Heart failure with preserved ejection fraction

Advances in management

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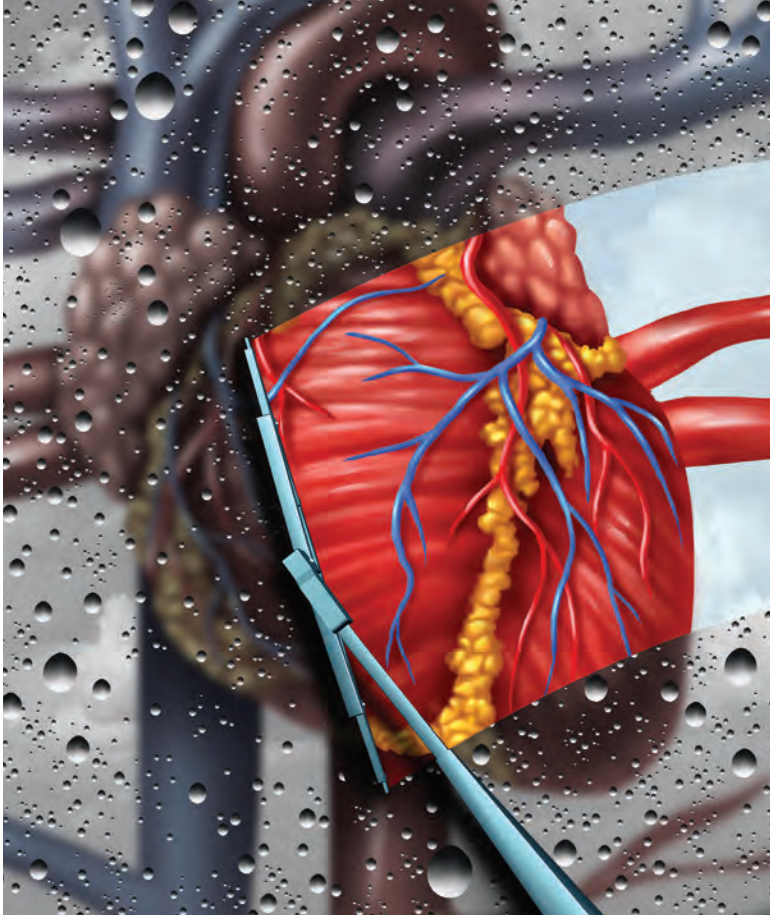

About 50% of heart failure presentations are due to heart failure with preserved ejection fraction (HFpEF). Compared with heart failure with reduced ejection fraction (HFrEF), HFpEF is a highly heterogeneous disease, and is associated with more comorbidities that do not gain mortality benefits from HFrEF therapies. However, recent advances, including the use of sodium-glucose cotransporter-2 inhibitors and patient phenotype profiling, are changing the management of HFpEF.

Heart failure with preserved ejection fraction (HFpEF) is estimated to affect 536,000 adults in Australia. It is a rapidly increasing problem, with a projected overall lifetime risk of around 20% at age 40 years.[1,2] This increasing risk is driven by an aging population and an increasing burden of associated cardiometabolic risk factors, including hypertension, diabetes, chronic kidney disease (CKD), atrial fibrillation (AF), obesity and obstructive sleep apnoea (OSA). The challenges in diagnosing HFpEF and a practical approach to assessing patients who present with shortness of breath or oedema are addressed in an accompanying article.[3] This article focuses on the management of HFpEF.

KEY POINTS

- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are the first proven treatment for heart failure with preserved ejection fraction (HFpEF) demonstrated to reduce heart failure hospitalisation or cardiovascular death and, more importantly for patients, to improve symptoms and quality of life. SGLT-2 inhibitors should be used in all patients with HFpEF without contraindications.
- Profiling patient comorbidities assists in defining appropriately directed medical therapy for certain patient groups, which may not have otherwise proved efficacious in trials of this heterogeneous HFpEF patient group.
- Optimising management of contributory cardiovascular comorbidities is pertinent, and includes obesity management, control of hypertension and exercise programs to improve functional capacity.
- Spironolactone may be helpful in certain populations, and is a useful adjunct in patients with concomitant hypertension.
- Other medical therapies that have proven benefits in other cardiovascular populations, including glucagon-like peptide-1 receptor agonists and intravenous iron, are undergoing further investigation to define their role in the HFpEF population.
- Evidence is emerging for the use of implantable pulmonary artery pressure monitors to guide decongestion and avoid heart failure hospitalisations.

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TABLE 1. SUMMARY OF HFpEF CLINICAL TRIALS BEFORE SGLT-2 INHIBITOR STUDIES[4-10]

Parameters	Clinical trial						
	PEP-CHF[4]	CHARM-Preserved[5]	I-PRESERVE[6]	J-DHF[7]	TOPCAT[8]	PARAGON-HF[9]	DIG[10]
Study population	• LVEF 40 to 50% • Structural abnormalities • Age ≥70 years	• LVEF ≥40% • NYHA Class II–IV	• LVEF >45% • Age ≥60 years	• LVEF >40% • Age ≥20 years	• LVEF ≥45% • HFH or elevated BNP level • Age ≥50 years	• LVEF ≥45% • Elevated BNP • Structural abnormalities • NYHA Class II–IV	LVEF >45%
Study drug	Perindopril	Candesartan	Irbesartan	Carvedilol	Spironolactone	Sacubitril/ valsartan	Digoxin
Study size	850	3023	4128	245	3445	4822	988
Primary endpoint	• Mortality *or* • HFH	• CV death *or* • HFH	• Mortality *or* • HFH	• CV death *and* • HFH	• CV death • Aborted cardiac arrest *or* • HFH	• CV death *and* • Total HFH	• HF death *or* • HFH
Primary outcome	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Other comments	Insufficient power	• Greater benefit with lower LVEF • Improved HFH	Neutral overall	Neutral overall	• Significant reduction in HFH • Greater benefit with LVEF <60%, with lower tertile of BNP and in women	Greater benefit in women and those with LVEF 45 to 57%	Trend for improved HFH but more angina

Abbreviations: BNP = brain natriuretic peptide; CV = cardiovascular; EF = ejection fraction; HFH = heart failure hospitalisation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SGLT-2 = sodium-glucose cotransporter-2.

Pharmacological management of HFpEF

Guideline-directed medical therapy (GDMT) exists for the management of HFrEF; however, specific GDMT has been lacking for HFpEF. The management of HFpEF has, therefore, traditionally focused on alleviating symptoms of fluid overload using diuretics, and managing risk factors and associated comorbidities. Clinical trials using conventional HFrEF agents have shown no improvement in the outcomes of those with HFpEF (Table 1).[4-10] However, the latest successful trials with sodium-glucose cotransporter-2 (SGLT-2) inhibitors herald the arrival of GDMT for the management of HFpEF.[11,12]

SGLT-2 inhibitors

SGLT-2 inhibitors are the first class of medications demonstrated in adequately powered randomised controlled studies to reduce the combined endpoint of heart failure (HF) hospitalisation or cardiovascular mortality in HFpEF. The two major trials of SGLT-2 inhibitors in patients with HFpEF have demonstrated a significant reduction of about 20% in the risk of hospitalisation for HF and cardiovascular death in those taking dapagliflozin (DELIVER trial) or empagliflozin (EMPEROR-Preserved trial) compared with placebo (Table 2).[11-13] The observed benefit of these drugs appeared to be additive to the existing treatments of mineralocorticoid antagonists (MRAs) and angiotensin receptor-neprilysin inhibitors (ARNIs), and was not influenced by the presence or absence of diabetes, baseline ejection fraction or sex.[14] More important, from a patient's perspective, were the significant improvements in symptoms, health-related quality of life and improved exertional tolerance.[13] However, it is important to note that the benefits shown in the trials were driven by a reduction in hospitalisations rather

than cardiovascular deaths.

Early introduction of the SGLT-2 inhibitor empagliflozin in the management of hospitalised patients during an acute decompensation episode has been shown to be safe and well tolerated, and observed benefits may be due to its diuretic effect.[15] Furthermore, the outcome benefits were seen as early as 18 days after starting treatment.[8] The main limitation of SGLT-2 inhibitor use is in patients with severe renal impairment, as empagliflozin requires an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73 m^2 or higher and dapagliflozin an eGFR of 25 mL/min/1.73 m^2 or higher at the time of initiation. However, SGLT-2 inhibitors have also been demonstrated to slow the progression of CKD.[16-18] Therefore, although SGLT-2 inhibitors should not be commenced in patients with an eGFR below these ranges, there is no routine requirement to discontinue them if the eGFR falls below these cut-offs after commencement. Indeed, the eGFR is anticipated to decrease in the initial two to four weeks after commencement of an SGLT-2 inhibitor, but will usually recover.[18] These highly compelling data have led to the first (and only) recommendation that all patients with HFpEF should be initiated on an SGLT-2 inhibitor in the absence of clear contraindications.[19]

TABLE 2. SUMMARY OF SGLT-2 INHIBITORS STUDIED IN HFpEF CLINICAL TRIALS[11,12]

Parameters	Clinical trial	
	EMPEROR-Preserved[12]	DELIVER-HF[11]
Study population	• LVEF >40% • Structural abnormalities or HFH • Elevated BNP level • NYHA Class II–IV • Age ≥18 years	• LVEF >40% • Structural abnormalities • Elevated BNP level • NYHA Class II–IV • Age ≥40 years
Study drug	Empagliflozin	Dapagliflozin
Study size	5988 (66.9% LVEF >50%)	6263 (66% LVEF >50%)
Primary endpoint	• CV death *or* • HFH	• Worsening HF *or* • CV death
Primary outcome	21% relative reduction in primary endpoint	18% relative reduction in primary endpoint
Other comments	Primary outcome irrespective of diabetic state, gender or baseline LVEF	Primary outcome irrespective of diabetic state, sex or baseline LVEF

Abbreviations: BNP = brain natriuretic peptide; CV = cardiovascular; HFH = heart failure hospitalisation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SGLT-2 = sodium-glucose cotransporter-2.

Angiotensin receptor-neprilysin inhibitors

In the PARAGON-HF trial, patients with a left ventricular ejection fraction (LVEF) of 45% or higher, elevated natriuretic peptide levels and evidence of structural heart disease were randomised to either the ARNI sacubitril/valsartan at a target dose of 97/103 mg twice daily or valsartan alone (not placebo or angiotensin-converting enzyme [ACE] inhibitors). These patients had a numerically lower, but not statistically significant, benefit of reduced total hospitalisations for HF and cardiovascular death.[9] Subsequent analysis showed greater benefit in those with an LVEF between 45 and 57%, and in women. Sacubitril/valsartan is approved for use in HFpEF in the US; however, there is no recommendation for such use in Australia.[19]

Mineralocorticoid antagonists

MRAs such as spironolactone have been shown to improve measures of diastolic dysfunction in patients with HFpEF.[20] The TOPCAT trial evaluated spironolactone versus placebo in patients with HF and LVEF of 45% or higher, and showed a small but not statistically significant reduction in the composite endpoint of death, aborted cardiac death or HF hospitalisations.[8] However, these results were confounded by limited adherence to therapy in one of the treatment regions, and subsequent analysis suggested a reduction in the risk of HF hospitalisation.[21] Furthermore, benefits were shown for some subgroups, including women and those with an LVEF below 60% and a lower tertile of B-type natriuretic peptide. Therefore, spironolactone may be considered for use as an adjunct to the diuretic regimen, as well as for managing hypertension. Appropriate monitoring of the serum creatine and potassium levels is required at initiation and follow up due to the risk of worsening kidney function and hyperkalaemia.

Angiotensin receptor blockers

Trials with angiotensin receptor blockers (ARBs) have shown mixed results. A trial of candesartan in patients with an LVEF of 40% or higher demonstrated a borderline significant reduction in the primary composite outcome of HF hospitalisation or cardiovascular death, but a moderate reduction in the individual component of HF hospitalisations when compared with placebo.[5] Trials of irbesartan have not demonstrated similar results.[4] Current data suggest sacubitril/valsartan is likely to be more effective than an ARB, and is preferred in select patients.

Nonpharmacological management of HFpEF

Nonpharmacological management of HFpEF focuses mainly on strategies to optimise contributing comorbidities,

including weight loss management and exercise, as well as a potential role for HF rehabilitation and emerging evidence for the use of device therapies.

Exercise and cardiac rehabilitation

Physical inactivity and obesity are strongly linked to an increased risk of HF, with worse health status and poorer prognosis in those with HFpEF.[22] Exercise is key for improving functional capacity, and guidelines recommend more than 150 minutes/week of preferably aerobic physical activity to also assist with weight loss.[23] Enrolment in cardiac rehabilitation programs, especially in patients with prior hospitalisation, may improve quality of life and functional capacity in patients with HFpEF.[24] Exercise with a view to weight loss and other weight reduction strategies are discussed below.

Device therapies in HFpEF

Device therapies that have been explored in HFpEF include the use of implantable pulmonary artery pressure (PAP) monitors and interatrial shunt devices. The use of PAP monitors to detect early rises in PAP and guide decongestion management have been shown to decrease HF hospitalisations.[25-27] Several interatrial shunt devices designed to create an internal shunt from the left to right atrium to prevent the rise in left atrial pressure with exercise, the hallmark and main driver of symptoms in HFpEF, have shown early promising results in small studies.[28] Further larger studies are currently underway.

Patient phenotype profiling and management of comorbidities

As HFpEF is a heterogeneous disease associated with variable comorbidities, it is important to identify these in order to tailor individual patient management. Some key comorbidities are discussed below.

Hypertension

Hypertension is highly prevalent in HFpEF, affecting 60% to 89% of the HFpEF population.[29,30] The role of blood pressure control is well established for the prevention of HF as well as in reducing the risk of other cardiovascular events in these patients, who often have other associated cardiometabolic risk factors. Recent consensus from the American College of Cardiology recommends a systolic blood pressure of lower than 130 mmHg in patients with HFpEF and hypertension who do not have symptomatic orthostasis.[30] Of note, blood pressure-lowering has not been associated with improved outcomes in

those with already established HFpEF; however, uncontrolled blood pressure may precipitate acute HF decompensation.[8] Choice of antihypertensive agents may be guided by tolerability, cost and comorbidities. Given the supporting data described previously, candesartan and spironolactone may be preferred agents. Beta blockers may be useful for patients with other indications, such as symptomatic coronary artery disease or atrial fibrillation with rapid ventricular response; however, they can contribute to chronotropic incompetence, which may further limit exercise tolerance in some patients.[31,32]

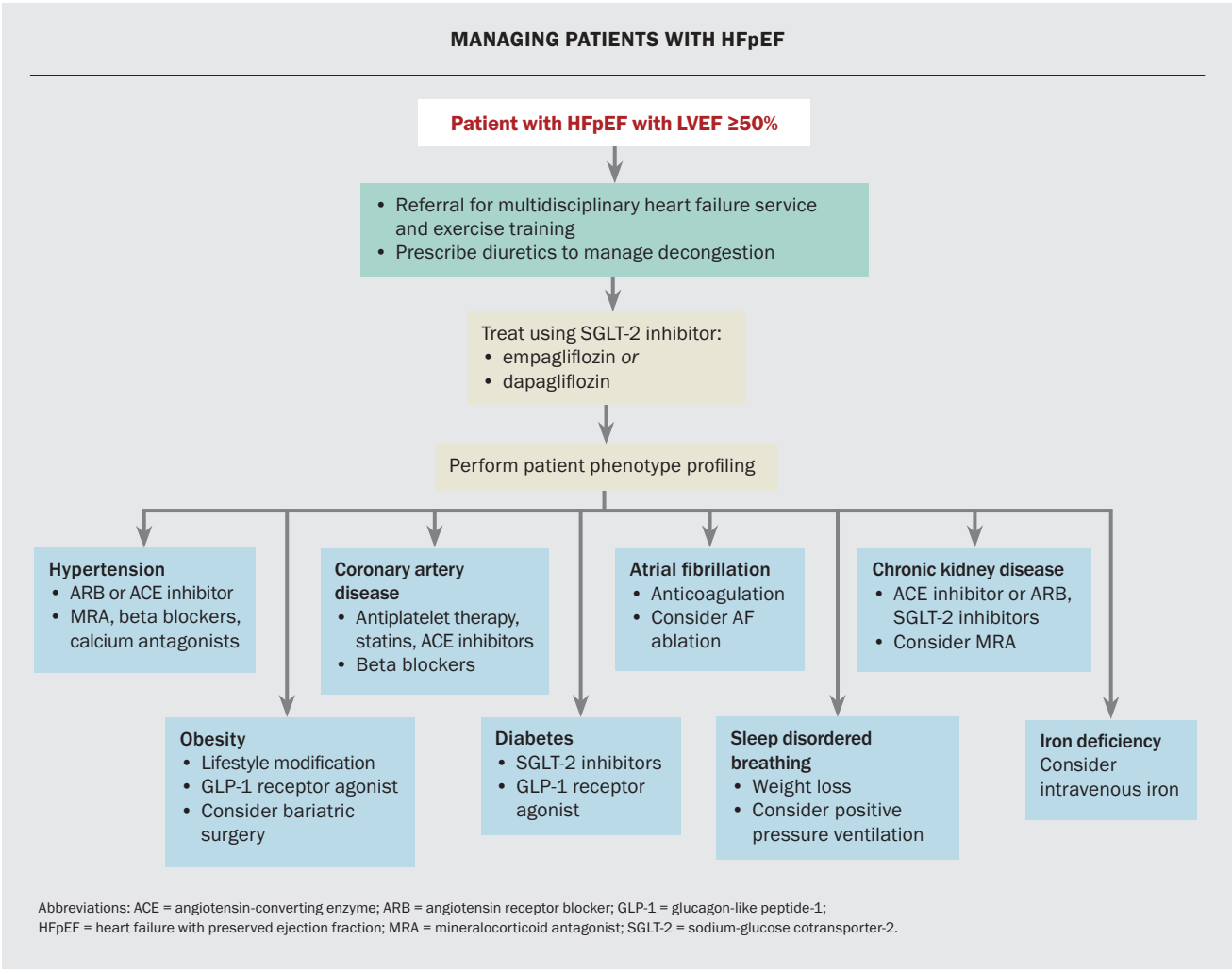
Obesity

Obesity is one of the strongest risk factors for developing HFpEF: body mass index is directly correlated with HF risk, and 80% of patients with HFpEF are either overweight or have obesity.[32-34] An increasing severity of obesity correlates with an increased risk for HF-associated hospitalisation, as well as increased risk of other cardiometabolic risk factors, AF and OSA.[32] Patients with HFpEF who are obese are younger and have poorer functional class.[32] Studies suggest a beneficial effect of weight loss, either via caloric restriction or bariatric surgery, on incident HF events and exercise tolerance, and these pathways may be considered in the appropriate patient.[35]

Support for preventing obesity and encouraging weight loss through lifestyle modifications, such as diet and exercise, are recommended. Pharmacological management with newer agents, including the glucagon-like peptide-1 (GLP-1) receptor antagonist semaglutide and the combined GLP-1/glucose-dependent insulinotropic-polypeptide agonist tirzepatide, has been shown to be effective in achieving weight loss in patients with obesity, with improvement in quality of life, irrespective of diabetic status.[36,37] A recent study in HFpEF populations showed significant benefits of semaglutide on patient symptoms and quality of life.[38] Further studies are underway to investigate its impact on clinical outcomes.[39] For those with a body mass index above 35 kg/m^2, referral to a multidisciplinary specialised obesity clinic may be considered, including discussion of surgical options.[40]

Coronary artery disease

Epicardial coronary artery disease is present in over 50% of patients with HFpEF, which may also contribute to symptoms of dyspnoea.[41] No prospective trials have evaluated the benefit of revascularisation on symptoms or



Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; GLP-1 = glucagon-like peptide-1; HFpEF = heart failure with preserved ejection fraction; MRA = mineralocorticoid antagonist; SGLT-2 = sodium-glucose cotransporter-2.

mortality in people with HFpEF. Revascularisation should, therefore, be pursued according to standard practice guidelines, alongside aggressive secondary prevention and risk factor optimisation. The long-acting nitrate isosorbide mononitrate has been shown to decrease activity levels compared with placebo, with no measurable benefit and is, therefore, not routinely recommended in HFpEF.[42]

Diabetes

Diabetes is prevalent in people with HFpEF, affecting up to 40% of patients, and correlates with a twofold risk of associated HF hospitalisation and mortality compared with those without diabetes.[43,44] Optimisation of diabetic control is recommended according to the *Australian Evidence-Based Clinical Guidelines for Diabetes*.[45]

Atrial fibrillation

AF and HF often coexist. AF has been shown to pertain to a worsened functional status and increased risk of hospitalisation, as well as mortality in those with HF.[46] No clear benefit in a rhythm (rate *vs* rhythm) or rate (strict *vs* lenient) control strategy have been reported.[47,48] An individualised approach is recommended and, as such, an attempt at achieving sinus rhythm with a rhythm control strategy may be beneficial to assess an associated improvement in symptoms. A small, open-label trial in older people with AF and HF suggested a benefit in functional capacity from digoxin for rate control at 12 months, which may be related to lower rates of dizziness, lethargy and hypotension, when compared with beta blockers.[49] Aggressive rate control should be avoided because of the potential to reduce stroke volume.

Sleep disordered breathing/ obstructive sleep apnoea

Sleep disordered breathing, of which OSA is the most common subtype, affects up to 55 to 80% of individuals with HFpEF, has adverse effects on quality of life and is associated with an increased

risk of depression.[50] Treatment of OSA has not been shown to have a definitive benefit on cardiovascular outcomes in HFpEF; however, smaller studies suggest positive improvements in both symptoms and objective measures of diastolic function and cardiovascular endpoints.[51-54] There is evidence that treating OSA in patients with treatment-resistant hypertension may be beneficial in controlling hypertension, as well as have possible benefits in reducing the risk of recurrent AF; therefore, screening for OSA, particularly in these cohorts, remains important.[55]

Chronic kidney disease

CKD is present in about 50% of patients with HFpEF and is associated with an up to threefold increase in mortality.[56,57] Patients with concomitant CKD and HFpEF will benefit from renin-angiotensin system inhibition in combination with an SGLT-2 inhibitor to delay decline in renal function.[18,58] Therefore, the use of these agents is strongly encouraged in the absence of other contraindications.

Iron deficiency

Iron deficiency is present in 50 to 75% of patients with HFpEF, and appears to be more prevalent in these patients than in those with HF with mid-range ejection fraction or HFrEF.[57,59] Iron deficiency in HFpEF is associated with worse symptoms and reduced exertional tolerance and overall quality of life.[60] Although iron replacement has been associated with reduced HF hospitalisation in patients with HFrEF, no clear data are available for those with HFpEF.[60-62] Trials are currently underway in patients with HFpEF (FAIR-HFpEF, PREFER-HF trials) to investigate the impact of intravenous iron versus placebo on exercise capacity.

Conclusion

HFpEF is common and results in poor quality of life, frequent hospitalisations and increased risk of death, as seen with HFrEF. SGLT-2 inhibitors are the first class of drugs recommended for all patients with HFpEF to improve symptoms and quality of life and reduce HF hospitalisations or cardiovascular death. Diuretics are recommended for the management of oedema or congestion. Due to the heterogeneity of symptoms and comorbidities in HFpEF, management of contributing comorbidities should be tailored to each patient. MT

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

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