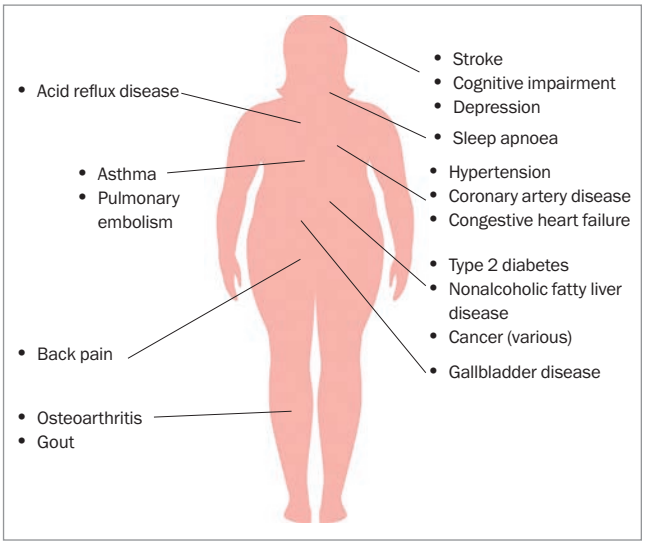

Figure 2. Obesity-related comorbidities.[23]

In HFpEF, intensive blood pressure control is recommended, aiming for less than 130/80 mmHg.[11] This target has been extrapolated from benefits in hypertension in general, because more intensive control of blood pressure is associated with improved cardiovascular outcomes. Two or more agents will usually be required, and may include a diuretic, which can assist volume control, and an MRA (finerenone is preferred to spironolactone), which is recommended to decrease HF hospitalisation.[22] Candesartan and sacubitril/valsartan have also shown modest cardiovascular benefits in clinical trials in HFpEF.[11] Higher blood pressure should be tolerated if there is symptomatic orthostasis, and beta blockers are generally avoided because of their negative chronotropic effects.[11]

Obesity

Obesity is associated with several comorbidities, including cardiovascular effects (Figure 2 and Table),[23] and should be considered a therapeutic target to reduce cardiovascular risk, alongside management of hypertension, dyslipidaemia and glycaemia (Figure 3).[8] It is more strongly associated with developing HFpEF than HFrEF.[24] Obesity complicates the diagnosis of HF, as symptoms overlap, clinical signs are harder to elicit, echocardiography may be difficult to obtain and interpret, and N-terminal pro-BNP levels can be relatively low or normal in obesity.[25] Consequently, HF (HFpEF in particular) may be under-recognised in people with obesity.

Table. Increased risk of comorbidities in people with obesity[23]

Comorbidity	Relative risk [95% CI] for men	Relative risk [95% CI] for women
Type 2 diabetes	6.7 [5.6–8.2]	12.4 [9.0–17.1]
Coronary artery disease	1.7 [1.5–2.0]	3.1 [2.8–3.4]
Congestive heart failure	1.8 [1.2-2.6]	1.8 [1.1–3.0]
Hypertension	1.8 [1.5–1.7]	2.4 [1.6–3.7]
Stroke	1.5 [1.3–1.7]	1.5 [1.3–1.7]
Osteoarthritis	4.2 [2.7–6.4]	2.0 [1.9–2.0]
Gallbladder disease	1.4 [1.0–2.0]	2.3 [1.2–4.6]

Abbreviation: CI = confidence interval.

In HFrEF, weight loss through lifestyle measures is recommended for people with severe obesity (body mass index [BMI] ≥35 kg/m^2) and has been shown to be safe, but further trials are needed to establish whether weight loss improves HF outcomes. Bariatric surgery in HFrEF is associated with fewer HF hospitalisations.[24]

The situation is different in HFpEF. Obesity drives HFpEF through haemodynamic, neurohormonal, inflammatory and mechanical effects, and an obesity-related HFpEF phenotype is now recognised.[26] Incretin mimetics, including semaglutide (a glucagon-like peptide-1 [GLP-1] receptor agonist) and tirzepatide (a dual GLP-1 and glucose- dependent insulinotropic polypeptide receptor agonist), are emerging as effective therapies for this condition. In pooled analyses of the STEP-HFpEF and STEP-HFpEF DM trials, semaglutide compared with placebo in patients with HFpEF and a BMI of 30 kg/m^2 or above improved HF-related symptoms and physical limitations, and reduced body weight.[27] More recently, the SUMMIT trial showed that tirzepatide compared with placebo in patients with HFpEF (ejection fraction ≥50%) and BMI of 30 kg/m^2 or above reduced the risk of the primary endpoint of death from cardiovascular causes or worsening HF (defined as an exacerbation of HF resulting in hospitalisation, intravenous therapy in an urgent care setting or intensification of oral diuretic therapy) (hazard ratio, 0.62; 95% confidence interval, 0.41–0.96; p = 0.026).[28]

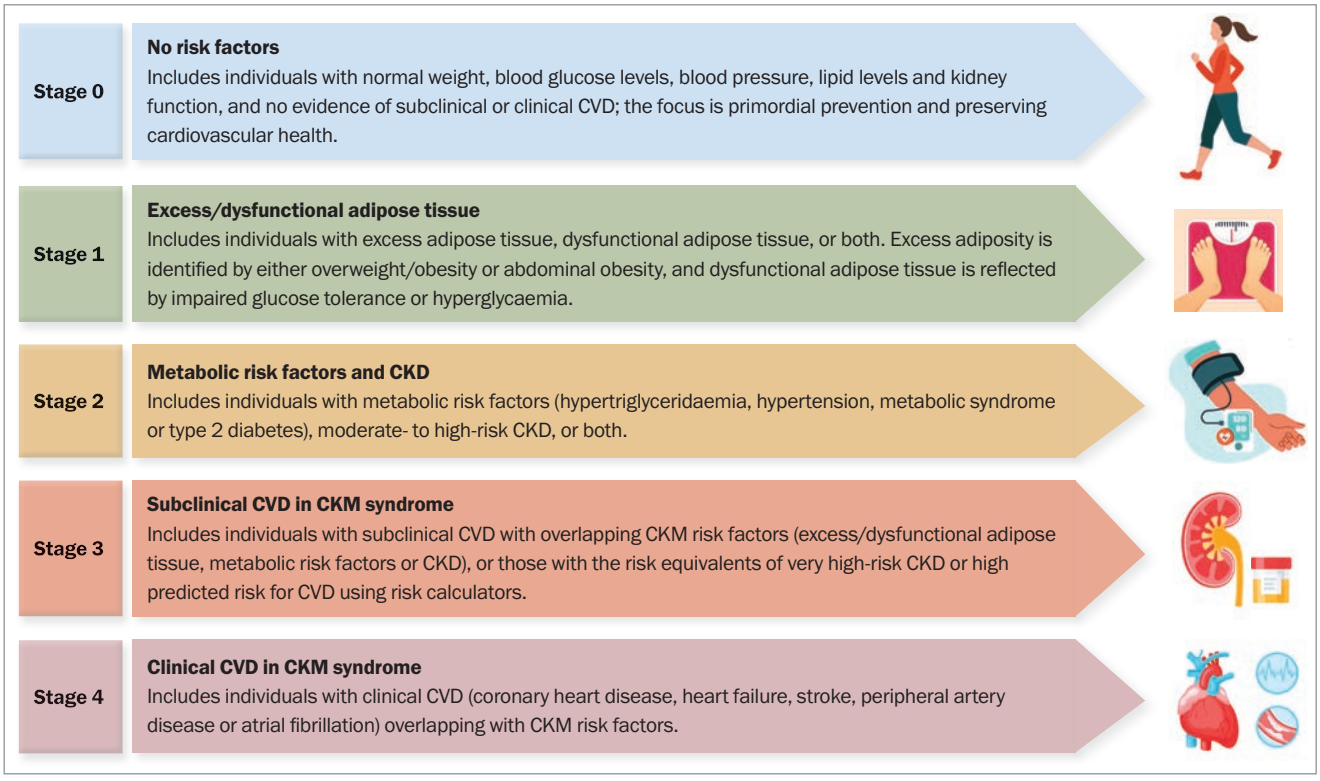

Figure 3. Stages of cardiovascular–kidney–metabolic (CKM) syndrome.[8]
Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease.

GLP-1 receptor agonists have recently been added into HF guidelines, with a strong recommendation as an adjunct to lifestyle interventions, including dietary advice and structured exercise programs, for patients with HFpEF and obesity to achieve weight loss and improve symptoms and quality of life. They are also suggested for reducing the risk of hospitalisation.[22] GPs have had almost 10 years of experience with using GLP-1 receptor agonists and are best positioned to consider these agents early in suitable HF patients to improve outcomes. Caution should be taken, however, to avoid worsening sarcopenia when weight loss measures are implemented.[29] Further trials with these agents are expected.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a common comorbidity in HF, often presenting with fewer symptoms in people with HFrEF than in other populations, and with less excessive daytime sleepiness.[30] A high index of suspicion and active screening are therefore necessary. It is also important to distinguish between OSA and central sleep apnoea.

The recent phase 3 SURMOUNT-OSA trial showed that a tirzepatide improved OSA (see the Box for full names of the clinical trials mentioned in this article).[31] In this trial, tirzepatide was compared with placebo in participants with obesity (BMI ≥30 kg/m^2) and moderate-to-severe OSA (apnoea–hypopnoea index [AHI] ≥15 events per hour), together with a calorie-restricted diet, lifestyle counselling and 150 minutes of exercise per week. Over 52 weeks, clinically significant reductions in the primary endpoint of change in AHI from baseline were seen in the tirzepatide group, irrespective of positive airway pressure use.[31] Substantial weight loss, improvements in patient-reported outcome measures and no new safety signals were also reported.

Recent HF guidelines now strongly recommend this therapy for patients with HF.[22] However, it should be noted that this trial was conducted in patients with obesity and OSA, and not specifically in patients with HF. Tirzepatide is approved by the TGA for OSA, but is not reimbursed on the PBS. In addition, for patients with HF and OSA, positive airway pressure or adaptive servo-ventilation should be considered. However, if central sleep apnoea is present in HFrEF, adaptive servo-ventilation should not be used, as it has been associated with harm.[12]

Type 2 diabetes management

SGLT-2 inhibitors improve glycaemic control and are strongly recommended in HF guidelines across the full spectrum of ejection fraction (HFrEF and HFpEF) to reduce HF-related morbidity and mortality.[32] SGLT-2 inhibitors are listed on the PBS for patients with diabetes at risk of, or with established, cardiovascular disease, independent of glycated haemoglobin (HbA_{1c}) levels. Other hypoglycaemic agents should be adjusted in people with type 2 diabetes to accommodate an SGLT-2 inhibitor if HF is present.

Clinical trial names

STEP-HFpEF
Semaglutide Treatment Effect in People With Obesity and Heart Failure With Preserved Ejection Fraction

STEP-HFpEF DM
Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus

SUMMIT
A Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity

SURMOUNT-OSA
A Study of Tirzepatide in Participants With Obstructive Sleep Apnea

DAPA-CKD
Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease

EMPA-KIDNEY
The Study of Heart and Kidney Protection With Empagliflozin

FIDELIO-DKD
Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease

FIGARO-DKD
Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease

FIDELITY
Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis

FINE-HEARTS
An Integrated Pooled Analysis of Finerenone across 3 Phase III Trials of Heart Failure and Chronic Kidney Disease and Type 2 Diabetes

FINEARTS-HF
The Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure

FLOW
Evaluate Renal Function With Semaglutide Once Weekly trial

Metformin remains a first-line agent in the treatment of people with type 2 diabetes and HF, provided the estimated glomerular filtration rate (eGFR) is 30 mL/min/1.73 m^2 or more and there is no severe hepatic impairment. Insulin, if required, causes sodium retention and may worsen fluid retention. In HFpEF and type 2 diabetes, a GLP-1 receptor agonist should be considered as the preferred first injectable to improve glycaemic control.

Currently, SGLT-2 inhibitors and GLP-1 receptor agonists are not PBS funded for concurrent use in type 2 diabetes. However, if a GLP-1 receptor agonist is prescribed for diabetes, an SGLT-2 inhibitor can still be reimbursed under the PBS if prescribed for HF (HFrEF or HFpEF) or chronic kidney disease (CKD).

Sulfonylureas are not the preferred treatment in HF, as some have been associated with an increased risk of HF.[33] If a sulfonylurea is used, patients should be monitored for worsening HF after initiation, and therapy should be used cautiously in older, frail patients at risk of hypoglycaemia. Drugs that should be avoided in the management of diabetes when HF is present include alogliptin, saxagliptin and thiazolidinediones.

Target HbA_{1c} levels of less than 7 to 7.5% (53 to 58 mmol/mol) is reasonable in patients with a lower comorbidity burden or less severe HF, whereas a higher HbA_{1c} target of 8 to 8.5% (64 to 69 mmol/mol) is acceptable in those with a higher burden of comorbidity, polypharmacy, risk of hypoglycaemia or advanced HF.[11]

Chronic kidney disease

The pathophysiology of HF and CKD are intertwined.[34] Renal dysfunction increases the risk of adverse effects from HF therapies, limits the therapeutic options and impairs diuretic response. Potassium levels and renal function should be monitored regularly. MRAs should be given at a reduced dose in people with renal dysfunction. Potassium binders, such as patiromer or sodium zirconium cyclosilicate, can be used in patients with HF and hyperkalaemia (>5.5 mEq/L) to facilitate the continued use of ACE inhibitors or MRA.[35,36] However, MRAs should be ceased if potassium levels cannot be maintained below 5.5 mEq/L. Digoxin dose should also be reduced and digoxin levels monitored in CKD.

Therapies that slow the expected decline in eGFR should be used in patients with HF. In HFrEF, ACE inhibitors, angiotensin II receptor blockers, angiotensin receptor-neprilysin inhibitor and SGLT-2 inhibitors have demonstrated renal protection.[37-40] An early decline in eGFR is expected after initiation, but this typically stabilises as the renal physiology adjusts, and the long-term decline is slower compared with placebo; this is not a reason to discontinue therapy. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has also shown renal benefit. In the FINE-HEART pooled analysis of cardiovascular, kidney and mortality outcomes, which combined FIDELIO-DKD, FIGARO-DKD and FINEARTS-HF, and in which over one-third of participants had HF with an ejection fraction of 40% or more (mildly reduced or preserved), finerenone preserved renal function and reduced HF hospitalisations.[41] Semaglutide also slowed eGFR decline in the FLOW trial of patients with CKD and diabetes, 19% of whom had HF.[42]

CKD and diabetes are important risk factors for developing HF (Figure 3). ACE inhibitors or angiotensin II receptor blockers continue to be recommended to prevent HF in patients with CKD, diabetes and hypertension or albuminuria.[43] SGLT-2 inhibitors and finerenone are now recommended for patients with type 2 diabetes or CKD to prevent HF.[22]

SGLT-2 inhibitors reduce cardiovascular mortality and are strongly recommended in guidelines for patients with CKD (with or without diabetes) and an eGFR of more than 20 to 25 mL/min/1.73 m^2 to reduce the risk of HF hospitalisation

and cardiovascular death.[22,44] This is based on the DAPA-CKD and EMPA-KIDNEY trials, and a meta-analysis of 13 large randomised controlled trials.[45-47] In the FIDELIO-DKD trial, FIGARO-DKD trial and FIDELITY pooled analyses, finerenone slowed the progression of kidney function and reduced cardiovascular events, and is now strongly recommended to prevent HF hospitalisations.[22,44,48-50] SGLT-2 inhibitors currently have a broad listing on the PBS for type 2 diabetes with high cardiovascular risk, CKD and HF, whereas finerenone is currently only PBS reimbursed for type 2 diabetes with CKD.

Iron deficiency and anaemia

Iron deficiency is common in HF because there is reduced intestinal iron absorption, increased gastrointestinal losses and altered iron metabolism due to changes in hepcidin.[51] Iron deficiency, with or without anaemia, is associated with impaired myocyte function, decreased exercise tolerance, increased HF hospitalisations and higher mortality.[51] Patients should be regularly screened for iron deficiency, defined as either ferritin levels of less than 100 mcg/L (absolute iron deficiency) or ferritin levels of 100 to 300 mcg/L with transferrin saturation of less than 20%. Screening is reasonable at the time of HF diagnosis, during hospitalisation or every four to six months in a clinic review.

Intravenous iron, with either ferric carboxymaltose or ferric derisomaltose, is strongly recommended to improve symptoms, exercise capacity and quality of life in people with HFrEF with iron deficiency with or without anaemia, and recommended to reduce HF hospitalisation and cardiovascular death.[22] Patients should be warned of the risk of iron staining if there is extravasation of iron and allergy.[52] Oral iron neither restores iron stores nor improves exercise tolerance or quality of life and should not be used.[53] There is no role of epoietin-stimulating agents, as these have been shown to cause harm in patients with HF.[54]

Respiratory tract infections

Viral respiratory infections are strongly associated with HF decompensation.[55] Observational studies have shown that influenza vaccination in patients with HF is associated with a reduction in all-cause mortality.[56] To lower the risk of HF hospitalisation, patients with HF should be vaccinated against respiratory infections, including influenza, pneumococcus, COVID-19 and, if possible, respiratory syncytial virus.[12,56]

Polypharmacy

Polypharmacy, defined as taking five or more medications, and hyperpolypharmacy, defined as taking 10 or more medications, is the rule rather than the exception with GDMT in HF.[57] The focus should be on the appropriateness of medications, rather than the number, taking into consideration the patient's goals and stage of life. Patient education and shared decision making improve medication adherence. Early medication review within one to two weeks after hospital discharge is important, as effective transition of care from hospital to community setting can help reduce readmission and mortality.[58] Medications that have multiple indications should be prioritised and fixed-dose combinations used if available to reduce pill burden.

Deprescribing of GDMT should be avoided, including when the ejection fraction recovers as this risks recurrence.[59] Medication lists should be reviewed frequently, and inappropriate and unnecessary medications considered for withdrawal, including over-the-counter and complementary medicines, unnecessary diuretics in euvolaemic patients and agents that may cause drug–drug interactions and worsen HF such as prednisolone, NSAIDs and COX-2 inhibitors.[60] Pharmacy-prepared blister packs reduce medication errors, improve adherence and allow review to check for missed doses. Dedicated tools are available for deprescribing.[57] A Medicare-funded Home Medicines Review by a credentialed pharmacist is useful to optimise medication use and improve safety.

Ageing and palliative care in patients with heart failure

Ageing can be associated with a multitude of other conditions in patients with HF, including cognitive decline, pain associated with arthritis, falls, frailty and continence issues. The goals of care should be individualised, with pragmatic decisions about which therapies to prioritise or potentially deprescribe. Disease progression in individuals with HF varies considerably and is difficult to predict.[3] The GP setting provides an opportunity to initiate discussions about prognosis and advance care planning with patients and their families. Palliative care can improve symptoms such as dyspnoea and support end-of-life planning, particularly decisions about the preferred location of dying.[61]

Conclusion

Most patients with HF are older, with a multitude of comorbidities competing for clinician attention. Comprehensive care should optimise GDMT and address comorbidities, including the associated conditions of ageing and frailty, in a way that aligns with patient goals. GPs are ideally placed to provide this care, as they see HF patients more frequently than specialists. GPs also understand their patients' psychosocial milieu and social determinants of health, and have a unique longitudinal relationship that supports them throughout their HF journey, including end-of-life care. **CT**

References

A list of references is included in the online version of this article (www.cardiologytoday.com.au).

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