



**HAL**  
open science

## Body mass index and cardiorenal outcomes in the EMPEROR-Preserved trial: Principal findings and meta-analysis with the DELIVER trial

Naveed Sattar, Javed Butler, Matthew M.Y. Lee, Josephine Harrington,  
Abhinav Sharma, Faiez Zannad, Gerasimos Filippatos, Subodh Verma, James  
L Januzzi, João Pedro Ferreira, et al.

### ► To cite this version:

Naveed Sattar, Javed Butler, Matthew M.Y. Lee, Josephine Harrington, Abhinav Sharma, et al..  
Body mass index and cardiorenal outcomes in the EMPEROR-Preserved trial: Principal findings and  
meta-analysis with the DELIVER trial. *European Journal of Heart Failure*, 2024, 10.1002/ejhf.3221 .  
hal-04529502

**HAL Id: hal-04529502**

**<https://hal.univ-lorraine.fr/hal-04529502>**

Submitted on 2 Apr 2024


**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# Body mass index and cardiorenal outcomes in the EMPEROR-Preserved trial: Principal findings and meta-analysis with the DELIVER trial

Naveed Sattar<sup>1\*</sup>, Javed Butler<sup>2</sup>, Matthew M.Y. Lee<sup>1</sup>, Josephine Harrington<sup>3</sup>, Abhinav Sharma<sup>4</sup>, Faiez Zannad<sup>5</sup>, Gerasimos Filippatos<sup>6</sup>, Subodh Verma<sup>7</sup>, James L. Januzzi<sup>8</sup>, João Pedro Ferreira<sup>5,9,10</sup>, Stuart J. Pocock<sup>11</sup>, Egon Pfarr<sup>12</sup>, Anne P. Ofstad<sup>13,14</sup>, Martina Brueckmann<sup>12,15</sup>, Milton Packer<sup>16</sup>, and Stefan D. Anker<sup>17</sup>

<sup>1</sup>School of Cardiovascular and Metabolic Health, University of Glasgow, BHF Glasgow Cardiovascular Research Centre (GCRC), Glasgow, UK; <sup>2</sup>Baylor Scott and White Research Institute, Dallas TX and University of Mississippi, Jackson, MS, USA; <sup>3</sup>Division of Cardiology, Department of Medicine, Duke University, Durham, NC, USA; <sup>4</sup>Division of Cardiology, McGill University Health Centre, McGill University, Montreal, Quebec, Canada; <sup>5</sup>Université de Lorraine, Inserm, Centre d'Investigations Cliniques, -Plurithématique 14-33 and Inserm U1116, CHRU Nancy, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; <sup>6</sup>National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens, Greece; <sup>7</sup>Division of Cardiac Surgery, St Michael's Hospital, Department of Surgery, and Pharmacology and Toxicology, University of Toronto, Toronto, ONT, Canada; <sup>8</sup>Massachusetts General Hospital and Baim Institute for Clinical Research, Boston, MA, USA; <sup>9</sup>Cardiovascular R&D Centre-UniC@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal; <sup>10</sup>Heart Failure Clinic, Internal Medicine Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; <sup>11</sup>Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; <sup>12</sup>Boehringer Ingelheim International GmbH, Ingelheim, Germany; <sup>13</sup>Boehringer Ingelheim Norway KS, Asker, Norway; <sup>14</sup>Oslo Diabetes Research Center, Oslo, Norway; <sup>15</sup>First Department of Medicine, Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; <sup>16</sup>Baylor University Medical Center, Dallas, TX, USA; and <sup>17</sup>Department of Cardiology (CVK) of German Heart Center Charité; German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany

Received 20 October 2023; revised 13 March 2024; accepted 14 March 2024

## Aims

Both low and high body mass index (BMI) are associated with poor heart failure outcomes. Whether BMI modifies benefits of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in heart failure with preserved ejection fraction (HFpEF) requires further investigation.

## Methods and results

Using EMPEROR-Preserved data, the effects of empagliflozin versus placebo on the risks for the primary outcome (hospitalization for heart failure [HHF] or cardiovascular [CV] death), change in estimated glomerular filtration rate (eGFR) slopes, change in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), and secondary outcomes across baseline BMI categories (<25 kg/m<sup>2</sup>, 25 to <30 kg/m<sup>2</sup>, 30 to <35 kg/m<sup>2</sup>, 35 to <40 kg/m<sup>2</sup> and ≥40 kg/m<sup>2</sup>) were examined, and a meta-analysis conducted with DELIVER. Forty-five percent had a BMI of ≥30 kg/m<sup>2</sup>. For the primary outcome, there was a consistent treatment effect of empagliflozin versus placebo across the BMI categories with no formal interaction (*p* trend = 0.19) by BMI categories. There was also no difference in the effects on secondary outcomes including total HHF (*p* trend = 0.19), CV death (*p* trend = 0.20), or eGFR slope with slower declines with empagliflozin regardless of BMI (range 1.12–1.71 ml/min/1.73 m<sup>2</sup> relative to placebo, *p* trend = 0.85 for interaction), though there was no overall impact on the composite renal endpoint. The difference in weight change between empagliflozin and placebo was −0.59, −1.48, −1.54, −0.87, and −2.67 kg in the lowest

\*Corresponding author. School of Cardiovascular and Metabolic Health, University of Glasgow, BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow, UK. Tel: +44 141 3303419, Email: naveed.sattar@glasgow.ac.uk

to highest BMI categories ( $p$  trend = 0.016 for interaction). A meta-analysis of data from EMPEROR-Preserved and DELIVER showed a consistent effect of SGLT2i versus placebo across BMI categories for the outcome of HHF or CV death. There was a trend toward greater absolute KCCQ-CSS benefit at 32 weeks with empagliflozin at higher BMIs ( $p = 0.08$ ).

## Conclusions

Empagliflozin treatment resulted in broadly consistent cardiac effects across the range of BMI in patients with HFpEF. SGLT2i treatment yields benefit in patients with HFpEF regardless of baseline BMI.

## Graphical Abstract

### Question: Does BMI modify the benefit of empagliflozin in HFpEF in EMPEROR-Preserved?

#### BMI (kg/m<sup>2</sup>) Wt Δ (kg)

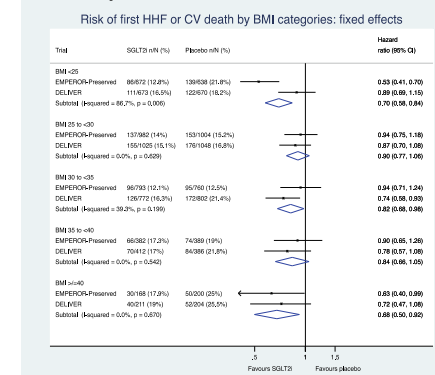
<25	-0.59
25 to <30	-1.48
30 to <35	-1.54
35 to <40	-0.87
≥40	-2.67

#### No BMI interactions with:

1° end-point (p=0.19)  
Total HHF (p=0.19)  
CV Death (p=0.20)  
eGFR slope (p=0.85)

+ Trend towards greater KCCQ-CSS benefit at higher BMIs

#### Meta-analysis + DELIVER ; P=0.25 for interaction



**Conclusion:** SGLT2i treatment yields benefit in patients with HFpEF regardless of baseline BMI

Body mass index (BMI) and cardiovascular (CV) outcomes in emperor-Preserved. CI, confidence interval; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HHF, heart failure hospitalization; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

## Keywords

Weight • HFpEF • Kidney disease • SGLT2 inhibitor

## Introduction

Excess adiposity (overweight or obesity) is a risk factor for heart failure (HF), and represents a potentially distinct phenotype in HF with preserved ejection fraction (HFpEF); of course, lower body mass index (BMI) levels also predict adverse outcomes in prevalent HF.<sup>1</sup> Obesity (defined as BMI  $\geq 30$  kg/m<sup>2</sup>) is highly prevalent in trials of patients with HFpEF (e.g. 45% in EMPEROR-Preserved,<sup>2</sup> 49% in PARAGON-HF,<sup>3</sup> 55% in TOPCAT,<sup>4</sup> 41% in I-PRESERVE<sup>5</sup>). With rising numbers of individuals living with excess adiposity (and HFpEF),<sup>6</sup> understanding the impact of baseline BMI on treatment

outcomes in HFpEF is important information. Since patients with HFpEF with comorbid obesity have reported lower quality of life than those with normal BMI, the impact of therapies on these patient-reported outcomes for patients with higher BMI is of particular importance.<sup>7</sup>

Recently, DELIVER, investigating dapagliflozin versus placebo in patients with HF and left ventricular ejection fraction (LVEF)  $>40\%$ , showed around 45% of patients with HFpEF recruited had a BMI of 30 kg/m<sup>2</sup> or more at baseline.<sup>8</sup> The authors reported that whilst there was no difference in the effect of dapagliflozin on outcomes by five different BMI categories, there were greater absolute

reductions in weight and increases in Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) in the highest BMI category group. Given this is the only trial to examine this important issue, we considered it important to test whether the benefits of empagliflozin in EMPEROR-Preserved varied by baseline BMI. Such work would usefully validate and extend relevant results reported in DELIVER.<sup>8</sup> It would also be useful to examine the benefits of empagliflozin on the rate of decline in the estimated glomerular filtration rate (eGFR). We therefore examined all key outcomes in the EMPEROR-Preserved by baseline BMI categories. In addition, we also meta-analysed the primary outcome by adding data previously published by the DELIVER investigators to produce a more powerful aggregated result across two trials.

## Methods

### Study design

EMPEROR-Preserved was an international, phase III, double-blind, parallel-group, placebo-controlled trial that enrolled 5988 patients with symptomatic HF, an LVEF >40%, elevated natriuretic peptide levels and evidence of structural cardiac changes or documented prior hospitalization for HF (HHF). Patients were randomized to empagliflozin 10 mg daily or placebo. The design and results of this trial have been published previously.<sup>2</sup> Of relevance to this study, at visit 1 (screening) BMI had to be <45 kg/m<sup>2</sup> and eGFR ≥20 ml/min/1.73 m<sup>2</sup>. The trial was approved by the ethics committee at each study site, and all patients provided written informed consent.

### Trial endpoints

The primary endpoint was the time to first HHF or cardiovascular (CV) death. The key secondary endpoints included first and recurrent HHFs and the rate of decline in the eGFR during double-blind treatment (eGFR slope). Other secondary endpoints included time to first HHF, CV death, and all-cause death and the change in KCCQ clinical summary score (CSS) from baseline to week 52. In addition, we analysed time to a first composite renal endpoint defined as time to first occurrence of (1) chronic dialysis; (2) renal transplantation; (3) sustained reduction of ≥40% in eGFR; or (4) sustained eGFR <15 ml/min/1.73 m<sup>2</sup> for patients with baseline eGFR ≥30 ml/min/1.73 m<sup>2</sup> or <10 ml/min/1.73 m<sup>2</sup> for patients with baseline eGFR <30 ml/min/1.73 m<sup>2</sup>.

For the current analyses patients were categorized according to their BMI at baseline in the following categories: <25, 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m<sup>2</sup>, according to the World Health Organization classification of obesity. We chose BMI 25 kg/m<sup>2</sup> as the lower cut-off and 40 kg/m<sup>2</sup> as the higher cut-off due to limited sample size below BMI 25 kg/m<sup>2</sup> and above 40 kg/m<sup>2</sup>. These subgroups also permitted a pooled comparison of BMI groups for the primary endpoint in DELIVER which conducted relevant analyses in 6203 patients.

### Statistical analyses

For time-to-first-event analyses, differences between the placebo and empagliflozin groups for the primary endpoint across the various BMI

categories were assessed for statistical significance using a Cox proportional hazards model, with pre-specified covariates of age, gender, geographical region, diabetes status at baseline, LVEF, and eGFR at baseline. These analyses were performed according to the intention-to-treat principle for all randomized patients and included data up to the end of the planned treatment period. Event rates per 100 patient-years and adjusted hazard ratios are reported for each BMI category. For the analysis of total (first and repeated) events, between-group differences were assessed using a joint frailty model, with CV death as a competing risk. For the analysis of changes in eGFR, weight and KCCQ, treatment effects were assessed based on changes from baseline using a mixed model for repeated measures (MMRM) adjusting for the covariates age, gender, geographical region, diabetes status, LVEF and eGFR, and in addition for weight at baseline for weight changes, and KCCQ at baseline for KCCQ changes. Between-group differences in the slope of change during the treatment period in eGFR were analysed using a random intercept, random slope model in the treated set. The MMRM, the slope model and the joint frailty model included the same covariates as the Cox model. To assess the consistency of effects across subgroups, subgroup-by-treatment interaction terms were added in the models. Analyses for safety were performed including all the patients who had received at least one dose of empagliflozin or placebo. Fixed-effect meta-analysis (inverse variance method) was performed for each outcome and for individual subgroups to generate pooled estimates for the effect of sodium–glucose cotransporter 2 inhibitors (SGLT2i) compared with placebo. Hazard ratios and 95% confidence intervals were used. Between-trial heterogeneity of treatment effect was assessed using the *I*<sup>2</sup> index and Cochran's *Q*-test. We tested treatment-by-subgroup heterogeneity of effect using Cochran's *Q*-test. Meta-analysis calculations were done using STATA (version 17.0).

All analyses (except the meta-analysis) were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). All *p*-values reported are two-sided, and *p* < 0.05 was considered as statistically significant in all cases. No adjustments for multiple testing were made.

## Results

Of the 5988 patients randomized, 1310 (21.9%) had BMI <25 kg/m<sup>2</sup>, 1986 (33.2%) had BMI 25 to <30 kg/m<sup>2</sup>, 1553 (25.9%) had BMI 30 to <35 kg/m<sup>2</sup>, 771 (12.9%) had BMI 35 to <40 kg/m<sup>2</sup>, and 368 (6.1%) had BMI ≥40 kg/m<sup>2</sup> at baseline. Thus, 45% were in the obese category at baseline.

Patients with higher BMIs were more likely to be younger, female, and White. Patients in higher BMI categories also tended to have worse New York Heart Association (NYHA) class, worse/lower KCCQ-CSS scores, higher rates of atrial fibrillation and diabetes mellitus, and higher LVEF and lower N-terminal pro-B-type natriuretic peptide concentrations (Table 1).

Empagliflozin consistently reduced the primary composite outcome of time to first HHF or CV death across baseline BMI categories, with no formal interaction (*p* trend = 0.19) (Figure 1). There were 148 patients with a baseline BMI <20 kg/m<sup>2</sup> and analyses of treatment effect on the primary endpoint by BMI as a continuous variable suggested consistent effects also in these lower ranges of BMI (data not shown). The effect of empagliflozin on eGFR slope was also consistent across BMI categories (*p* trend = 0.85; Figure 2), although there was no benefit on the composite renal endpoint, overall or in BMI subgroups (online

**Table 1** Baseline characteristics by body mass index categories

	<25 kg/m <sup>2</sup> (n = 1310)	25 to <30 kg/m <sup>2</sup> (n = 1986)	30 to <35 kg/m <sup>2</sup> (n = 1553)	35 to <40 kg/m <sup>2</sup> (n = 771)	≥40 kg/m <sup>2</sup> (n = 368)	p-value trend
Age, years	73.5 ± 10.1	72.9 ± 9.1	71.4 ± 8.9	69.8 ± 8.8	67.0 ± 9.8	<0.0001
BMI, kg/m <sup>2</sup>	22.54 ± 1.93	27.52 ± 1.43	32.28 ± 1.44	37.20 ± 1.40	42.61 ± 1.66	<0.0001
Female sex, n (%)	554 (42.3)	815 (41.0)	699 (45.0)	393 (51.0)	215 (58.4)	<0.0001
Race, n (%)						
White	723 (55.2)	1512 (76.1)	1307 (84.2)	684 (88.7)	316 (85.9)	<0.0001
Black/African American	52 (4.0)	68 (3.4)	79 (5.1)	34 (4.4)	25 (6.8)	
Asian	447 (34.1)	272 (13.7)	81 (5.2)	18 (2.3)	6 (1.6)	
Other including mixed races	87 (6.6)	133 (6.7)	86 (5.5)	35 (4.5)	21 (5.7)	
Missing	1 (0.1)	1 (0.1)	0	0	0	
NYHA class, n (%)						
II	1125 (85.9)	1689 (85.0)	1247 (80.3)	577 (74.8)	245 (66.6)	<0.0001
III	178 (13.6)	293 (14.8)	303 (19.5)	189 (24.5)	120 (32.6)	
IV	5 (0.4)	3 (0.2)	3 (0.2)	5 (0.6)	2 (0.5)	
KCCQ-CSS	76.94 ± 19.35	72.56 ± 20.09	68.77 ± 20.27	62.60 ± 22.23	59.19 ± 23.15	<0.0001
KCCQ-CSS, median (IQR)	81.25 (64.58, 93.23)	76.04 (59.38, 89.58)	70.83 (54.17, 85.42)	64.38 (45.31, 80.89)	61.98 (41.15, 77.34)	
Systolic blood pressure, mmHg	130.2 ± 15.9	131.3 ± 15.5	132.5 ± 15.3	133.2 ± 15.7	135.2 ± 15.8	<0.0001
Weight, kg	60.7 ± 9.4	75.7 ± 9.9	89.4 ± 11.9	102.2 ± 13.5	115.6 ± 16.3	<0.0001
LVEF, %	54.2 ± 9.0	53.9 ± 8.9	54.3 ± 8.7	55.1 ± 8.3	55.5 ± 8.5	0.0030
NT-proBNP, pg/ml, median (IQR)	1170 (601, 2111)	993 (506, 1773)	898 (467, 1608)	900 (427, 1534)	784 (438, 1356)	<0.0001 (based on log-transformed results)
eGFR, ml/min/1.73 m <sup>2</sup>	62.4 ± 20.1	60.7 ± 19.0	59.8 ± 19.7	58.6 ± 20.3	61.5 ± 22.3	0.0002
Medical history, n (%)						
Atrial fibrillation <sup>a</sup>	645 (49.2)	993 (50.0)	811 (52.2)	416 (54.0)	192 (52.2)	0.0191
Diabetes mellitus	461 (35.2)	894 (45.0)	853 (54.9)	488 (63.3)	242 (65.8)	<0.0001
Heart failure medication, n (%)						
ACEi/ARB/ARNI	942 (71.9)	1620 (81.6)	1304 (84.0)	653 (84.7)	313 (85.1)	<0.0001
Beta-blockers	1093 (83.4)	1694 (85.3)	1377 (88.7)	692 (89.8)	311 (84.5)	<0.0001
Mineralocorticoid receptor antagonists	506 (38.6)	727 (36.6)	583 (37.5)	288 (37.4)	140 (38.0)	0.7676
Loop or high ceiling diuretics	816 (62.3)	1276 (64.2)	1067 (68.7)	590 (76.5)	305 (82.9)	<0.0001

Data are mean ± standard deviation unless stated otherwise.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

<sup>a</sup>Defined as atrial fibrillation reported in any electrocardiogram before treatment intake or history of atrial fibrillation reported in medical history.

supplementary Table S7). Similarly, reduced hazard of total HHF seen in patients randomized to empagliflozin versus placebo was preserved across all BMI categories (*p* trend = 0.19).

Overall, an average weight loss of 1.3 kg from baseline to week 52 was observed with empagliflozin as compared with placebo. The difference of weight change between empagliflozin and placebo was −0.59, −1.48, −1.54, −0.87, and −2.67 kg in the lowest to highest BMI categories (Figure 3), with evidence of formal interaction (*p* trend = 0.016), suggesting greater weight loss at higher baseline BMI. Improvements in KCCQ-CSS were more consistent and clearer at higher BMIs than at lower BMIs (Figure 4), with *p* value for trend = 0.080 at 32 weeks. The frequency and incidence rates of adverse events are given in online supplementary Table S2. Overall, the number of empagliflozin patients reporting adverse events (AEs) were not higher compared to placebo in any BMI subgroup. With regard to AEs of special interest, there were slightly higher frequencies of renal failure and genital infections in the upper BMI categories. A higher incidence of genital infections with empagliflozin versus placebo was seen across most BMI categories.

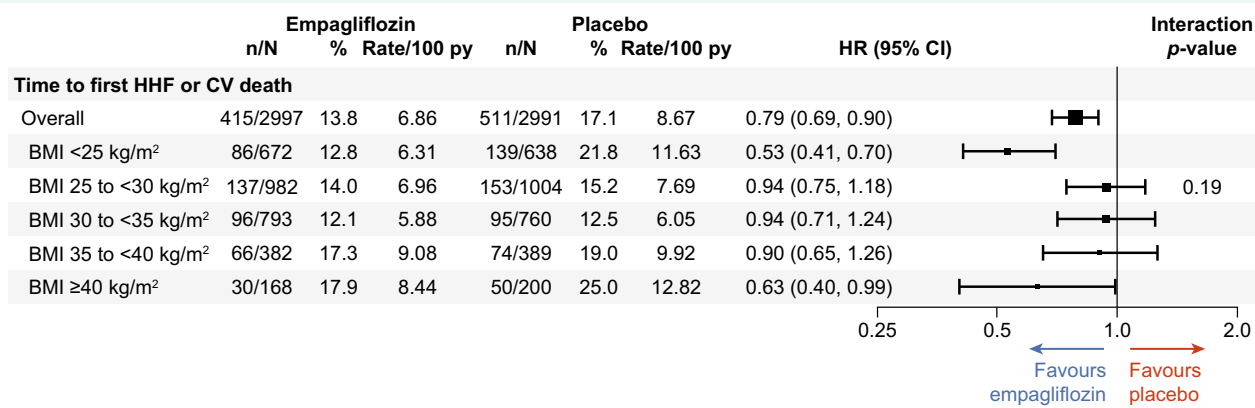
## Meta-analysis

Combining the primary outcome (time to first HHF or CV death) results by similar BMI categories across EMPEROR-Preserved

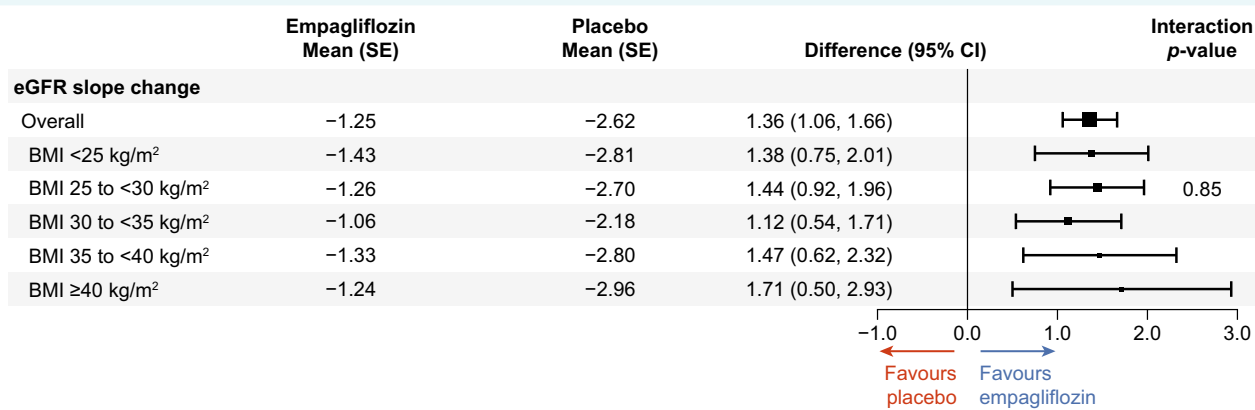
(*n* = 5988) and DELIVER (*n* = 6203) trials thereby lending more power, revealed point estimates below one (thus favouring SGLT2i) for all five categories (Figure 5). There was a low degree of heterogeneity in the meta-analysed estimates by BMI category (*I*<sup>2</sup> = 26.0%, *p* = 0.248).

## Discussion

In EMPEROR-Preserved, there was no significant interaction of BMI on the hazards of primary outcome of CV death or HHF, or on the secondary endpoints of total HHF, CV death, first HHF, first renal composite, or all-cause death with empagliflozin versus placebo in patients with HFpEF. The robustness of this conclusion was also supported by a meta-analysis of the primary outcome data with the DELIVER trial. In addition, no effect modification of BMI on eGFR slope was noted, though the relevance of this remains uncertain given eGFR slopes can be confounded, and there was no benefit on the composite renal outcome. There were no new safety findings and no clear evidence of different safety concerns by BMI categories. Weight loss with empagliflozin was also very modest (mean −0.41 kg) in those in the lowest baseline BMI category. Collectively, these data suggest that empagliflozin may be initiated in patients with HFpEF irrespective of BMI (Graphical Abstract).



**Figure 1** Effect of empagliflozin versus placebo on the primary endpoint by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI). CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; py, patient-year.



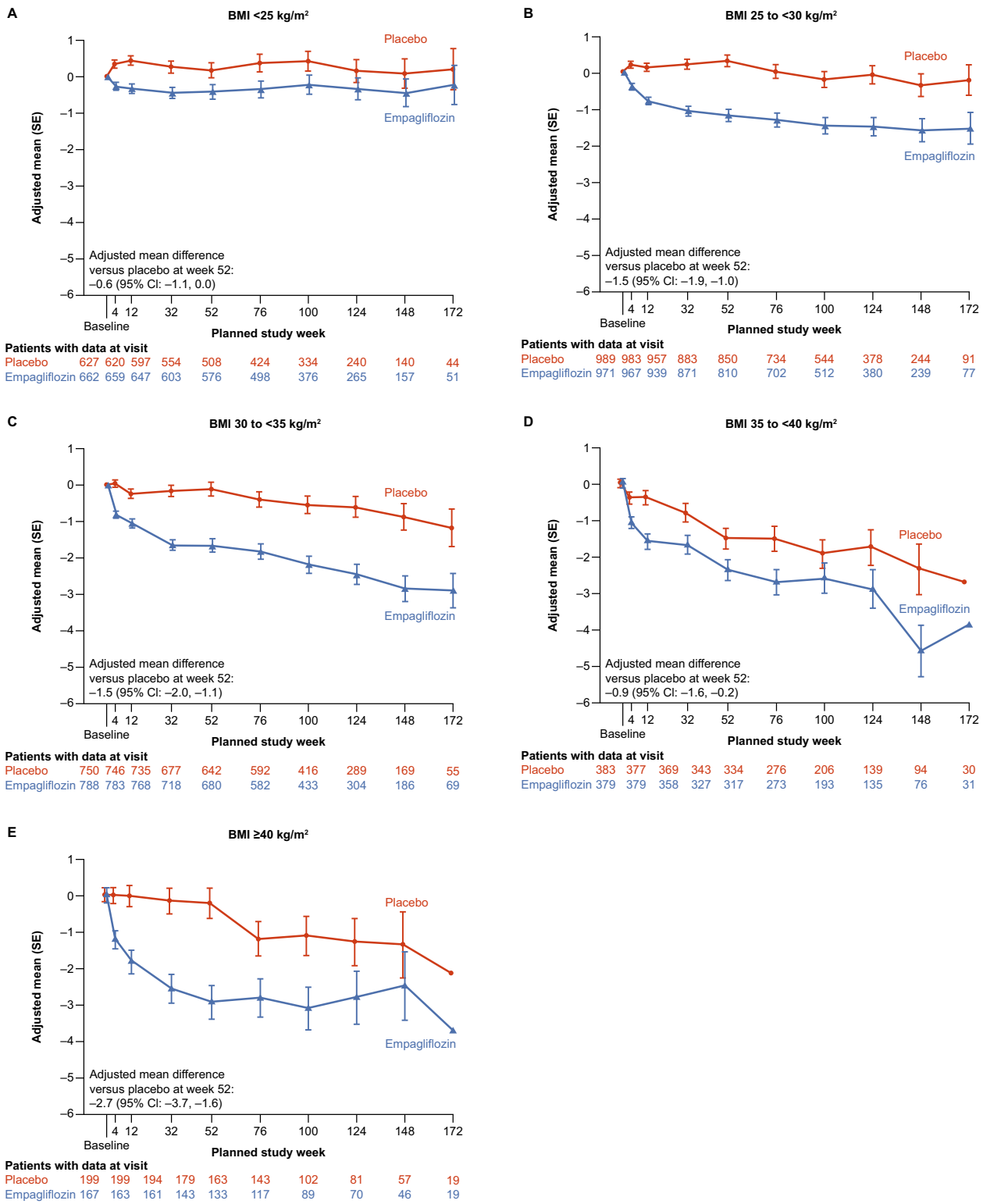
**Figure 2** Effect of empagliflozin versus placebo on estimated glomerular filtration rate (eGFR) slope by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI). SE, standard error.

Consistent with prior research, we noted that patients with higher BMI and HFpEF were significantly younger and more likely to be female.<sup>9,10</sup> In addition, patients with higher BMIs were also significantly more likely to have a higher NYHA class and significantly worse KCCQ score, findings similar to what has been reported elsewhere.<sup>9</sup> Also, patients randomized to empagliflozin who were overweight or obese had statistically more weight loss than patients randomized to placebo. Such results lend external validity to these new observations. Though absolute differences in weight were modest at ~1.3 kg, any effort to help support weight loss is likely to be meaningful to patients. Our results also suggest that absolute amount of weight lost was greatest for those in higher BMI categories, where weight loss is most likely to provide clinical benefit, and lowest in the lower BMI categories.

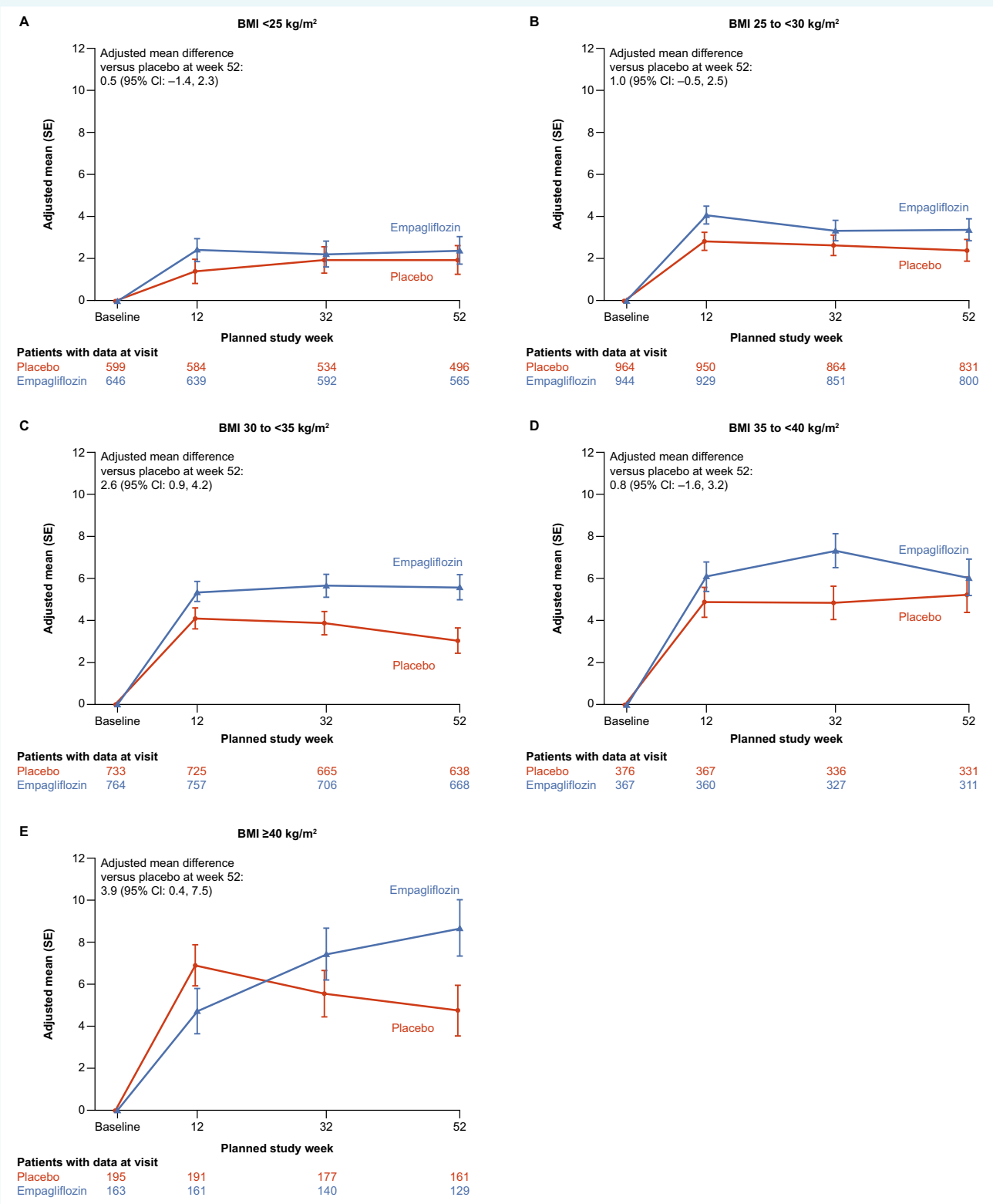
Visually, greatest benefit across many of the outcomes appeared to be for those with either normal (lowest) BMI category or severe obesity, but this is fundamentally confounded by extremely varying sample sizes and uneven power. The insignificant interaction p-value observed for each of these outcomes should reassure both

providers and patients that the benefits of empagliflozin are preserved across the spectrum of BMI. Furthermore, we find that this visual pattern is attenuated by the larger sample size achieved in a meta-analysis combining results from EMPEROR-Preserved with DELIVER across BMI category.

We did observe a trend toward larger improvements in KCCQ-CSS score with higher BMI at 32 weeks, with a p-value for trend=0.080. These data are broadly consistent with the DELIVER data where a significant interaction (p=0.03) was noted at 8 months for a similar analysis with KCCQ-TSS.<sup>8</sup> They also accord with a recent paper examining predictors of health status in EMPEROR-Preserved.<sup>11</sup> Thus, it appears patients with higher BMIs likely derive a larger absolute benefit in terms of KCCQ improvement. Prior literature<sup>12</sup> suggests patients living with both HFpEF and obesity and starting dapagliflozin experience meaningful improvements in KCCQ-CSS and KCCQ-TSS within 12 weeks: given the higher symptom burden experienced by those at higher BMIs, these observed improvements in KCCQ may be particularly relevant.



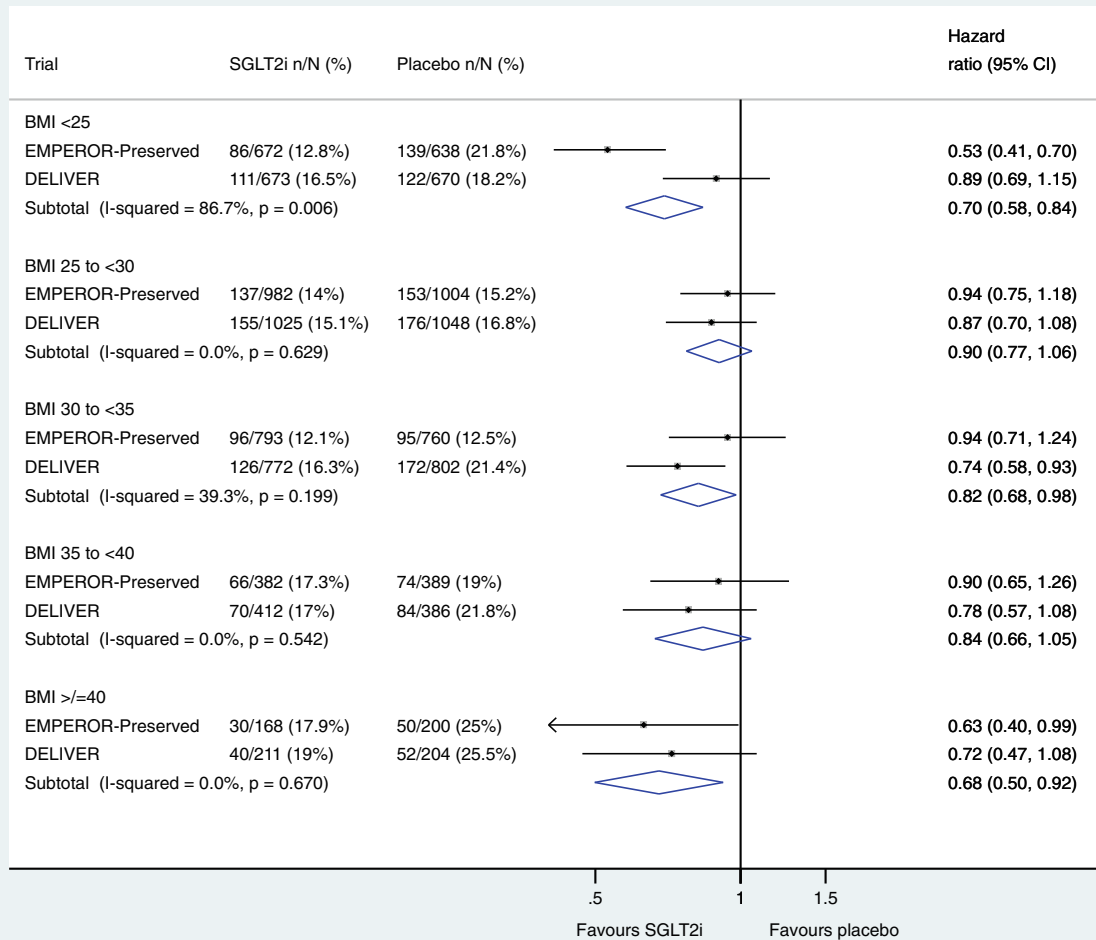
**Figure 3** (A–E) Change from baseline in body weight by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI) given at each time point as per the x-axis, as well as number of patients with data at each visit. Adjusted mean weight change in kg by treatment groups from baseline to week 52 (from lowest to highest BMI category) were as follows: 0.18 (P) and -0.41 (E), 0.29 (P) and -1.20 (E), -0.13 (P) and -1.67 (E), -1.50 (P) and -2.36 (E), -0.23 (P) and -2.90 (E). E, empagliflozin; P, placebo; SE, standard error.



**Figure 4** (A–E) Change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI) given at each time point as per the x-axis, as well as number of patients with data at each visit. SE, standard error.



### Risk of first HHF or CV death by BMI categories: fixed effects



**Figure 5** Meta-analysis of the primary outcome in EMPEROR-Preserved and DELIVER by baseline body mass index (BMI) categories. Point estimates and 95% confidence intervals (CI) with the meta-analysed estimate in the blue diamond. Subgroup interaction  $p = 0.25$ . HR, hazard ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Notably, in a meta-analysis of results across BMI category from both EMPEROR-Preserved and DELIVER, we find that the meta-analysed hazards of a composite of CV death or HHF is broadly consistent across BMI categories ( $I^2 = 26.0\%$ ,  $p = 0.248$ ; Figure 5). EMPEROR-Preserved also adds data on the consistent slowing of eGFR slopes across all BMI categories, though the relevance of this is uncertain given that there was no overall benefit on the first renal composite outcome in the trial, nor in subgroups. Even so, these BMI analyses in the two HFpEF trials suggest patients with either BMI  $<25 \text{ kg/m}^2$  or  $\geq 40 \text{ kg/m}^2$  benefit from SGLT2i just as well as do patients with BMI between these limits, with some evidence for greater absolute symptomatic benefits at higher BMI levels. This latter finding is interesting given recent notable symptomatic (KCCQ) benefits seen with semaglutide in

the STEP-HFpEF trial<sup>13</sup> where mean weight loss levels at 10.7% relative to placebo were greater than seen with SGLT2i in DELIVER or EMPEROR-Preserved, speculatively suggesting complementary mechanisms of action.

There are limitations to our analysis. EMPEROR-Preserved excluded patients with a BMI of  $\geq 45 \text{ kg/m}^2$ , limiting any evaluation of more extreme degrees of obesity. Similarly, very few underweight (BMI  $<18.5 \text{ kg/m}^2$ ) were enrolled. Perhaps most importantly, BMI is an incomplete measure of body composition,<sup>14</sup> and our analysis may therefore not capture the true impact of increasing degrees of adiposity on outcomes in this patient population. Nevertheless, BMI remains the most clinically used measure and as such these results do have clinical translation.

In conclusion, these data from EMPEROR-Preserved suggest that the SGLT2i empagliflozin is safe and effective across the

spectrum of BMI for patients with HFpEF. There was also suggestive evidence that patients living with obesity may derive larger absolute risk benefits in improved health status. These results and the meta-analysis of data with DELIVER further suggest there is no reason to withhold SGLT2i treatment in patients with HFpEF based on baseline BMI.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## Acknowledgements

The authors thank Liz Coyle, University of Glasgow, for her excellent assistance in the preparation of this article.

## Funding

The EMPEROR-Preserved trial (ClinicalTrials.gov: NCT03057951) was funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. Graphical support was provided by 7.4 Limited and Elevate Scientific Solutions and supported financially by Boehringer Ingelheim. N.S. acknowledges funding support from the British Heart Foundation Research Excellence Award (RE/18/6/34217). The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

**Conflict of interest:** N.S. reports personal fees from Abbott Laboratories, Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Menarini-Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and grants to his university from AstraZeneca, Boehringer Ingelheim, Novartis and Roche Diagnostics. J.B. reports consulting fees from Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd., and Vifor. M.M.Y.L. reports grants to his university from AstraZeneca, Boehringer Ingelheim and Roche Diagnostics; and committee member contributions in trials sponsored by Bayer and Cytokinetics. J.H. completed work for this while on T32 grant T32HL069749. A.S. is supported by CIHR grant # 451301, Fonds de Recherche Santé Quebec (FRSQ) Junior 1 clinician scholars program, Roche Diagnostics, Boehringer Ingelheim, Novartis, AstraZeneca, Novo Nordisk, Boston Scientific, BMS-Pfizer, Akcea, Janssen, Takeda, AREA19 (as advisor). F.Z. reports steering committee or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, Novo Nordisk, and Vifor Fresenius. G.F. reports lecture fees and/or committee member contributions in trials sponsored by Bayer, Medtronic, Vifor, Servier, Novartis, Amgen, and Boehringer Ingelheim; and research support from the European Union. S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge Translation Research Group, Eli Lilly, HLS Therapeutics, Janssen, Novartis, Novo Nordisk, Pfizer, PhaseBio, S & L Solutions Event Management Inc, and Sanofi; is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. J.L.J. is a Trustee of the American College of Cardiology, is a Director at Imbria

Pharmaceuticals, an Advisor at Jana Care; has received grant support from Abbott, Applied Therapeutics, HeartFlow Inc, Innolife and Roche Diagnostics, consulting income from Abbott, Janssen, Novartis, Merck, and Roche Diagnostics, and participates in clinical endpoint committees/data safety monitoring boards for Abbott, Abbvie, Bayer, CVRx, Intercept, Pfizer and Takeda. J.P.F. reports consulting fees from Boehringer Ingelheim; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). S.J.P. reports consulting fees and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Boehringer Ingelheim; and is a Trial Executive Committee member of Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). E.P., A.P.O., and M.B. are employees of Boehringer Ingelheim. M.P. reports consulting fees from Abbvie, Actavis, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Casana, CSL Behring, Cytokinetics, Johnson & Johnson, ELC, Moderna, Novartis, ParatusRx, Pfizer, Relypsa, Salamandra, Synthetic Biologics, and Theravance; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). S.D.A. reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Occlutech, Pfizer, Repairon, Sensible Medical, Servier, Vectorious, and V-Wave; named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents.

## References

1. Packer M. The conundrum of patients with obesity, exercise intolerance, elevated ventricular filling pressures and a measured ejection fraction in the normal range. *Eur J Heart Fail* 2019;**21**:156–162. <https://doi.org/10.1002/ehf.1377>
2. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385**:1451–1461. <https://doi.org/10.1056/NEJMoa2107038>
3. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al.; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620. <https://doi.org/10.1056/NEJMoa1908655>
4. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al.; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392. <https://doi.org/10.1056/NEJMoa1313731>
5. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al.; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–2467. <https://doi.org/10.1056/NEJMoa0805450>
6. Shah SJ, Borlaug BA, Kitzman DW, McCulloch AD, Blaxall BC, Agarwal R, et al. Research priorities for heart failure with preserved ejection fraction: National Heart, Lung, and Blood Institute Working Group summary. *Circulation* 2020;**141**:1001–1026. <https://doi.org/10.1161/CIRCULATIONAHA.119.041886>
7. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, et al. Quality of life in heart failure with preserved ejection fraction: Importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail* 2020;**22**:1009–1018. <https://doi.org/10.1002/ehf.1788>
8. Adamson C, Kondo T, Jhund PS, de Boer RA, Cabrera Honorio JW, Claggett B, et al. Dapagliflozin for heart failure according to body mass index: The DELIVER trial. *Eur Heart J* 2022;**43**:4406–4417. <https://doi.org/10.1093/eurheartj/ehac481>
9. Reddy YNV, Lewis GD, Shah SJ, Obokata M, Abou-Ezzedine OF, Fudim M, et al. Characterization of the obese phenotype of heart failure with preserved ejection fraction: A RELAX trial ancillary study. *Mayo Clin Proc* 2019;**94**:1199–1209. <https://doi.org/10.1016/j.mayocp.2018.11.037>

10. Savji N, Meijers WC, Bartz TM, Bhambhani V, Cushman M, Nayor M, et al. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *JACC Heart Fail* 2018;**6**:701–709. <https://doi.org/10.1016/j.jchf.2018.05.018>
11. Siddiqi TJ, Anker SD, Filippatos G, Ferreira JP, Pocock SJ, Böhm M, et al. Health status across major subgroups of patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2023;**25**:1623–1631. <https://doi.org/10.1002/fejhf.2831>
12. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. *Nat Med* 2021;**27**:1954–1960. <https://doi.org/10.1038/s41591-021-01536-x>
13. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al.; STEP-HFpEF Trial Committees and Investigators. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med* 2023;**389**:1069–1084. <https://doi.org/10.1056/NEJMoa2306963>
14. Rothman KJ. BMI-related errors in the measurement of obesity. *Int J Obes (Lond)* 2008;**32**:S56–S59. <https://doi.org/10.1038/ijo.2008.87>