Advances in detection, prevention and treatment of heart failure in type 2 diabetes: part II

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Abstract

This review is the second of two that aim to cover the advances in heart failure (HF) prevention, detection and treatment relevant to people with type 2 diabetes (T2DM). Part I focuses on HF classification and prevention, specifically lifestyle changes and primary preventative techniques including smoking cessation, physical activity, weight loss, lipid and glucose control. This concluded: 1) intensive blood glucose control is not in itself a necessary or sufficient treatment target for HF prevention, and a multifaceted preventative approach is likely to have a greater effect; 2) the most compelling evidence for HF risk reduction is for sodium glucose co-transporter 2 inhibitors although glucagon-like peptide 1 receptor agonists may also have a role; and 3) patients likely to derive most benefit are those at highest risk of developing overt HF, which probably represent the majority of people with T2DM. Part II of this review will cover early detection of cardiac dysfunction and treatment of established heart failure. Particular emphasis is placed on heart failure with preserved ejection fraction.

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Stages C and D – treatment of established heart failure

Diabetes is a complex multisystem disorder, often accompanied by multimorbidity. In many instances, pharmacological management can be challenging due to the interaction between multi-organ dysfunction, drug contraindications or side effects, and variations in guidelines. Wherever possible, cases should be discussed within a multidisciplinary team to ensure that optimum therapies are instituted.[1]

In the vast majority of cases, management of symptomatic heart failure (HF) in people with type 2 diabetes (T2DM) is the same as for people without T2DM. Goals of treatment via a patient-centred approach are: 1) avoidance of signs and symptoms of congestion, to improve exercise tolerance and quality of life; and 2) rapid initiation, up-titration and maintenance of guideline-directed foundational HF medications to prevent HF hospitalisation and lengthen survival. A detailed description of HF management is beyond the scope of this article and has been extensively reviewed elsewhere.[1,2] Herein we summarise only the most recent developments. Due to differences in the efficacy of available treatments, stratification of HF based on left ventricle ejection fraction (LVEF) is necessary; in accordance with most large-scale clinical trials, we define heart failure with preserved ejection fraction (HFpEF) as those with an LVEF $\geq$40% and HFrEF as those with an LVEF <40%. Heart failure with improved ejection fraction (HFimpEF) is defined as a baseline LVEF <40%, $\geq$10% improvement in LVEF and subsequent LVEF measured at LVEF >40%.[3]

Heart failure with preserved ejection fraction

Lack of efficacy of traditional heart failure medications

HFpEF is the predominant manifestation of HF in T2DM, accounting for up to 83% of people with T2DM and newly identified HF.[4]

Until as recently as 2021, none of the established HF medications used to treat HFrEF had been convincingly shown to improve clinical outcomes in people with HFpEF. For example, in 2019 the hotly anticipated PARAGON-HF trial (44% of participlants had diabetes) of the angiotensin-receptor neprilysin-inhibitor sacubitril-valsartan did not demonstrate a reduction in cardiovascular (CV) death or HF hospitalisation in patients with HFpEF (with an LVEF $\geq$45%) compared to valsartan.[5] Emerging real-world data suggest that beta blockers may in fact be harmful in patients with HFpEF, particularly those with higher ejection fraction (EF).[6] Lastly, the mineralocorticoid receptor antagonist spironolactone demonstrated no reduction in CV death and HF hospitalisation in a similar HFpEF cohort to PARAGON-HF,[7] although there is some debate regarding the study findings due to inconsistencies in trial data from Russia and Georgia and there may yet be some benefit of spironolactone in HFpEF.[8] All in all, treatment options for HFpEF were extremely limited. The FIDELITY pooled analysis

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investigated the effect of the non-steroidal mineralocorticoid receptor antagonist finerenone, versus placebo, in patients with T2DM and chronic kidney disease.[9] Alongside renal protective effects, there was a significant improvement in the composite CV outcome, driven by a reduction in HF hospitalisation.[9] Finerenone is not yet established as an alternative to eplerenone or spironolactone, but may be an important consideration for future research.

Sodium glucose co-transporter 2 inhibitors

Publication of the EMPEROR-Preserved and DELIVER trials of the sodium glucose co-transporter 2 inhibitors (SGLT2i) empagliflozin and dapagliflozin, respectively, in people with chronic HFpEF have since changed the landscape of HF management.[10,11] Both trials similarly found that treatment with SGLT2i was associated with lower rates of HF hospitalisation compared to placebo, irrespective of the presence of diabetes (Table 1).

Unsurprisingly, there has been intense interest in the mechanisms by which SGLT2i exert their rapid CV effects,[12,13] for significant benefits appear in less than two weeks following treatment initiation.[14] Several small mechanistic studies utilising advanced cardiac imaging techniques have been published, in which the effects of SGLT2i appear pleiotropic. Small reductions in left ventricle (LV) mass (~5%) and myocardial extracellular volume have been described,[15-17] but no convincing improvements in myocardial energetics or blood flow have been demonstrated.[18-20] We posit that the modest but multifactorial effects of SGLT2i on lowering blood glucose, body weight and blood pressure, coupled with a diuretic effect, work in tandem targeting several HF pathways.[21] In any case, alongside loop diuretics to treat congestion, SGLT2i are now regarded as a foundational treatment in HFpEF and should be prescribed in all eligible patients.

Glucagon-like peptide-1 agonists

Although small trials have shown that lifestyle-mediated weight loss improves exercise capacity in obesity-related HFpEF,[22] only modest body weight reductions (~5 to 10%) are achieved even with intensive lifestyle modification and long-term sustainability is limited.[23] Alternatively, bariatric surgery achieves more marked (>15%) and sustained weight loss (in up to a fifth of patients),[24] remission of diabetes (in up to one third of patients)[25] and reductions in downstream major adverse CV events (including HF hospitalisation) in obese patients with CV disease.[26] Large-scale availability and fitness for surgery of HF patients with multimorbidity, however, hinders widespread feasibility of bariatric surgery. The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RA) as safe, tolerable and efficacious weight loss pharmacotherapies has brought new hope for the treatment of obesity and its related complications, including HFpEF.

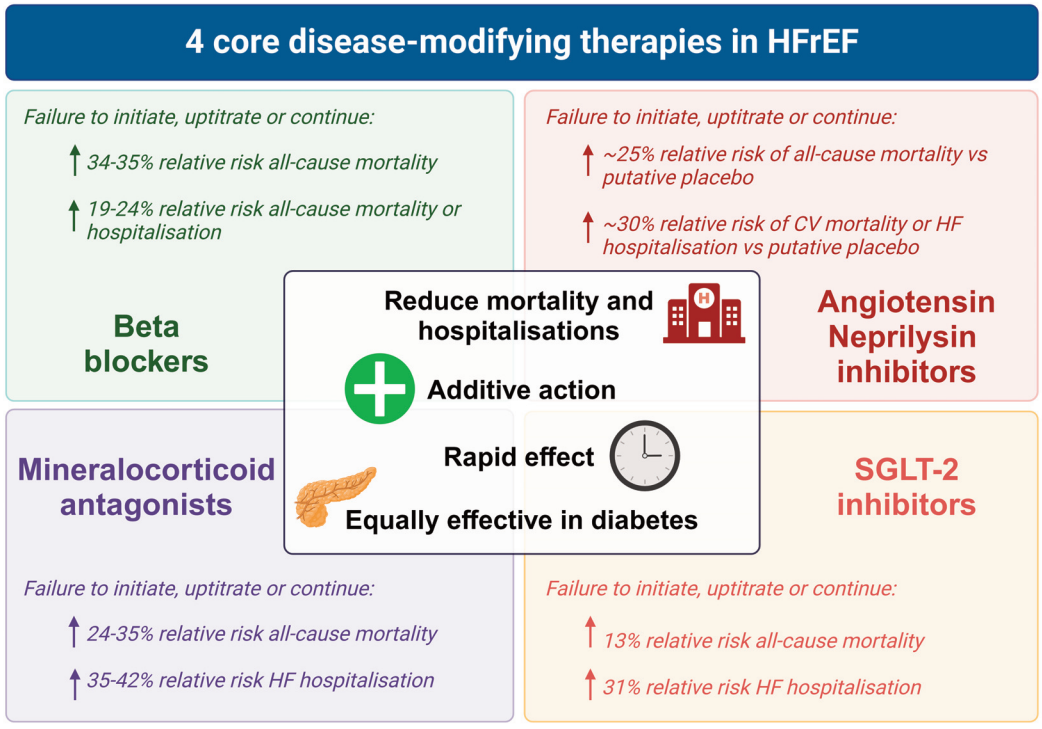
Obesity-related HFpEF has emerged as a distinct pathological entity, mediated by a combination of direct deleterious effects on cardiac structure and function combined with systemic multi-organ damage.[27] Patients with obesity-related HFpEF have more fluid retention, worse symptom burden and lower exercise capacity than those with normal weight HFpEF.[28] The STEP-HFpEF Trial was a multicentre, international, placebo-controlled, randomised trial aiming to determine whether treatment with the GLP-1 RA semaglutide, in addition to weight loss, would improve symptom burden and exercise capacity in obesity-related HFpEF, but the trial excluded people with diabetes.[29] Compared with placebo, participants in the semaglutide arm experienced an anticipated and marked reduction in body weight (mean change -13.3%, compared with -2.6% for placebo), consistent with previous weight loss trials of semaglutide.[30] Crucially, greater improvements in HF symptoms (Kansas City Cardiomyopathy Questionnaire clinical summary score, KCCQ-CSS, the co-primary outcome measure together with percent weight reduction) and exercise capacity (six-minute walk test, a secondary outcome measure) were observed in the active treatment arm compared with the placebo arm. The absolute improvement in HF symptoms with semaglutide was especially promising: KCCQ-CSS increased from ~59 to ~76 points overall (median overall change 16 points), representing a moderate to large clinical improvement in symptoms.[31] These improvements in symptoms were far in excess of the change in KCCQ scores in the DELIVER and EMPEROR-Preserved trials, where only small increases of between ~2 to 5 points, respectively, were observed. Less impressive in STEP-HFpEF was the increase in six-minute walk distance, which increased from 316 to 338 metres in the semaglutide arm: a mere 7% improvement in exercise capacity. Although the study did not include people with T2DM, an ongoing trial is looking specifically at a diabetic cohort (STEP HFpEF DM).[32] Weight loss treatments in overweight and obese individuals are likely to play a major role in treatment of HFpEF in the future.

Heart failure with reduced ejection fraction

Four cornerstones of therapy and avoidance of treatment inertia

The four cornerstones of pharmacological therapy for HFrEF (Figure 1) are now well recognised,[33,34] with beneficial effects of therapy being demonstrated within just 30 days of initiation.[33,35,36] The cumulative impact of treatment with all four drug classes in HFrEF has been estimated to represent an absolute risk reduction in all-cause mortality of over 25%, with a number needed to treat of just four patients.[37] A principal aspect of contemporary HF treatment is early implementation of guideline-directed medical therapy; far too many patients are not prescribed beneficial disease-modifying therapies that have a cumulative impact on clinical outcomes (Figure 1). Avoidance of treatment inertia, therefore, cannot be emphasised enough. The recent STRONG-HF study demonstrated that rapid uptitration of guideline-directed therapy, after an acute admission with decompensated HF, improved HF symptoms and quality of life whilst reducing the risk of HF readmission and all-cause death at 180 days.[38] Deferring treatment of an angiotensin-converting enzyme inhibitor, beta blocker and aldosterone antagonist for one year leads to an absolute increase in mortality of 12 in 100 patients, according to a meta-analysis of randomised controlled trials. This is consistent with

Figure 1. Summary of the four major pillars of treatment for heart failure with reduced ejection fraction, adapted from Fonarow[52]



CV, cardiovascular; HF, hospitalisation; HFrEF, heart failure with reduced ejection fraction; SGLT-2, Sodium glucose co-transporter 2

a 1% increase in absolute mortality per month delay for 'low-risk' HF patients.[39]

Despite recognition that treatment inertia in HFrEF has marked impact on patient outcomes, observational studies highlight the scale of the problem. The CHAMP-HF study assessed initiation of therapy for chronic HF in the US and found that just 1% of eligible patients were receiving target doses of guideline-directed therapy at the time.[40] More recently, the EVOLUTION-HF study, which evaluated prescribing patterns in the US, Japan and Sweden following HF hospitalisation, noted that delays in prescribing disease-modifying agents were more pronounced for novel therapies and in patients with co-morbidities such as T2DM.[41] Alongside education and increased awareness for patients and clinicians, adapting organisational structures and providing an integrated multidisciplinary approach to follow-up can help to tackle clinical inertia.[42]

Finally, adherence to prescribed medications can often be overlooked. In a cohort of people with T2DM attending primary care, 28.1% did not adhere to medications to treat diabetes, hypertension or lipid-lowering therapies.[43] Similarly, in HF cohorts, non-adherence has been reported at between 33.3-45.9%, and has been shown to have negative effects on clinical outcomes.[44,45] For a person living with diabetes, 90% of their disease management is self-care,[46] and therefore patient engagement and education is pivotal to providing effective care. Meta-analyses evaluating a variety of strategies to improve adherence, including disease and medication education, self-monitoring and interactions with the multi-disciplinary team, have shown improved mortality and risk of HF hospitalisation in comparison to control cohorts.[47,48]

Despite the known side effects of therapy, HFrEF is a progressive and high-risk condition where the risks of not initiating appropriate medications are great, especially in people with T2DM.[49] Our overarching recommendation for HFrEF treatment in T2DM is to initiate treatment in a timely manner and utilise combination therapy, which is more effective than uptitration of single drug classes.[33-35,50] Medication adherence is a key part of HF self-care.[47]

Heart failure with improved ejection fraction

Patients who have historically had a reduced LVEF that has completely (LVEF >50%) or partially (LVEF 40-50%) improved are considered a separate subgroup. It is well recognised that LVEF can improve in HFrEF, but there are limited evidence-based data for these patients.[4,51] An expert consensus from the *Journal of the American College of Cardiology* has defined HF with recovered LVEF as: 1) documentation of baseline LVEF<40%; 2) ≥10% improvement in LVEF; and 3) subsequent measurement LVEF >40%.[4]

Despite improvements in morbidity and mortality, HF hospitalisations, exercise tolerance and HF biomarkers, a significant proportion of patients with an HFimpEF remain at risk of deterioration, and it is difficult to identify which patients are at the highest risk.[4,51] Molecular changes that occur in adverse LV remodelling remain dysregulated in the recovered ventricle.[4] Therefore these patients should be considered as in 'remission'

Table 1. Key placebo-controlled randomised trials evaluating the efficacy of SGLT2i in HFpEF

Study	Drug	Total sample size (n)	Key inclusion criteria	Age, diabetes	Follow-up (months)	Key findings
EMPEROR-Preserved[10]	Empagliflozin 10mg OD	5,988	NYHA II-IV HF, raised natriuretic peptides, LVEF >40%	72 years, 49% diabetes	26	Composite of CV death and hospitalisation for HF; HR 0.79, 95% CI 0.69 to 0.90, primarily driven by reduction in HF hospitalisation; HR 0.71, 95% CI 0.60 to 0.83.
DELIVER[11]	Dapagliflozin 10mg OD	6,263	HF, raised natriuretic peptides, LVEF >40%	72 years, 45% diabetes	28	Composite of CV death and worsening HF (urgent HF visit or hospitalisation); HR 0.82, 95% CI 0.73 to 0.92, primarily driven by reduction in HF hospitalisation; HR 0.79, 95% CI 0.69 to 0.91.

CI, confidence interval; CV, cardiovascular; EF, ejection fraction; HF, heart failure; LV, left ventricle; NYHA, New York Heart Association; HR, hazard ratio; OD, once daily.

Key messages

- Pharmacological management of heart failure can be challenging, particularly in multimorbid patients; where possible, cases should be discussed within a multidisciplinary team to ensure that optimum therapies are instituted.
- Loop diuretics and sodium glucose co-transporter 2 inhibitors are now regarded as the foundational treatments for heart failure with preserved ejection fraction.
- Treatment inertia leads to poorer outcomes; treatment of heart failure with reduced ejection fraction should be commenced in a timely manner and the four core therapies used in combination with one another wherever possible.

rather than cured,[4] and current guidance recommends that disease-modifying therapies are continued after LVEF recovers.[3,4]

Conclusions

Type 2 diabetes and HF are inextricably linked, such that consideration of HF prevention, detection and treatment should remain at the forefront of management of all people with T2DM. We have outlined crucial preventive strategies across the A to D spectrum of HF that could mitigate disease development and progression. In those at risk of developing symptomatic HF (Stages A and B), emphasis should be placed on aggressive risk factor control and early initiation of SGLT2i. In those with established HF (Stages C and D), particularly those with reduced ejection fraction, rapid commencement and maintenance of foundational HF therapies avoids treatment inertia and improves outcomes. Although major advances in HF have been made, there remain multiple outstanding challenges and clinical outcomes are unacceptably poor in people with T2DM, most notably related to early detection of Stage B HF. Urgent work is still needed to facilitate early initiation of preventive treatments.

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