Emerging Horizons in Heart Failure with Preserved Ejection Fraction: The Role of SGLT2 Inhibitors

Rebecca Heath · Håkon Johnsen · W. David Strain · Marc Evans

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a condition with increasing disease burden. Prevalence of HFpEF is increasing, reflecting an increasingly elderly and comorbid population, as well as reinforcing the need for more treatments for this disease. The pathophysiology of HFpEF is complex. Some inflammatory processes seen in HFpEF are shared with diabetes mellitus (DM) and there is an association seen between the two conditions. It is therefore no wonder that treatments for diabetes may have some effect on heart failure outcomes. Current treatment strategies in HFpEF are limited, with treatments focusing on symptom control rather than morbidity or mortality benefit. However, there are now promising results from the EMPEROR-Preserved study that show significantly reduced cardiovascular death or hospitalisation for heart failure (HHF) in patients taking empagliflozin, compared to those taking placebo. These results indicate a promising future for sodium-glucose co-transporter 2 (SGLT2) inhibitors in HFpEF. The ongoing DELIVER trial (investigating the use of dapagliflozin in HFpEF) is awaited but could provide further evidence of support for SGLT2 inhibitors in HFpEF. With hospital admissions for HFpEF increasing in the UK, the economic impact of treatments that reduce HHF is vast. The European Society of Cardiology (ESC) recently added SGLT2 inhibitors to their guidelines for treatment of heart failure with reduced ejection fraction (HFrEF) following DAPA-HF and EMPEROR-Reduced trials and we suggest that similar changes be made to guidelines to support the use of SGLT2 inhibitors in the management of HFpEF in upcoming months.

Keywords: HFpEF; Empagliflozin; Heart failure; Diagnosis; Treatment; Pathophysiology; SGLT2 inhibitor

R. Heath (✉) · H. Johnsen · M. Evans
University Hospital Llandough, Cardiff and Vale
University Health Board, Cardiff, UK
e-mail: Rebecca.heath@wales.nhs.ukH. Johnsen
e-mail: Hakon.johnsen@wales.nhs.uk

W. D. Strain
University of Exeter, Exeter Medical School, Exeter, UK

Key Summary Points

Heart failure with preserved ejection fraction (HFpEF) is a disease of growing incidence and prevalence.

Previously there have been no significantly beneficial treatments for this disease and treatment focused on symptom control; this is in contrast to heart failure with reduced ejection fraction for which there are multiple treatments with proven morbidity and mortality impact.

Sodium-glucose co-transporter 2 inhibitors provide the first promising treatment option for HFpEF following the EMPEROR-Preserved study which has shown reduction in hospitalisation with heart failure and cardiovascular death in patients with HFpEF treated with empagliflozin.

INTRODUCTION

Heart failure (HF) is a chronic condition characterised by a number of signs and symptoms, e.g. elevated jugular venous pulse (JVP), peripheral oedema and breathlessness and fatigue, respectively. Diagnosis is based on presence of signs and/or symptoms of HF and echocardiographic findings evidencing cardiac dysfunction. Further classification involves measurement of left ventricular ejection fraction (LVEF). Ejection fraction (EF) values vary slightly depending on guidelines, but it is generally accepted that HF with reduced ejection fraction (HFrEF) is defined as HF with an EF of less than or equal to 40%. Patients with an ejection fraction between 41% and 49% have HF with mildly reduced ejection fraction (HFmrEF). HF with preserved ejection fraction (HFpEF) is accepted as being a challenging diagnosis. Therefore, the European Society of Cardiology (ESC) recommends a simplified

approach to diagnosis: signs and symptoms of HF, an LVEF of more than or equal to 50%, and objective evidence of cardiac structural and/or functional abnormalities consistent with presence of left ventricular (LV) diastolic dysfunction/raised LV filling pressures (such as LV hypertrophy, left atrial enlargement or raised natriuretic peptides) [1, 2]. Diagnosis involves the use of history, clinical examination, natriuretic peptide levels and echocardiography. However, some patients with HFpEF will get symptoms only on exertion, but do not have clinical signs at rest and therefore the aforementioned diagnostic testing may be inconclusive; this is where other investigations such as exercise stress testing, cardiopulmonary exercise testing and invasive haemodynamic testing can also be used to diagnose HFpEF or else confirm or exclude other diagnoses too. Patients with HFpEF tend to be older, female and are more likely to have comorbidities such as hypertension, atrial fibrillation, diabetes mellitus (DM), chronic lung disease, chronic kidney disease and anaemia [3].

Disease burden is an increasing issue. Studies have found the prevalence of HFpEF is increasing, and that up to 50% of patients with the clinical syndrome of HF have HFpEF [2, 4, 5]. There appears to be general agreement that the incidence of HFpEF is increasing and is more prevalent in women than men, when compared with HFrEF [2, 6]. This, perhaps, reflects the increased recognition of the diagnosis of HFpEF, or perhaps is a reflection of an increasingly comorbid population. HF is thought to affect around 26 million people worldwide [2].

HF has long been a researched and clinically interesting diagnosis. There are a multitude of causes such as coronary artery disease, alcohol misuse, cardiotoxic chemotherapy, valvular disease, hypertension, infiltrative disease (such as amyloidosis and sarcoidosis), congenital heart disease and many more. However, many of the causes of HF are more associated with HFrEF than HFpEF. Risk factors for HFpEF appear to stem from comorbidities such as hypertension, obesity and diabetes, as well as being more prevalent with increasing age and in female individuals [2]. The recognition of LV diastolic dysfunction and a normal ejection

fraction with the clinical syndrome of HF has been around for decades, although the underlying pathophysiology in HFpEF is perhaps poorly understood when compared with HFrEF [7]. Essentially, systolic function is normal in HFpEF (with the exception of some findings of reduced systolic function during stress) as the heart is able to contract normally, but there is an inability of the LV to relax normally to allow adequate ventricular filling. This therefore results in an increased left ventricular end diastolic pressure (LVEDP) [7].

"Diastolic dysfunction" was the term used to describe HFpEF in the past; however, this was adjusted as diastolic dysfunction can also be observed in HFrEF and is not specific to HFpEF. Indeed, some of the understood pathophysiology is about diastolic dysfunction, including the knowledge of myocardial stiffness being a cause. The amount and type of collagen in the extracellular matrix as well as actions of cardiomyocytes lead to this increased myocardial stiffness [2]. Increased degradation of collagen type 1 (leading to a build-up in the extracellular matrix) is also seen in arterial hypertension—which is a known risk factor for HFpEF [2]. Slow LV relaxation is seen in HFpEF, especially at higher heart rates, which, along with myocardial stiffness and impaired ventricular-arterial coupling all leading to reduced stroke volume, may explain the abnormal systolic function seen in patients under stress in HFpEF despite normal systolic function at rest [2, 8]. Vascular stiffening (e.g. reduced aortic distensibility) is also a key factor in HFpEF, and is also seen in the common associated conditions of hypertension, diabetes and old age [2]. The processes aforementioned can lead to pulmonary hypertension and limited systolic reserve during stress [8]. The general understanding of late is that HFpEF is caused by the presence of co-existing inflammatory conditions (e.g. diabetes) causing systemic microvascular endothelial inflammation and vascular dysfunction, along with reduction in nitric oxide and cyclic guanosine monophosphate levels which can then lead to hypertrophy and exacerbated cardiomyocyte stiffness as well as fibrosis [7]. Contributing factors include chronotropic incompetence, left atrial dysfunction and atrial fibrillation [8].

HFpEF is becoming a growing problem in people with diabetes, and DM is associated with increased morbidity and mortality in HFpEF. Approximately 30–40% of patients with HFpEF suffer with DM [9], and people with type 2 diabetes mellitus (T2DM) have up to three times higher risk of developing cardiovascular disease, particularly HFpEF [10]. HFpEF and DM share some of the same inflammatory processes such as endothelial dysfunction, interstitial and perivascular fibrosis, advanced glycated end products deposition and hypertrophy [9]; additionally impaired insulin signalling is also thought to contribute to HFpEF [11]. Other shared pathological processes include sodium retention, release of proinflammatory cytokines and impaired skeletal muscle function [12], in addition to the shared risk factors of obesity and hypertension. With links already seen between HF and DM many decades ago, e.g. in the Framingham Heart Study [13], it is no wonder that treatments for diabetes may have some effect on HF outcomes (Fig. 1).

Prognoses in HFrEF and HFpEF appear to be equally limited; 5-year mortality for HFrEF and HFpEF has been found to be 75.3% and 75.7%, respectively [14]. However, treatments for HFpEF are particularly limited and concentrate on symptom management, when compared to treatment options for HFrEF.

CURRENT TREATMENT STRATEGIES IN HFPEF

The known HF medications of angiotensin-converting enzyme (ACE) inhibitors (± neprilysin inhibitor), beta blockers and mineralocorticoid receptor antagonists are for use in HFrEF only. Unfortunately, unlike HFrEF, there are no treatments for HFpEF (as a unifying diagnosis) that have been proven to reduce morbidity and mortality [1, 7, 8], despite the worrying trend of increasing prevalence of this condition. There were reduced hospitalisation trends for candesartan [15], spironolactone [16] and sacubitril/valsartan [17] but no significant reduction in primary end points. Treatment
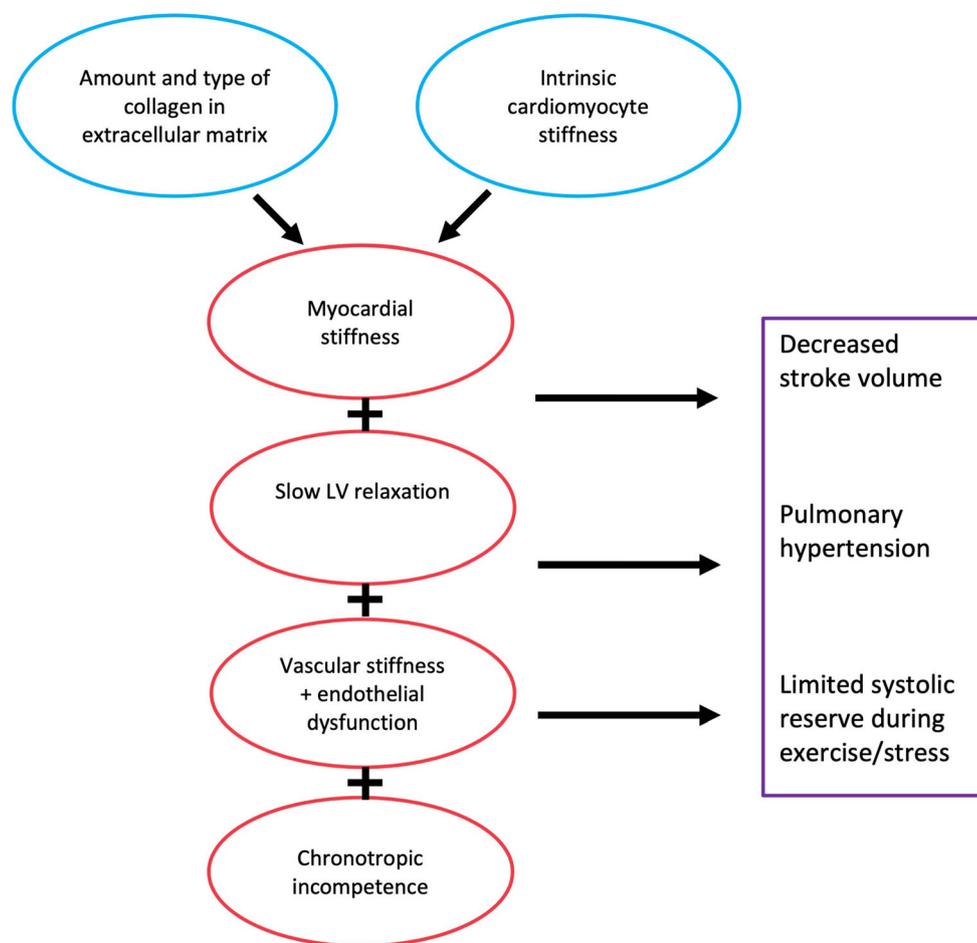
Fig. 1 A simplified diagram depicting the pathophysiology of HFpEF [2, 7, 8]

therefore focuses on symptomatic management of fluid overload, rate control of atrial fibrillation and blood pressure management. Treatment should be individually based, with treatment focusing on underlying comorbidities (this may of course mean patients are on treatments such as ACE inhibitors and beta blockers anyway).

Sodium-glucose co-transporter 2 (SGLT2) inhibitors were very recently added to the ESC guidelines for treatment of HFrEF after EMPEROR-Reduced and DAPA-HF trials showed reduced risk of cardiovascular death or hospitalisation for HF in patients with HFrEF [18, 19]. EMPEROR-Preserved has since been published, with very promising outcomes for patients with HFpEF, which we discuss in this review.

The purpose of this review is to highlight and discuss data from the recently published EMPEROR-Preserved study, as well as review previously published data on SGLT2 inhibitors and its effect on HFpEF in the context of the EMPEROR-Preserved study. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SGLT2 INHIBITORS IN HFREF

Emerging clinical trials have found SGLT2 inhibitors to be beneficial when added to the standard treatment of patients with HFrEF [18, 20]. Patients suffering from HFpEF,

however, have very few treatment options that have proven to be effective.

The Dapagliflozin in Patients with HF and reduced Ejection Fraction (DAPA-HF) study from 2019 investigated the efficacy of SGLT2 inhibitors in patients with established HF and reduced ejection fraction, regardless of the patient being diagnosed with T2DM. The DAPA-HF study found that death from cardiovascular causes reduced from 11.5% in the placebo group to 9.6% in the group being commenced on dapagliflozin [18]. Dapagliflozin also reduced the risk of hospitalisation or urgent medical visit resulting in intravenous therapy for HF from 13.7% in the placebo group to 10.0% in the group being commenced on dapagliflozin [18]. Furthermore, the benefits of dapagliflozin in HFrEF were found to be consistent regardless of the patient being diagnosed with T2DM or not [18].

SGLT2 INHIBITORS IN HFPEF

The Empagliflozin in HF with a Preserved Ejection Fraction (EMPEROR-Preserved) study from 2021 investigated the efficacy of an SGLT2 inhibitor in patients with HF and preserved ejection fraction. The EMPEROR-Preserved study investigated the combined occurrence of cardiovascular death or hospitalisation for HF (HHF) as a primary outcome, occurrence of all hospitalisations for HF as a first secondary outcome and the rate of decline in eGFR as a second secondary outcome [21]. Additionally, subgroup analysis of patients according to EF was performed.

The EMPEROR-Preserved study found that treatment with empagliflozin reduced the occurrence of HHF and cardiovascular death as a combined primary outcome. Specifically, SGLT2 inhibition led to a 21% lower relative risk of the primary outcome in the cohort of patients treated with empagliflozin. The study found a reduced number of hospitalisations from 11.8% in the placebo group to 8.6% in patients being treated with empagliflozin [21]. However, it did not show any statistical difference in cardiovascular death (or death from

other causes) between patients taking empagliflozin and the placebo [21].

Whereas several studies investigating sacubitril/valsartan, spironolactone and candesartan in HFpEF have been unable to provide undisputable proof for their effectiveness in patients with an EF of 50% or more [15–17, 22, 23], subgroup analysis of the EMPEROR-Preserved patient cohort showed that empagliflozin reduced the number of primary outcome events (cardiovascular death or HHF) in patients with an EF ranging between 50% and 60% and more than 60%, when compared with placebo.

Furthermore, the EMPEROR-Preserved study also investigated the protective effect of empagliflozin on the kidneys. The study demonstrated that patients receiving empagliflozin had a slower decline in estimated glomerular filtration rate (eGFR) when compared with patients receiving placebo: a decline in eGFR of 1.25 mL per year in patients receiving empagliflozin compared with a decline in eGFR of 2.62 mL in patients receiving placebo [21].

The results from the EMPEROR-Preserved study suggest that empagliflozin is beneficial for patients with HFpEF. This study is the first randomised controlled trial (RCT) to demonstrate a mortality benefit and significant morbidity benefit in patients with HFpEF, who have previously been limited to treatments for symptom control and risk factor management.

POTENTIAL MECHANISMS IMPROVED BY SGLT2 INHIBITORS ON HFPEF

Two main pathological mechanisms have been suggested to play a role in the increased myocardial stiffness characterising HFpEF: increased accumulation of type 1 collagen in the extracellular matrix and intrinsic stiffness of the cardiomyocytes [2]. Recent studies suggest that empagliflozin and SGLT2 inhibitors exert their pleiotropic effect in HFpEF through various mechanisms.

A study published in 2018 where cardiomyocytes from humans and rats were exposed to empagliflozin and then investigated with the aim of discovering the mechanism of

empagliflozin on cardiomyocytes concluded with empagliflozin exerting a direct effect on the cardiomyocytes [21]. The findings of the study suggested that reduced myocardial stiffness was caused by increased phosphorylation of myofilament regulatory proteins causing reduced diastolic myofilament stiffness in both human and rat cardiomyocytes [21]. Furthermore, the results suggest that the levels of diastolic and systolic Ca^{2+} were unaffected by exposure to empagliflozin [21]. In contrast, another study published in 2018 demonstrated that empagliflozin does in fact alter Ca^{2+} levels in failing cardiomyocytes [24]. The study found that exposure to empagliflozin does reduce the leakage of Ca^{2+} from sarcoplasmic reticulum (SR) and increase Ca^{2+} transient amplitude in cardiomyocytes, improving diastolic function [24].

Moreover, a study published in 2021 investigated cardiomyocytes of human and murine origin exposed to empagliflozin with the aim of further studying the mechanism of empagliflozin in HFpEF. Kolijn et al. obtained results suggesting a further mechanism reducing myocardial stiffness: exposure to empagliflozin resulted in a significant reduction in oxidative stress and inflammation in HFpEF cardiomyocytes, and also improved endothelial vasorelaxation [25], in turn improving ventricular relaxation.

Another interesting mechanism of action of SGLT2 inhibitors is the effect it has on the cardiorenal axis. SGLT2 inhibitors restore the impaired glomerular feedback mechanism present in HF, and also cause increased production of erythropoietin by the kidneys [26]. SGLT2 inhibitors achieve their effects by increasing natriuresis and thereby increasing the amount of sodium offered to the juxtaglomerular apparatus; this results in vasoconstriction of the afferent arteriole, and potentially reducing renal hyperfiltration [27]. Enhanced erythropoiesis is a consequence of the reduced blood flow, subsequently improving haemoglobin and haematocrit levels [27].

In summary, the evidence is now suggesting that SGLT2 inhibitors improve HF by exerting their effect on various mechanisms: reducing myocardial stiffness, improving the intracellular electrolyte balance, reducing oxidative inflammation, enhanced erythropoiesis and improved kidney function. All these beneficial effects are exerted by SGLT2 inhibitors irrespective of their glycaemic effect.

PRACTICAL IMPLICATIONS

Amongst the exclusion criteria for the EMPEROR-Preserved study were myocardial infarction within 90 days of the commencement of the study and acute decompensation of HF (see Table 1). The EPHESUS study from 2003 proved that eplerenone reduces death and hospitalisations in patients having recently experienced an acute myocardial infarction complicated by left ventricular systolic dysfunction (LVSD). This patient cohort was offered further treatment to improve the prognosis [28]. In patients with recent myocardial infarctions that are not complicated by LVSD the treatment options that improve prognosis are still limited. Therefore, a study investigating the addition of an SGLT2 inhibitor to patients with an acute myocardial infarction and a preserved ejection fraction could be very interesting regarding future management.

Another exclusion criterion that needs further investigation is the addition of empagliflozin in patients with acute decompensated HF. Subgroup analysis of the SOLOIST-WHF study suggests that an SGLT2 inhibitor is beneficial in acute decompensation of HFpEF; this study included 1222 patients who were randomised to either sotagliflozin or placebo groups, but only 20.9% of the sotagliflozin group and 21% of the placebo group had an LVEF > 50% [20]. This study is also limited by the short duration of the trial and a relatively small patient cohort which reduces the statistical strength of the trial. In contrast to the SOLOIST-WHF study, a future investigation should aim to include both patients with diabetes and patients without diabetes and aim to include more patients suffering from an acute decompensation of HFpEF, increasing the degree of evidence supporting the beneficial effects of an SGLT2 inhibitor in the management of HFpEF.

Table 1 Inclusion and exclusion criteria used in the EMPEROR-Preserved study [20]

Inclusion criteria	Exclusion criteria
Age 18 years or over (20 years or over in Japan)	Myocardial infarction, coronary artery bypass graft surgery or other major cardiovascular surgery, stroke or TIA in past 90 days prior to visit 1
Patients with chronic HF NYHA class II-IV and preserved EF (LVEF > 40%) and elevated NTpro-BNP > 300 pg/mL for patients without AF, or > 900 for patients with AF, analysed at central laboratory at visit 1	Heart transplant recipient or listed for heart transplant
Structural heart disease within 6 months prior to visit 1, or documented HHF within 12 months prior to visit 1	Acute decompensated HF
Stable dose of oral diuretic (if prescribed)	Systolic blood pressure of 180 mmHg or above at visit 2
Signed and dated consent form	Symptomatic hypotension and/or systolic blood pressure less than 100 mmHg
	Indication of liver disease
	Impaired renal function, defined as eGFR less than 20 mL/min/1.73 m^2 or requiring dialysis
	History of ketoacidosis
	Current or prior use of SGLT2 inhibitor
	Currently enrolled in another investigational device or trial
	Known allergy or hypersensitivity to empagliflozin or other SGLT2 inhibitor
	Women who are pregnant, nursing, or who plan to become pregnant during the trial

Adapted from clinicaltrials.gov

HF heart failure, *NYHA* New York Heart Association, *EF* ejection fraction, *LVEF* left ventricular ejection fraction, *NTpro-BNP* N-terminal pro brain natriureic peptide, *HHF* hospitalisation for heart failure, *TIA* transient ischaemic attack, *eGFR* estimated glomerular filtration rate

The National Heart Failure Audit (2018–2019) found 74,969 total admissions to hospital in England and Wales with HF over a 12-month period (for 89% of these HF was coded as the patient's primary diagnosis), with an increase in the number of patients with HFpEF compared to previous years and an average length of stay of 9 days for patients admitted to cardiology wards [29]. The potential economic impact of the findings in EMPEROR-Preserved, in particular the significantly reduced hospital admissions, is not only significant to patient outcomes but also financially for the National Health Service.

There are multiple ongoing trials that could potentially provide an exciting prospect for HFpEF management. A pilot trial of polydiuretic therapy, including an SGLT2 inhibitor, in a small number of patients with HFpEF is ongoing with results due next year [30]. Additionally, following a reduction of HHF in the spironolactone group in the TOPCAT study [16] (but without significant reduction in the composite primary end point of death from cardiovascular

causes, aborted cardiac arrest, or HHF), there are now multiple ongoing trials looking at the use of mineralocorticoid receptor antagonists in HFpEF [31–33]. The outcomes of which are all due over the next 3 years.

CONCLUSION

As our acceptance of HFpEF as its own diagnosis increases along with its prevalence, we have eagerly been awaiting a treatment that will show proven morbidity and mortality benefit. The finding of a treatment that reduces the risk of HHF and CV death in HFpEF is unheard of and merits extensive support. SGLT2 inhibitors may have begun as a treatment for DM, but they have revealed themselves as promising treatments for other conditions and diseases. Their benefits in HF, but particularly in HFpEF cannot be ignored and we excitedly await further results from ongoing studies as mentioned in this review article.

The ESC recently added SGLT2 inhibitors to the management guidelines for HFrEF following good outcomes from DAPA-HF [18] and EMPEROR-Reduced [19] over the last 2 years. We hope that further supporting evidence for SGLT2 inhibitors in the management of HFpEF follows with the results of the ongoing DELIVER trial expected soon, and that as a result similar changes to guidelines may be added to support the use of SGLT2 inhibitors in the management of HFpEF.

ACKNOWLEDGEMENTS

Disclosures. Rebecca Heath and Håkon Johnsen have no conflicts of interest to declare. W. David Strain has received unrestricted educational grants and speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli-Lily, Novartis, Novo Nordisk, and Takeda outside the submitted work and is supported by the NIHR Exeter Clinical Research Facility and the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the South West Peninsula. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR Exeter Clinical Research Facility, the NHS, the NIHR or the Department of Health in England. Marc Evans has received honoraria from AstraZeneca, Novo Nordisk, Takeda and NAPP, and research support from Novo Nordisk outside the submitted work, and has received financial support for consultancy from Novartis, Merck Sharp & Dohme Corp. and Novo Nordisk, and has served on the speaker's bureau for Novartis, Lilly, Boehringer lngelheim, Merck Sharp & Dohme Corp., Novo Nordisk, Janssen and Takeda. Marc Evans is also the Editor-in-Chief of *Diabetes Therapy*. Marc Evans is also co-Editor-in-Chief of this journal.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021;42(36):3599–726. https://doi.org/10.1093/eurheartj/ehab368.

2. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32(6):670–9.

3. Goyal P, Almarzooq ZI, Evelyn M, et al. Characteristics of hospitalizations for heart failure with preserved ejection fraction. Am J Med. 2016;129(6):635.e15-635.e26.

4. Gomez-Soto FM, Andrey JL, Garcia-Egido A, et al. Incidence and mortality of heart failure: a community-based study. Int J Cardiol. 2011;151(1):40–5.

5. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14:591–602.

6. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev. 2017;3(1):7–11.

7. Davidson A, Raviendran N, Murali CN, Myint PK. Managing heart failure with preserved ejection fraction. Ann Transl Med. 2020;8(6):395.

8. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2014;11:507–15.

9. Meagher P, Adam M, Civitarese R, Bugyei-Twum A, Connelly KA. Heart failure with preserved ejection fraction in diabetes: mechanisms and management. Can J Cardiol. 2018;34(5):632–43.

10. Lazar S, Rayner B, Campos GL, McGrath K, McClements L. Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus. Transl Metab Syndr Res. 2020;3:1–5.

11. Riehle C, Abel ED. Insulin signaling and heart failure. Circ Res. 2016;118:1151–69.

12. McHugh K, DeVore AD, Wu J, et al. Heart failure with preserved ejection fraction and diabetes: JACC State-of-the-art review. J Am Coll Cardiol. 2019;73(5):602–11.

13. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham Study. Am J Cardiol. 1974;34:29–34.

14. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol. 2017;70(20):2476–86.

15. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet. 2003;362:777–81.

16. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–92.

17. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381:1609–20.

18. McMurray J, Solomon S, Inzucchi S, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.

19. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413–24.

20. Bhatt D, Szarek M, Steg P, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117–28.

21. Pabel S, Wagner S, Bollenberg H, et al. Empagliflozin directly improves diastolic function in human heart failure. Eur J Heart Fail. 2018;20(12):1690–700.

22. Solomon S, Claggett B, Lewis E, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with

preserved ejection fraction. Eur Heart J. 2015;37(5): 455–62.

23. Lund L, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018;20(8):1230–9.

24. Mustroph J, Wagemann O, Lücht C, et al. Empagliflozin reduces Ca/calmodulin-dependent kinase II activity in isolated ventricular cardiomyocytes. ESC Heart Fail. 2018;5(4):642–8.

25. Kolijn D, Pabel S, Tian Y, et al. Empagliflozin improves endothelial and cardiomyocyte function in human heart failure with preserved ejection fraction via reduced pro-inflammatory-oxidative pathways and protein kinase Gα oxidation. Cardiovasc Res. 2020;117(2):495–507.

26. Pabel S, Hamdani N, Luedde M, Sossalla S. SGLT2 inhibitors and their mode of action in heart failure: has the mystery been unravelled? Curr Heart Fail Rep. 2021;18(5):315–28.

27. Mazer C, Hare G, Connelly P, et al. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. Circulation. 2020;141(8):704–7.

28. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309–21.

29. NICOR. National Heart Failure Audit (NHFA) 2020 summary report (2018/19 data). 2021. https://www.nicor.org.uk/national-cardiac-audit-programme/heart-failure-heart-failure-audit/ Accessed 08 Oct 2021.

30. Polydiuretic therapy for heart failure with preserved ejection fraction and diabetes mellitus. N=20. NCT04697485. 2021. https://clinicaltrials.gov/ct2/show/NCT04697485 Accessed 08 Nov 2021.

31. Spironolactone initiation registry randomized interventional trial in heart failure with preserved ejection fraction (SPIRRIT). N=3200. NCT02901184. 2021. https://clinicaltrials.gov/ct2/show/NCT02901184. Accessed 08 Nov 2021.

32. Study to evaluate the efficacy and safety of finerenone on morbidity in participants with heart failure and left ventricular ejection fraction greater or equal to 40% (FINEARTS-HF). N=5500. NCT04435626. 2021. https://clinicaltrials.gov/ct2/show/NCT04435626. Accessed 08 Nov 2021.

33. Spironolactone in the treatment of heart failure (SPIRIT-HF). N=1300. NCT04727073. 2021. https://clinicaltrials.gov/ct2/show/NCT04727073. Accessed 08 Nov 2021.