Heart failure in patients with diabetes

Intersecting comorbidities and an evolving treatment landscape

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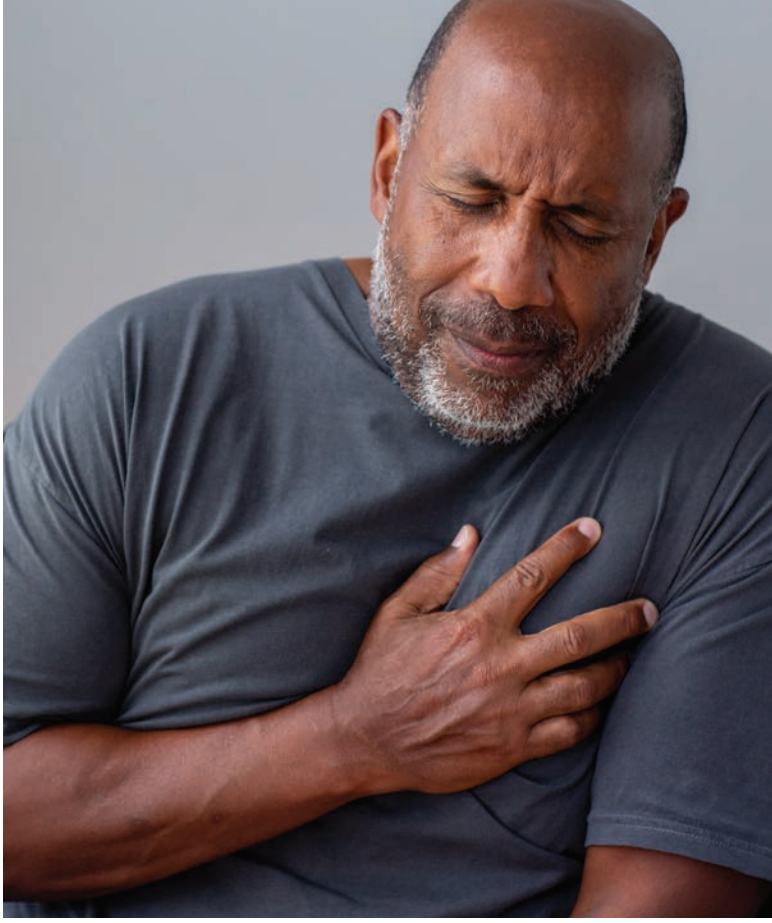

Heart failure (HF) and diabetes are common, increasingly prevalent conditions among people in Australia, and are frequently encountered in primary care. The combination of HF and diabetes confers a poor prognosis, and management can be challenging. Sodium-glucose cotransporter-2 inhibitors and finerenone (a mineralocorticoid receptor antagonist) have recently altered the treatment landscape for both HF and diabetes, and provide important additions to the 'therapeutic arsenal' against cardio-renal-metabolic disease.

Heart failure (HF) and diabetes mellitus are commonly encountered comorbidities. HF affected about 511,000 adults in Australia (2.1%) in 2017, and this number is projected to grow to 657,000 by 2025.[1] Diabetes affected an estimated 1.3 million people in Australia (5.3%) in 2022, with a rising prevalence.[2] These increases are driven by an ageing population and the increasing prevalence of obesity, hypertension, hypercholesterolaemia, vascular disease and obstructive sleep apnoea. In patients with HF, about 30% also have diabetes, which is associated with higher rates of mortality, HF hospitalisation and poorer quality of life, compared with patients with HF without diabetes.[3]

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Key points

- **Heart failure and diabetes are common and increasingly prevalent conditions that frequently coexist, making their management more complex.**
- **Heart failure confers a high mortality and morbidity. Patients with both heart failure and diabetes have a significantly poorer prognosis than those with either condition in isolation.**
- **Patients with heart failure with reduced ejection fraction should be treated with four classes of medications, unless intolerant or contraindicated: an angiotensin receptor neprilysin inhibitor or ACE inhibitor, a heart failure-specific beta blocker, a mineralocorticoid receptor antagonist (MRA) and a sodium-glucose cotransporter-2 (SGLT-2) inhibitor.**
- **Patients with heart failure with preserved ejection fraction should be considered for an SGLT-2 inhibitor, which is the only class of medication that has been shown to achieve significant improvements in cardiovascular mortality and heart failure-related hospitalisation.**
- **Patients with type 2 diabetes mellitus have high rates of heart failure, and preventative treatments are recommended. SGLT-2 inhibitors should be considered to reduce the risk of heart failure in all patients with type 2 diabetes, as well as finerenone (a third-generation MRA) to reduce the risk of heart failure, in patients with type 2 diabetes and macroalbuminuric chronic kidney disease.**
- **SGLT-2 inhibitors have multiple beneficial effects beyond achieving glycaemic control alone. They represent an important therapeutic advance in the management of cardio-renal-metabolic disease.**

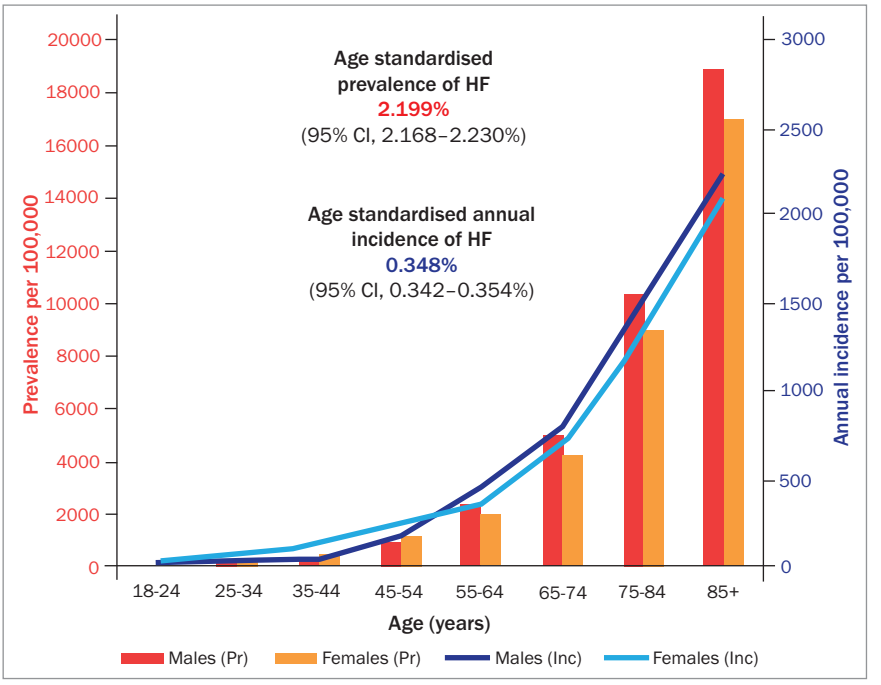


Figure 1. Prevalence and incidence of heart failure in the Australian population.[15] The prevalence and incidence increase with age, disproportionately affecting older patients.

Abbreviations: CI = confidence interval; HF = heart failure; Inc = incidence; Pr = prevalence.

Complex interaction between diabetes and heart failure

Patients with diabetes have a two- to fivefold increased risk of developing HF, compared with age-matched controls without diabetes.[4-6] This higher incidence of HF in patients with diabetes persists after adjusting for age, hypertension, hypercholesterolaemia and coronary artery disease.

Multiple trials have explored the relationship between glycaemic control and cardiovascular outcomes, such as the Action in Diabetes and Vascular Disease-PreterAx and DiamicroN Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Veterans Affairs Diabetes Trial (VADT) and UK Prospective Diabetes Study.[7-10] The findings of these trials suggested that improved glycaemic control did not translate to improved cardiovascular outcomes. A meta-analysis of 37,229 patients suggested that improved glycaemic control did not reduce the risk of HF or HF hospitalisation.[11] The risk of cardiovascular events and HF in patients with diabetes is not related to hyperglycaemia alone but is conferred by multiple factors beyond glycaemic control.

Diabetes results in the dysregulation of neurohormonal, vascular and cellular mechanisms, which ultimately contributes to myocardial damage and HF.[12-14] Neurohormonal changes include activation of the renin–angiotensin–aldosterone pathway, impaired cardiac sympathetic innervation and adrenergic hyperactivity. Microvascular dysfunction occurs because of endothelial-mediated impairment in coronary flow reserve, contributing to tissue hypoxia that can contribute to HF, through recurrent ischaemic insults. Cellular changes include increased oxidative stress, endoplasmic reticulum stress, changes in mitochondrial bioenergetics and substrate utilisation (with reduced myocardial glucose utilisation and increased fatty acid utilisation), accumulation of advanced glycated end-products, abnormalities in contractile proteins and impaired cellular relaxation.

Importantly, these biological mechanisms provide potential therapeutic targets in the treatment of HF and diabetes. Targeting these pathways may improve the prognosis and trajectory of diabetes and HF, beyond glycaemic control.

Prevalence and the Australian context

The prevalence of both HF and diabetes in Australia is increasing over time and will represent a substantial burden of disease and healthcare utilisation in the future.

The prevalence of HF increases with age, disproportionately affecting older patients, with more than one-third of people affected being over the age of 75 years (Figure 1).[15,16] This represents a substantial burden of healthcare utilisation within the primary care setting. Patients with HF visit their GPs 12.4 times a year on average and account for 3.6% of all patients presenting to GPs.[17,18]

Australian studies suggest that HF may be under-recognised in primary care, which may contribute to the lower use of guideline-directed medical therapy.[16,19] Clinicians are encouraged to maintain a heightened HF awareness, particularly among older patients presenting for other health issues.

In patients with HF, an estimated 29% have comorbid diabetes or have a fourfold higher prevalence of type 2 diabetes compared with people without HF in the community setting.[3,20] In patients hospitalised for decompensated HF, this number may be higher; an Australian cohort of HF admissions found that 49% had diabetes based on glycated haemoglobin (HbA_{1c}) measurements.[21] In patients with diabetes, an estimated 25% have comorbid HF or have a two- to fivefold risk of developing HF compared with people without diabetes.[4,5,13]

Myocardial dysfunction develops before clinical HF in patients with diabetes, involving dysregulated neurohormonal, vascular and cellular mechanisms associated with diabetes. Echocardiography studies have shown that asymptomatic systolic and/or diastolic dysfunction is detectable in up to 68% of patients who have had type 2 diabetes for five years without overt HF.[22] Myocardial damage is, therefore, an early, undetected complication of diabetes. Diabetic cardiomyopathy describes this myocardial vulnerability. In patients with diabetes, independent risk factors for the development of HF include advanced age, greater duration of disease, insulin use and the presence of coronary artery disease or chronic kidney disease.[23]

Heart failure is a high morbidity condition, and with diabetes is worse

HF confers a high mortality and morbidity. Survival rates range from 81 to 91% at one year, and 52 to 63% at five years.[18,24-26] Patients with HF with preserved ejection fraction (HFpEF) have slightly better survival compared with those with HF with reduced ejection fraction (HFrEF), although the difference is small.[27] Effective management of HF is important, as survival is significantly decreased following any and each subsequent HF hospitalisation.[28]

Diabetes is the second most common major comorbidity in patients with HF (29%), following chronic kidney disease (41%).[3] In patients with HF, the presence of diabetes is independently associated with a significant increase in all-cause mortality and HF hospitalisation, compared with HF patients without diabetes.[3] Patients with HF and comorbid type 2 diabetes have a reduced median survival by 1.1 years (from 4.6 years to 3.5 years), compared with those without type 2 diabetes.[29] In patients with diabetes, similarly, the presence of HF increases mortality, compared with patients without HF.[30] This increased mortality remains after adjusting for other confounders. Therefore, the combination of HF and diabetes poses unique management challenges.

Medical therapy for HFrEF

The *2018 National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia* strongly recommended three classes of medications to reduce mortality and HF hospitalisation in patients with HFrEF:

- ACE inhibitor, or angiotensin receptor blocker (ARB) if ACE inhibitors are contraindicated or not tolerated
- HF-specific beta blocker
- mineralocorticoid receptor antagonist (MRA).[31]

Since the publication of these guidelines, clinical trials evaluating novel therapies for HF have also shown improved outcomes, with benefits in mortality and HF hospitalisation. Subsequently, a consensus statement by Australian HF clinicians was published in 2022, providing updated recommendations.[32]

The additional benefit of neprilysin inhibition combined with renin–angiotensin system inhibition was shown in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study.[33] This double-blinded, randomised controlled trial showed that the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril-valsartan significantly reduced mortality, reduced HF hospitalisation and improved HF symptoms, compared with the ACE inhibitor enalapril, with an even greater benefit seen in patients with coexistent type 2 diabetes. Post-hoc analyses identified the benefit of early initiation of sacubitril-valsartan within 30 days to reduce HF hospitalisation, thereby supporting its use earlier in the treatment pathway, along with the PIONEER-HF study findings, which showed benefit to early ARNI versus ACE inhibitor use.[34-36] Consequently, it is strongly recommended that an ARNI should be considered first-line for HFrEF (and is preferred over an ACE inhibitor), provided it does not compromise the commencement of other first-line HFrEF therapies.[32] If hypotension is a concern, then an upfront ACE inhibitor strategy may be considered with a switch to an ARNI once stabilised.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have also been evaluated in randomised controlled trials for patients with HFrEF (with or without type 2 diabetes), and have shown significant reductions in cardiovascular events, total mortality and HF hospitalisation, compared with placebo. The only two SGLT-2 inhibitors indicated and PBS listed for HF treatment in Australia are dapagliflozin and empagliflozin. In the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, use of dapagliflozin showed significant reductions in the composite primary endpoint of cardiovascular death or worsening HF, as well as significant reductions in both cardiovascular mortality and HF hospitalisation.[37] In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR- Reduced) trial, use of empagliflozin showed significant reductions in the composite primary endpoint of cardiovascular death or HF hospitalisation, driven by a significant reduction in HF hospitalisation.[38] A meta-analysis combining the data from the DAPA-HF and EMPEROR-Reduced trials showed that SGLT-2 inhibitors significantly reduced the incidence of all-cause mortality, cardiovascular mortality, first hospitalisation for HF and first kidney composite event.[39] Importantly, these benefits of SGLT-2 inhibitors were similar irrespective of the presence of diabetes. Consequently, it is strongly recommended that an SGLT-2 inhibitor (dapagliflozin or empagliflozin) is commenced in patients with HFrEF, regardless of the presence of diabetes.[32]

The *Guidelines* and consensus statement, when considered together, strongly recommend four classes of medications in all patients with HFrEF (unless contraindicated or intolerant): an ARNI (preferred, or an ACE inhibitor), HF-specific beta blocker, MRA and SGLT-2 inhibitor.[31,32] This is consistent with recommendations made in recent European and American practice guidelines.[40,41] A suggested treatment algorithm for initiating these four therapies is provided in the Flowchart.[32]

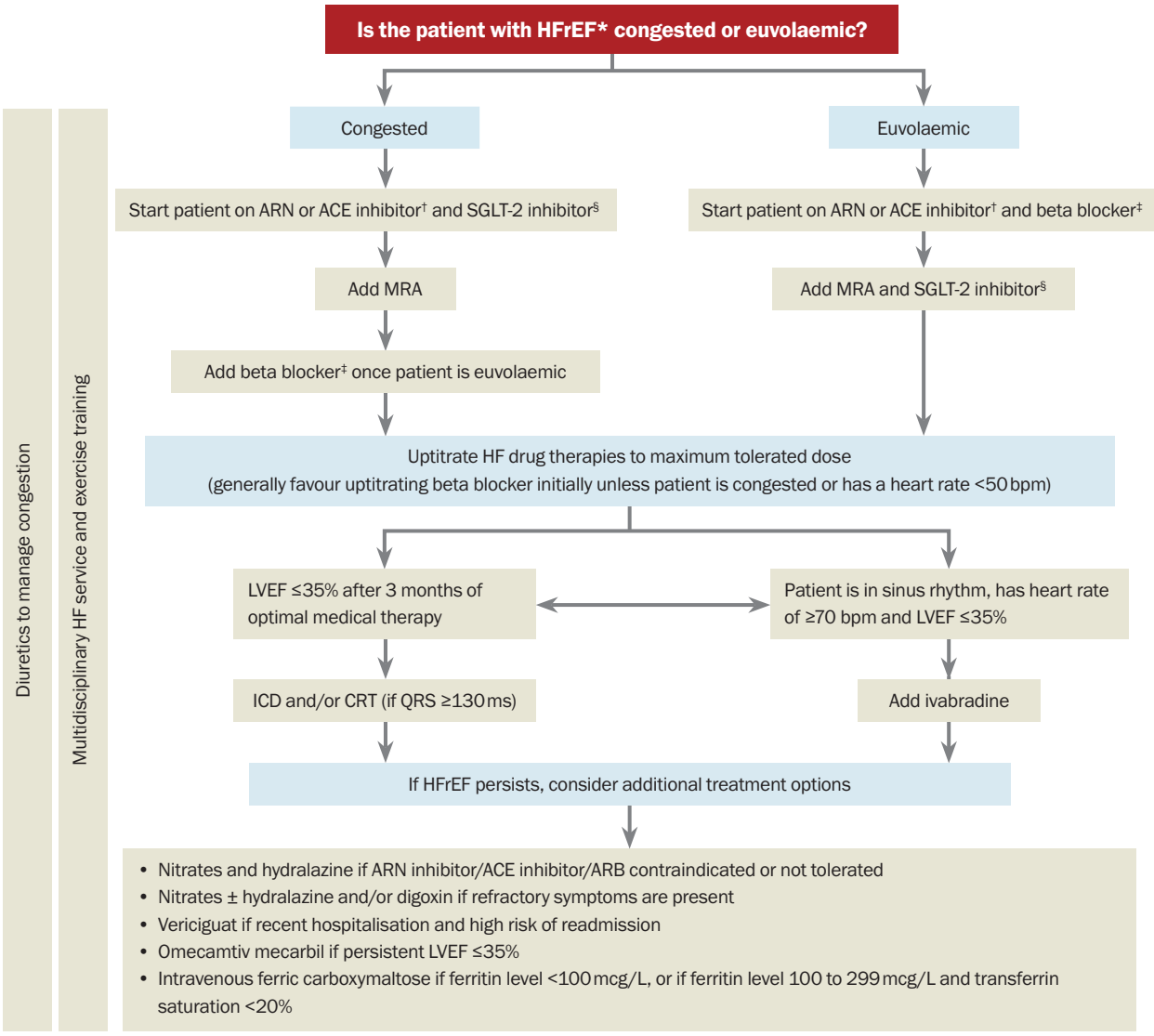
Medical therapy for HFpEF

Previously, medical therapy for HFpEF had not demonstrated robust evidence for benefit. Clinical trials for HFpEF have evaluated perindopril, candesartan, irbesartan, carvedilol, spironolactone, sacubitril- valsartan and digoxin, but these trials failed to show benefit.[42-48] However, candesartan and spironolactone specifically showed reductions in HF hospitalisation, and can be considered in selected patients.[41,43,46]

Before 2021, no medication had shown a benefit in mortality in patients with HFpEF and, hence, management of HFpEF had focused on the relief of congestion and optimisation of comorbidities, particularly hypertension and atrial fibrillation.[49]

Subsequently, SGLT-2 inhibitors became the first class of medication to achieve significant improvements in primary outcomes in patients with HFpEF in clinical trials. Empagliflozin was shown in the EMPEROR-Preserved trial to significantly reduce cardiovascular death or HF hospitalisation by 21%, compared with

Management of patients with heart failure and reduced ejection fraction[32]



Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARN = angiotensin receptor neprilysin; bpm = beats per minute; CRT = cardiac resynchronisation therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillators; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT-2 = sodium-glucose cotransporter-2.

*All patients with HFrEF are recommended to be started on a combination of the 'big four' pharmacological therapies of ARN or ACE inhibitors, beta blockers, MRAs and SGLT-2 inhibitors.

†ARN inhibitor preferred. An ACE inhibitor can be considered as an alternative if problematic hypotension, and consider switching to an ARN inhibitor later.

‡Use beta blocker with outcome trial proven HFrEF efficacy (i.e. carvedilol, bisoprolol, metoprolol succinate or nebivolol).

§Use SGLT-2 inhibitor with outcome trial proven HFrEF efficacy (i.e. dapagliflozin or empagliflozin).

Adapted from Sindone AP, De Pasquale C, Amerena J, et al. Med J Aust 2022; 217: 212-217.[32]

placebo.[51] Dapagliflozin was shown in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial to significantly reduce cardiovascular death or worsening HF by 18%, compared with placebo.[50] These benefits were irrespective of the presence of type 2 diabetes, and baseline left ventricular ejection fraction. Consequently, it is recommended that an SGLT-2 inhibitor (dapagliflozin or empagliflozin) is considered in patients with HFpEF, regardless of the presence of diabetes.[32]

Medical therapy for type 2 diabetes

Glucose-lowering medications for diabetes may have variable effects on the risk of developing HF, which should be considered in the selection of glucose-lowering therapy (Table).[52-57] Thiazolidinediones have been shown in a meta-analysis to significantly increase the risk of HF requiring hospitalisation.[54] Similarly, dipeptidyl peptidase-4 inhibitors (predominantly saxagliptin) have been shown in a meta-analysis to increase the risk of HF requiring hospitalisation compared with no use, although the difference was borderline.[55] Sulfonylureas and insulins

Table. Glucose-lowering medications and their impact on the risk of HF[52-57]

Class	Study	Impact on HF	Statistics
Insulin	Review of data from the Kaiser Permanente Northwest Registry (n=8063) looking at incident HF diagnosis; data based on observational, nonrandomised data[52]	Increase	>2-fold increase*
Sulfonylureas (second generation)†	Analysis of data from the UK General Practice Research Database (n=91,521) looking at first occurrence of HF; data based on observational, nonrandomised data[53]	Increase	HR 1.18 (1.04–1.34) (p=0.01)†
Thiazolidinediones	Meta-analysis of data from patients with prediabetes and diabetes (n=20,191); HF defined as requiring hospitalisation[54]	Increase	RR 1.72 (1.21–2.42) (p=0.002)
Dipeptidyl peptidase-4 inhibitors	Meta-analysis of data from randomised controlled trials; acute HF defined as requiring hospitalisation[55]	Increase (only with saxagliptin)	OR 1.13 (1.00–1.26) (p=0.05)
Glucagon-like peptide-1 receptor agonists	Meta-analysis of data from four cardiovascular outcome studies; HF defined as requiring hospitalisation[56]	No significant impact	HR 0.93 (0.83–1.04) (p=0.20)
Sodium-glucose cotransporter-2 inhibitors	Meta-analysis of data from three cardiovascular outcome studies; HF defined as requiring hospitalisation[57]	Decrease	HR 0.77 (0.71–0.84)‡ (p<0.0001)

*When insulin was added compared with when either metformin or sulfonylurea was added to treatment regimen.
†Compared with metformin monotherapy.
‡Composite of HF hospitalisation and cardiovascular death.
Abbreviations: HF = heart failure; HR = hazard ratio; OR = odds ratio; RR = relative risk.

may also increase the risk of developing HF, although these findings are based on observational data only.[52,53] Metformin has been shown in some studies to reduce the risk of new-onset HF, although this is based on observational data only.[52,58,59]

Prevention of heart failure in patients with type 2 diabetes

Patients with type 2 diabetes are at a higher risk of developing HF. Studies have identified that SGLT-2 inhibitors and finerenone may be recommended to reduce the risk of developing HF in patients with type 2 diabetes.

Use of SGLT-2 inhibitors in patients with type 2 diabetes has shown consistent reductions in the development of cardiovascular disease, including reductions in HF and HF hospitalisation.[57,60,64] Consequently, SGLT-2 inhibitors are recommended in patients with type 2 diabetes who are at high risk of cardiovascular disease, to decrease the risk of developing HF.[32]

Finerenone is a selective, nonsteroidal MRA that has been evaluated in patients with type 2 diabetes and macroalbuminuric chronic kidney disease (estimated glomerular filtration rate [eGFR] greater than 25 mL/min/1.73 m^2). The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial showed that in patients with type 2 diabetes and macroalbuminuric chronic kidney disease, finerenone significantly reduced a composite cardiovascular primary endpoint (driven predominantly by decreased HF hospitalisation) and reduced new-onset HF.[65,66] Consequently, finerenone should be considered to reduce the risk of developing HF in patients with type 2 diabetes and macroalbuminuric chronic kidney disease.[32] In Australia, finerenone is PBS listed to delay the progressive decline of kidney function in patients with type 2 diabetes and macroalbuminuric diabetic kidney disease, in addition to standard of care, including ACE inhibitors or ARBs, and SGLT-2 inhibitors, unless contraindicated or intolerant. Medical therapies for patients with type 2 diabetes with or without HF are outlined in Figure 2.

SGLT-2 inhibitors

SGLT-2 inhibitors have emerged as important treatments in the 'therapeutic arsenal' for HF and diabetes. Evidence supports their use for:

- add-on therapy for glycaemic control in patients with type 2 diabetes
- a reduction in cardiovascular death in patients with type 2 diabetes and existing cardiovascular disease
- the prevention of HF in patients with type 2 diabetes and high cardiovascular risk
- the treatment of HFrEF, to decrease mortality and decrease HF hospitalisation (irrespective of the presence of diabetes)
- the treatment of HFpEF, to decrease mortality and decrease HF hospitalisation (irrespective of the presence of diabetes).

Mechanisms of benefit

The benefits of SGLT-2 inhibitors are related to their multiple mechanisms of action across the cardio-renal-metabolic systems, beyond glycaemic control.[67-70] SGLT-2 inhibitors inhibit glucose resorption at the proximal tubules, causing glycosuria, which lowers glycaemia and reduces HbA_{1c} levels by about 0.8%.[71] The accompanying natriuretic and diuretic effect reduces tubuloglomerular feedback and intraglomerular pressure, contributing to nephroprotective effects. This early natriuresis with reduced plasma volume, reduced blood pressure, reduced afterload

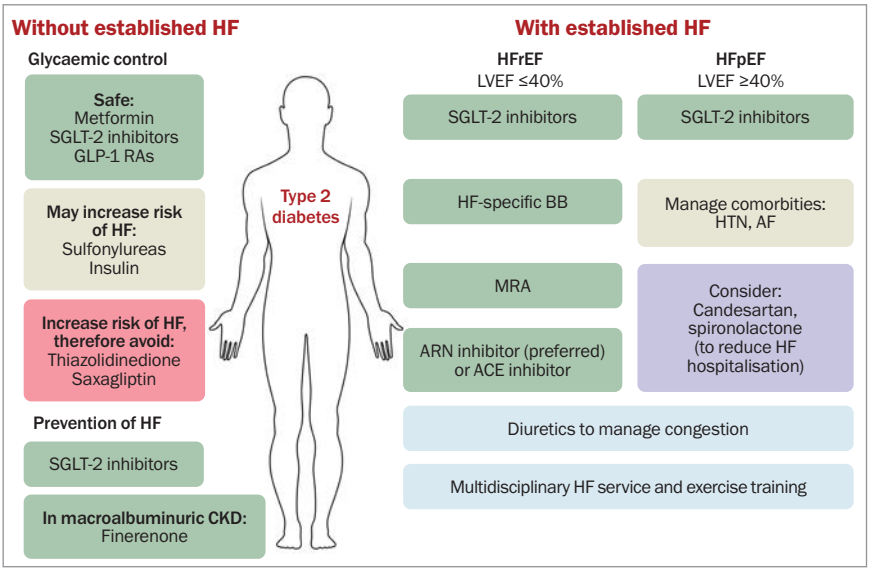


Figure 2. Medical therapies for patients with type 2 diabetes mellitus with and without established HF.
Abbreviations: ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARN = angiotensin receptor neprilysin; BB = beta blocker; CKD = chronic kidney disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; GLP-1 RA = glucagon-like peptide-1 receptor agonist; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT-2 = sodium-glucose cotransporter-2.

and improved vascular function all contribute to a beneficial effect in patients with HF. Glycosuria and caloric loss contribute to weight loss, increased insulin sensitivity, lipid metabolism and reduced lipotoxicity. There are also associated reductions in adipose-mediated inflammation and proinflammatory cytokines, a shift towards ketogenesis as the metabolic pathway for the heart and kidneys, reduced oxidative stress, increased erythropoietin levels, reduced uric acid levels and reduced accumulation of advanced glycation end-products. These complex and interconnected mechanisms contribute to the cardioprotective and renoprotective effects of SGLT-2 inhibitors.

Practical considerations

The recommended dosing of SGLT-2 inhibitors for HF is empagliflozin 10 mg daily, or dapagliflozin 10 mg daily, in keeping with the doses used in the placebo-controlled EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF and DELIVER trials.[37,38,50,51] The main limitation to the use of SGLT-2 inhibitors is renal impairment, which is common in both HF and diabetes. Empagliflozin should not be commenced in patients with eGFR less than 20 mL/min/1.73 m^2. Dapagliflozin should not be commenced in patients with eGFR less than 25 mL/min/1.73 m^2. Once commenced at higher eGFRs, they can be continued, if tolerated, until the eGFR falls below 20 mL/min/1.73 m^2, at which time consideration may be given to cessation, in consultation with a renal physician. On initiation of an SGLT-2 inhibitor, there is an expected initial reduction in the eGFR at four weeks (short-term 'dip') followed by longer-term renoprotective effects ('eGFR preservation').[72] Studies have shown an initial 'dip' average of about 2 to 5 mL/min/1.73 m^2, with about 30 to 50% of patients showing a decline in the eGFR of more than 10% from baseline.[73,74] Patients who experience a more than 10% early decrease in the eGFR had significantly improved long-term outcomes, including a slower chronic rate of decline in eGFR in the long term, reiterating the importance to 'stay the course' and continue the SGLT-2 inhibitor through the initial eGFR decline.[73]

Although the glucose-lowering effects and renoprotective effects of SGLT-2 inhibitors are somewhat attenuated in patients with a lower eGFR, the cardioprotective effects of SGLT-2 inhibitors remained consistent across the spectrum of renal dysfunction, and reductions in HF hospitalisation may actually be accentuated in patients with a lower eGFR.[57,75,76] Other risks are hypoglycaemia (predominantly if a patient is receiving another medication that is prone to causing hypoglycaemia) and mild hypotension, and low risks of diabetic ketoacidosis and Fournier's gangrene. Patients should be advised to temporarily withhold SGLT-2 inhibitors for three days before receiving general anaesthesia, when unwell (particularly with respiratory or gastrointestinal infection) or when needing to fast for prolonged periods of time, and counselled regarding genitourinary hygiene. SGLT-2 inhibitors should not be used in patients with type 1 diabetes, as they increase the risk of diabetic ketoacidosis.[77]

Conclusion

HF and diabetes are frequently encountered conditions that carry a serious prognosis, with high mortality and morbidity. The interplay between diabetes and HF is complex. Diabetes confers an increased risk of HF beyond glycaemic control, involving the dysregulation of neurohormonal, vascular and cellular mechanisms. Newer agents, which target these pathophysiological mechanisms, have significantly altered the treatment landscape of cardio-renal-metabolic disease in the past decade, and their use will become increasingly prevalent. It is important that clinicians are familiar with the role, indications, side effects and management of these medications. **ET**

References

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

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