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VIEWPOINT

Sodium–glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: reasons for optimism

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Over the last three decades, several lifesaving therapies for the treatment of heart failure with reduced ejection fraction (HFrEF) have emerged; however, this is not the case for heart failure with preserved ejection fraction (HFpEF). Sodium–glucose co-transporter 2 (SGLT2) inhibitors have emerged as a novel foundational therapy in patients with HFrEF.[1,2] Initially developed as a treatment for diabetes, accumulating evidence from the DAPA-HF (Dapagliflozin and Prevention of Adverse outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trials have proven that the benefits of SGLT2 inhibitors extend to patients beyond type 2 diabetes mellitus to those with HFrEF as well, irrespective of diabetes status.[1,2] It remains uncertain, however, if SGLT2 inhibitors will confer similar benefits in patients with HFpEF. While trials in this patient population are ongoing, the current models of HFpEF pathophysiology, the pharmacodynamic profile of SGLT2 inhibitors, and secondary analyses of previous trials, all provide hope that these drugs may indeed benefit patients with HFpEF.

Pathophysiology of heart failure with preserved ejection fraction

The pathophysiology of HFpEF is complex, multifactorial with a variety of aetiologies, and remains hotly debated. Although the exact pathophysiological mechanisms involved in HFpEF remain uncertain, prevalent theories centre around derangements in four organ systems with overlapping systemic pathophysiologic underpinnings that are thought to play a key role in the development and progression of HFpEF.[3]

Cardiac abnormalities

Multiple cardiac structural and functional abnormalities are seen commonly in patients with HFpEF. Increased passive myocardial stiffness due to impaired titin phosphorylation states has been proposed as a mechanistic process for the development of HFpEF.[4] Impaired left ventricular (LV) stiffness and relaxation, which cause elevated LV filling pressures, contribute to dyspnoea and impaired exercise capacity in patients with HFpEF.[5] The underlying myocardial inflammation also triggers LV hypertrophy and diastolic dysfunction.[6] While LV ejection fraction (LVEF) is normal in HFpEF, myocardial contractility and LV systolic mechanics are impaired and associated with worse prognosis in HFpEF.[5] Impaired chronotropic response of the heart has also been observed in some patients with HFpEF, which may further contribute to exercise limitation.

Vascular dysfunction

Reduced aortic distensibility has been shown in some patients with HFpEF and is linked with impaired exercise capacity. Combined ventricular–arterial stiffening aggravates this and results in higher blood pressure changes for any variation in afterload or preload, which further impairs diastolic dysfunction, LV remodelling and fibrosis. This ventricular–aortic uncoupling has been shown to be associated with dyspnoea and fatigue.[5] Moreover, impaired nitric oxide signalling, oxidative stress and inflammation have been shown to potentially contribute to coronary microvascular dysfunction, which may lead to myocardial injury at rest and further reduction of cardiac reserves.[5,6]

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Renal abnormalities

There is an important bi-directional relationship between kidney and heart dysfunction. Venous congestion in HFpEF can lead to activation of the renin–angiotensin–aldosterone system, which promotes oxidative stress, and systemic inflammation coupled with release of proinflammatory adipocytokines that augment renal retention of sodium and water.[5] Increased retention of sodium and water perpetuates a state of volume overload, which causes an increase in cardiac filling pressures. Moreover, albuminuria has been hypothesized to be linked with abnormal cardiac mechanics and is an important risk factor for HFpEF.[6] While the role of the kidney in HFpEF seems certain, the specific mechanism remains elusive.

Adiposity

Obesity is a distinct and common HFpEF phenotype associated with insulin resistance. Obese HFpEF patients have increased cardiac filling pressures, impaired myocardial energetics and concentric LV hypertrophy, which leads to diastolic dysfunction.[7] Epicardial adipose tissue deposition in the surrounding myocardium and vessels due to altered adiponectin and leptin regulation is widely implicated in ventricular dysfunction and coronary artery calcification associated with HFpEF.[3] Increased epicardial fat further triggers release of proinflammatory cytokines, cell-signalling molecules and enzymes such as aldosterone, neprilysin and leptin, which causes cardiac remodelling. In addition, visceral adiposity is associated with a systemic inflammatory state, which results in cytokine mediated damage of myocardium, endothelium and renal parenchyma.[6] Moreover, abnormal energy metabolism in cardiomyocytes may also stem from an increase in xanthine oxidase activity, which is reflected as an increase in uric acid in the body.[8] In addition, impaired oxidation of ketone bodies, which can provide additional source of energy for the cardiomyocytes, coupled with decreased lipolysis of the epicardial adipose tissue deposited in surrounding myocardium, may further promote cardiometabolic-induced inflammation and the development of HFpEF.[9]

Optimism for sodium–glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction

Accumulated evidence from prior trials serves as the key factor for optimism regarding the potential therapeutic effects of SGLT2 inhibitors. SGLT2 inhibitors simultaneously target multiple pathways (*Figure 1*) and produce favourable effects on multiple organ systems thought to be involved in HFpEF. SGLT2 inhibitors can interfere with the primary pathophysiological mechanisms driving the underlying aetiology of HFpEF, such as systemic inflammation, oxidative stress, and neurohormonal activation, reduction of which can attenuate adverse cardiovascular events in this cohort.[3] The mechanistic pathways of SGLT2 inhibitors have been shown to reduce cardiac hypertrophy and inflammation.[3] It is postulated that SGLT2 inhibitors may reduce the epicardial adipose tissue surrounding the myocardium, which might ultimately lead to improved distensibility. The direct pleiotropic effects of SGLT2 inhibitors have also shown to reduce excessive diastolic tension and decrease LV mass, which improves cardiac preload.[10]

SGLT2 inhibitors are also hypothesized to improve microcirculatory dysfunction, thereby reducing vascular stiffness and systemic blood pressure.[10] An improvement in endothelial function often occurs in conjunction with kidney benefits observed with SGLT2 inhibitors. SGLT2 inhibitors promote natriuresis, which may lead to a decrease in plasma and interstitial volume, while increasing red blood cell mass and haematocrit. Elevation of haematocrit observed with SGLT2 inhibitors may lead to reverse renal remodelling and alleviate oxidative stress.[11]

In addition, SGLT2 inhibitors may ameliorate symptoms of HFpEF in part due to their interference with metabolic pathways. SGLT2 inhibitors induce ketogenic metabolism, which results in utilization of energy-efficient ketones over less efficient fatty acid and

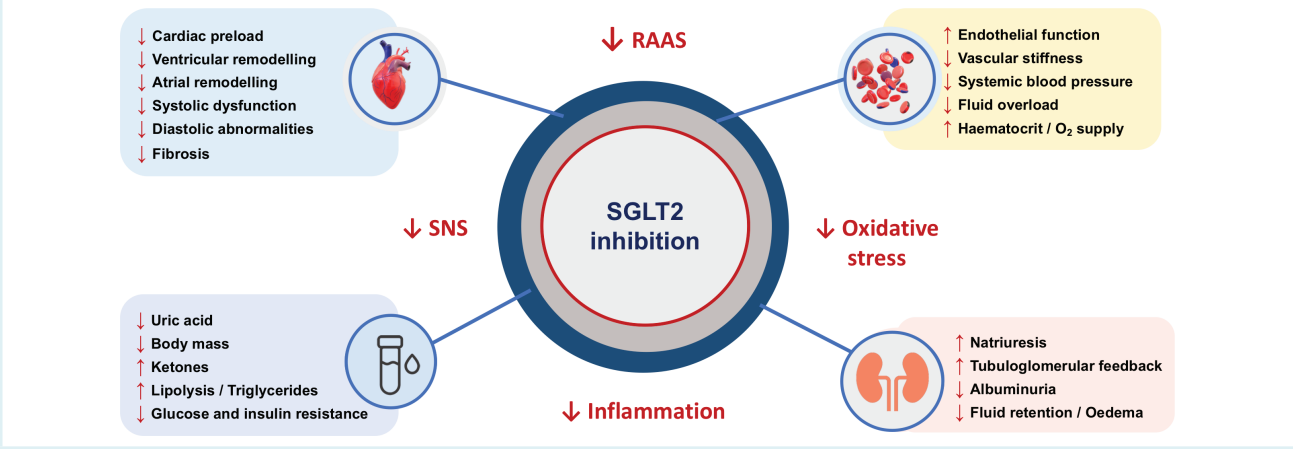

Figure 1 Possible mechanisms detailing why sodium–glucose co-transporter 2 (SGLT2) inhibitors may work in heart failure with preserved ejection fraction. RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

Table 1 Contemporary clinical trials of sodium–glucose co-transporter 2 inhibitors reporting results of participants with heart failure with preserved ejection fraction

Trial	Type of trial	Drug	Participants with HFpEF at baseline, *n* (%)	Definition of HFpEF	HF outcome[a]
DECLARE-TIMI 58[14]	CVOT	Dapagliflozin	1316 (7.7)	LVEF ≥45%	HHF: HR 0.72 (0.50–1.04)
SOLOIST-WHF[15]	Kidney trial	Sotagliflozin	256 (20.9)	LVEF ≥50%	Composite HHF and CV death: HR 0.48 (0.27–0.86)
SCORED[16]	Kidney trial	Sotagliflozin	1667 (15.8)	LVEF ≥50%	Composite HHF and CV death: HR 0.72 (0.52–0.99)
VERTIS-CV[17]	CVOT	Ertugliflozin	1007 (12.2)	LVEF >45%	HF: HR 0.70 (0.39–1.26)
EMPEROR-Preserved[18]	HF	Empagliflozin	5988 (100)	LVEF >40%	Results awaited
DELIVER[19]	HF	Dapagliflozin	6263 (100)	LVEF >40%	Results awaited

VERTIS-CV and DECLARE TIMI-58 categorized ejection fraction <45% with known HF as HFrEF; SOLOIST-WHF categorized ejection fraction <50% as HFrEF.
CV, cardiovascular; CVOT, cardiovascular outcome trial; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.
[a]Results presented as HR with 95% confidence intervals.

glucose oxidation to generate myocardial energy, thereby improving efficiency and function of both myocardium and the kidneys.[3] Following SGLT2 inhibitor therapy, an increased glucagon-to-insulin ratio is hypothesized to lead to increased lipid mobilization, which is primarily responsible for weight loss. In addition, these novel therapeutics may potentially lower serum uric acid concentrations by increasing renal urate excretion, and have been shown to have a positive impact on peri-nephric fat.[12]

Supportive data

Current clinical evidence of SGLT2 inhibitors in HFpEF, albeit limited, is encouraging. A recent meta-analysis of SGLT2 inhibitor trials in HFpEF suggested reduction in composite of heart failure (HF) hospitalization and cardiovascular mortality.[13] Moreover, analysis of contemporary clinical trials show similar results in patients with baseline HFpEF (*Table 1*).[14–19] Furthermore, the optimism regarding favourable effects of SGLT2 inhibitors in HFpEF in the upcoming EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; NCT03057951) trial also stems from the results of a prior large trial which demonstrated clinical benefit with the same intervention.[18] In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin significantly reduced the risk of HF hospitalization by 35% and HF mortality or hospitalization by 39% in patients with or without baseline HF.[20,21] The HF cohort comprised of 10% of the overall trial population, however, the lack of detailed characterization of type of HF in these patients precludes strong inference to be drawn whether the HF benefits were observed in patients with HFpEF or HFrEF.

Although not known for certain, it is plausible that majority of the HF patients enrolled in EMPA-REG OUTCOME trial had HFpEF. This is hypothesized as the HF hospitalization event rates observed in the placebo arm were similar to event rates observed in other HFpEF trials such as PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) (74 per 1000 patient-years), CHARM-Preserved (Candesartan in Patients with Chronic Heart Failure and Preserved Ejection Fraction) (69 per 1000 patient-years), PARAGON-HF (Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction) (50 per 1000 patient-years), TOPCAT (Spironolactone for Heart Failure with Preserved Ejection Fraction) (46 per 1000 patient-years), and I-PRESERVE (Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction) (43 per 1000 patient-years) (*Figure 2A*).[22–26] In contrast, HFrEF trials have had higher event rates for HF hospitalization in the placebo arm. This can be substantiated by inferring event rates of HF hospitalization in trials such as EMPEROR-Reduced (155 per 1000 patient-years), DAPA-HF (98 per 1000 patient-years), CHARM-Alternative (Candesartan in Patients with Chronic Heart Failure and Reduced Systolic Function Intolerant to Angiotensin-Converting Enzyme Inhibitors) (128 per 1000 patient-years), CHARM-Added (Candesartan in Patients with Chronic Heart Failure and Reduced Systolic Function Taking Angiotensin-Converting Enzyme Inhibitors) (110 per 1000 patient-years) and PARADIGM-HF (Angiotensin-Neprilysin Inhibition vs. Enalapril in Heart Failure) (78 per 1000 patient-years).[1,2,27–29]

Similar trends can be observed for event rates of all-cause mortality, where EMPA-REG OUTCOME results (55 per 1000 patient-years) were comparable with event rates observed in other HFpEF trials (range 30 to 59 per 1000 patient-years) compared with HFrEF trials (range 91 to 115 per 1000 patient-years) (*Figure 2B*). These results suggest that majority of the EMPA-REG OUTCOME population with HF may have indeed been constituted of HFpEF patients, and we therefore expect largely similar benefits observed in the HF subgroup of EMPA-REG OUTCOME in EMPEROR-Preserved as well (*Figure 3*).

In light of the current clinical evidence, it is also plausible that the potential applicability of SGLT2 inhibitors may extend to patients with heart failure with mildly reduced (or mid-range) ejection fraction (HFmrEF) as well. The 2016 Heart Failure Association (HFA)

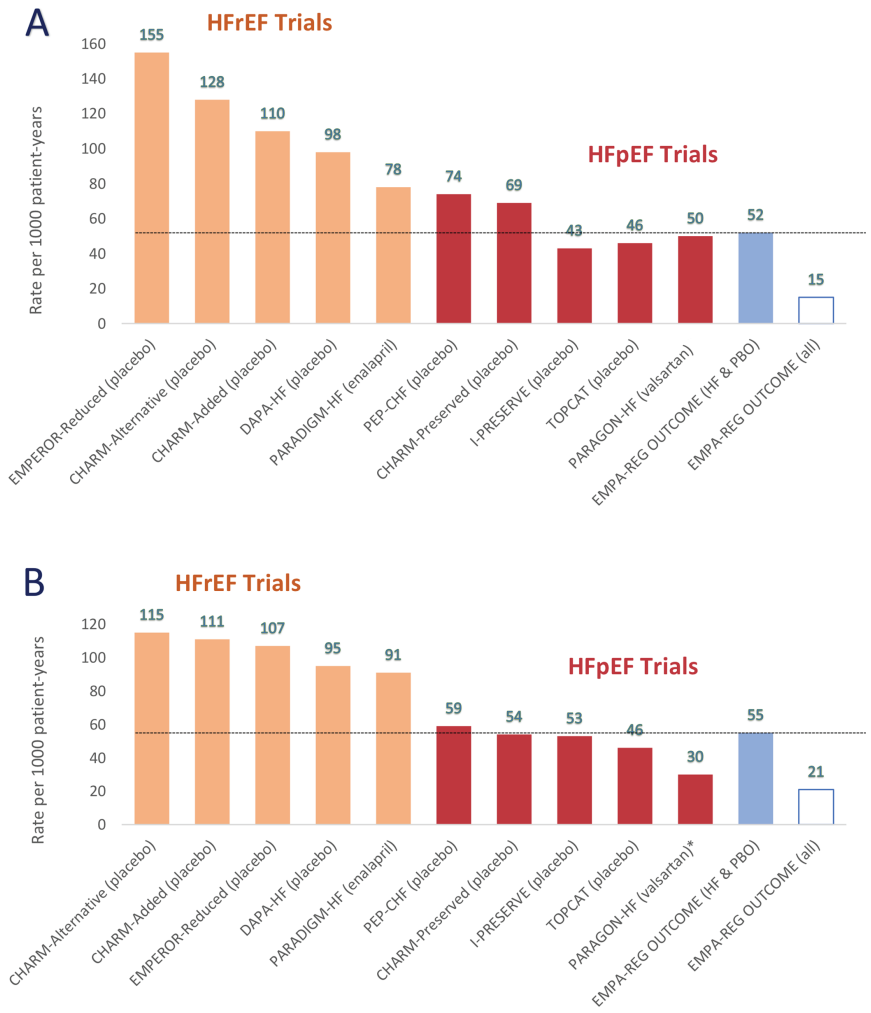

Figure 2 Comparison of placebo event rates (only first events) across heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF) trials. (*A*) Heart failure (HF) hospitalization rates. (*B*) All-cause mortality rates. *Represents cardiovascular mortality rate.

and European Society of Cardiology (ESC) guidelines define HFmrEF as LVEF 40–49% and HFpEF as LVEF >50%.[30] Given that majority of the HFpEF trials, including the ongoing EMPEROR-Preserved and DELIVER (Dapagliflozin evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; NCT03619213) trials, have enrolled patients with LVEF >40% (*Table 1*), the beneficial effects of SGLT2 inhibitors can potentially be observed in both HFmrEF and HFpEF.[18,19] For this reason, the EMPEROR-Preserved trial aims to conduct subgroup analysis stratified via LVEF, which may provide further insight to clinical benefits of SGLT2 inhibitors in both HFmrEF and HFpEF populations.

It is important to acknowledge that different diagnostic criteria are employed to diagnose HFpEF. The American College of Cardiology/American Heart Association guidelines recommend a diagnostic approach via exclusion of severe renal, pulmonary, or hepatic disease in patients with elevated natriuretic peptide biomarkers, preserved LVEF and dyspnoea.[31] In contrast, the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend using echocardiographic parameters including mitral E/A ≥2 or two of the following criteria: mitral average E/e′ >14, left atrial volume index >34 mL/m^2, or tricuspid regurgitation velocity >2.8 m/s to categorize HFpEF.[32] The recent HFA/ESC guidelines, however, advocate for a more comprehensive approach in diagnosing HFpEF by assessing for HF symptoms, utilizing diagnostic laboratory parameters, electrocardiograms and electrocardiography and conducting functional testing in the absence of any overt non-cardiac cause of dyspnoea.[33] This further substantiates the significance of the upcoming EMPEROR-Preserved and DELIVER trials, which utilize a comprehensive diagnostic approach to evaluate HFpEF.[18,19] The results of SGLT2 inhibitors in both of these trials would therefore aid in ascertaining the magnitude of therapeutic response in patients diagnosed with HFpEF through various different parameters. Future expert consensus and guideline groups should comprehensively evaluate the most accurate diagnostic approach which may be universally applicable in diagnosing HFpEF.

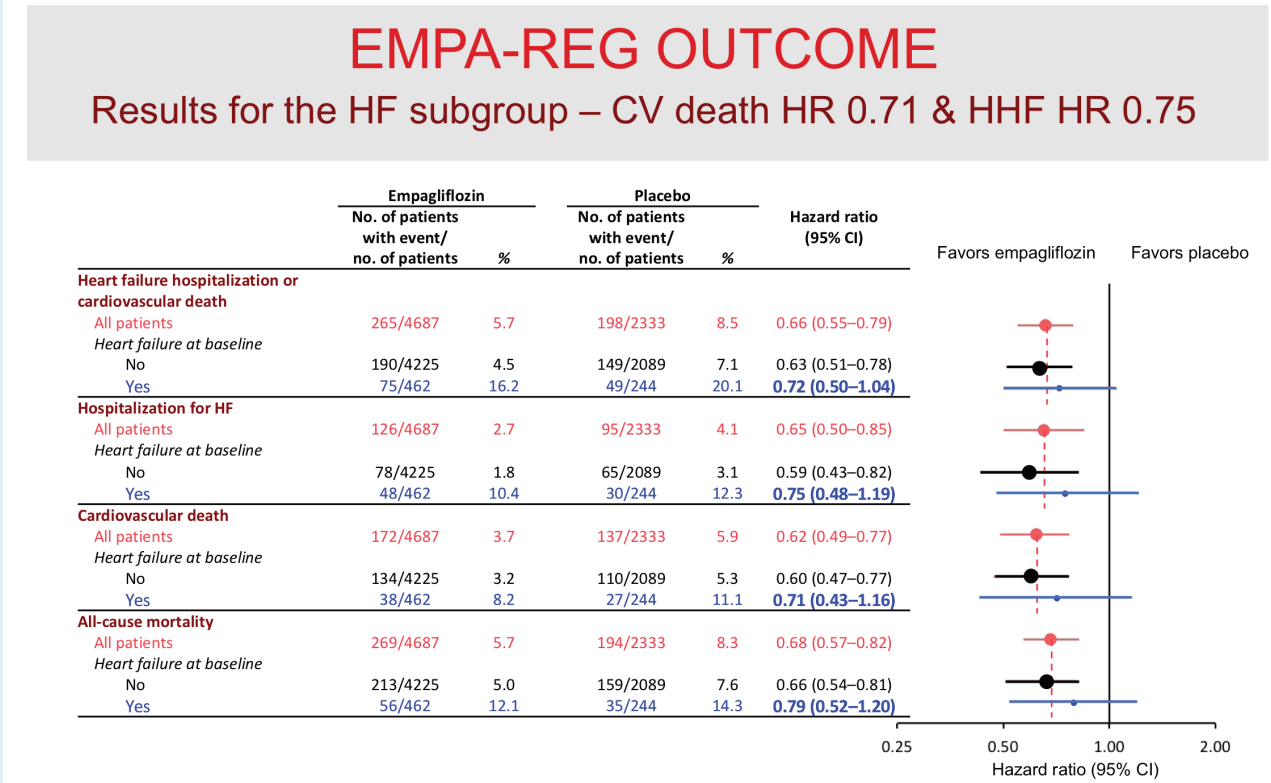

Figure 3 Results for the heart failure (HF) subgroup from the EMPA-REG OUTCOME trial. CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio. Adapted from Fitchett *et al.*[21]

Conclusion

SGLT2 inhibitors simultaneously target multiple pathophysiological processes implicated in HFpEF, which may result in improving clinical outcomes in these patients. This is supported by early clinical data as well. The ongoing EMPEROR-Preserved and DELIVER trials will provide critical insights into the potential advantage this novel class of drugs may have for patients with HFpEF.[18,19]

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References

1. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljumgman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
2. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-la Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
3. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. *Heart* 2021;**107**:1032–1038.

4. Borbély A, Van Der Velden J, Papp Z, Bronzwaer JGF, Edes I, Stienen GJM, Paulus WJ. Cardiomyocyte stiffness in diastolic heart failure. *Circulation* 2005;**111**:774–781.
5. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011;**32**:670–679.
6. Shah SJ, Borlaug BA, Kitzman DW, McCulloch AD, Blaxall BC, Agarwal R, Chirinos JA, Collins S, Deo RC, Gladwin MT, Granzier H, Hummel SL, Kass DA, Redfield MM, Sam F, Wang TJ, Desvigne-Nickens P, Adhikari BB. Research priorities for heart failure with preserved ejection fraction: National Heart, Lung, and Blood Institute Working Group Summary. *Circulation* 2020;**141**: 1001–1026.
7. Rao VN, Fudim M, Mentz RJ, Michos ED, Felker GM. Regional adiposity and heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:1540–1550.
8. Gu J, Fan YQ, Zhang HL, Zhang JF, Wang CQ. Serum uric acid is associated with incidence of heart failure with preserved ejection fraction and cardiovascular events in patients with arterial hypertension. *J Clin Hypertens* 2018;**20**:560–567.
9. Selvaraj S, Kelly DP, Margulies KB. Implications of altered ketone metabolism and therapeutic ketosis in heart failure. *Circulation* 2020;**141**:1800–1812.
10. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *JACC Basic Transl Sci* 2020;**5**:632–644.
11. Sano M, Goto S. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. *Circulation* 2019;**139**:1985–1987.
12. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 2019;**21**:1291–1298.
13. Butler J, Usman MS, Khan MS, Greene SJ, Friede T, Vaduganathan M, Filippatos G, Coats AJS, Anker SD. Efficacy and safety of SGLT2 inhibitors in heart failure: systematic review and meta-analysis. *ESC Heart Fail* 2020;**7**:3298–3309.
14. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019;**139**:2528–2536.
15. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–128.
16. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, Cherney DZI, Dwyer JP, Scirica BM, Bailey CJ, Díaz R, Ray KK, Udell JA, Lopes RD, Lapuerta P, Steg PG; SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021;**384**:129–139.
17. Cosentino F, Cannon CP, Cherney DZI, Masiukiewicz U, Pratley R, Dagogo-Jack S, Frederich R, Charbonnel B, Mancuso J, Shih WJ, Terra SG, Cater NB, Gantz I, McGuire DK; VERTIS CV Investigators. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV trial. *Circulation* 2020;**142**:2205–2215.
18. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, Kimura K, Zeller C, George J, Brueckmann M, Zannad F, Packer M; EMPEROR-Preserved Trial Committees and Investigators. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved trial. *Eur J Heart Fail* 2019;**21**: 1279–1287.
19. Solomon SD, Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Lindholm D, Wilderäng U, Öhrn F, Claggett B, Langkilde AM, Petersson M, McMurray JJV. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail* 2021;**23**:1217–1225.
20. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
21. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME® Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016;**37**:1526–1534.
22. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
23. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003;**362**:777–781.
24. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620.
25. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
26. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–2467.
27. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
28. McMurray JJV, Östergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–771.
29. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
30. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
31. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;**70**:776–803.
32. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;**29**:277–314.
33. Pieske B, Tschöpe C, De Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019;**40**:3297–3317.