Obesity is common in patients with HFpEF and is associated with higher rates of heart failure hospitalization and worse health status. Treatment with dapagliflozin improves cardiovascular outcomes across the spectrum of BMI, leads to greater symptom improvement in patients with obesity, compared with those without, and has the additional benefit of causing modest weight loss.

**Aims**

Body mass index was analysed by World Health Organization (WHO) categories and as a continuous variable using restricted cubic splines. Body mass index ranged from 15.2 to 50 kg/m² with a mean value of 29.8 (standard deviation ± 6.1) kg/m². The proportions, by WHO category, were: normal weight 1343 (21.5%); overweight 2073 (33.1%); Class I obesity 1574 (25.2%); Class II obesity 798 (12.8%); and Class III obesity 415 (6.6%). Compared with placebo, dapagliflozin reduced the risk of the primary outcome to a similar extent across these categories: hazard ratio (95% confidence interval): 0.89 (0.69–1.15), 0.87 (0.70–1.08), 0.74 (0.58–0.93), 0.78 (0.57–1.08), and 0.72 (0.47–1.08), respectively (P-interaction = 0.82). The placebo-corrected change in weight at 12 months was: –0.88 (0.69–1.15), 0.87 (0.70–1.08), 0.74 (0.58–0.93), 0.78 (0.57–1.08), and 0.72 (0.47–1.08), respectively (P-interaction = 0.82). The placebo-corrected change in Kansas City Cardiomyopathy Questionnaire total symptom score with dapagliflozin at 8 months was: –0.45 (–1.19, 0.30), 1.29 (0.80, 1.77), 1.42 (0.97, 1.87), and 2.84 (2.49, 3.19) points, respectively (P-interaction = 0.03). The placebo-corrected change in weight at 12 months was: –0.88 (–1.28, –0.47), –0.65 (–1.04, –0.26), –1.42 (–1.89, –0.94), –1.17 (–1.94, –0.40), and –2.50 (–4.4, –0.64) kg (P-interaction = 0.002).

**Conclusions**

Obesity is common in patients with HFpEF and is associated with higher rates of heart failure hospitalization and worse health status. Treatment with dapagliflozin improves cardiovascular outcomes across the spectrum of BMI, leads to greater symptom improvement in patients with obesity, compared with those without, and has the additional benefit of causing modest weight loss.

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**References**

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Consequently, many patients with heart failure with preserved ejection fraction (HFpEF) are obese, especially women and younger patients. What was the influence of body mass index (BMI) on symptoms and outcomes in the DELIVER trial and did it affect the benefits of dapagliflozin?

**Key Question**
Many patients with heart failure with preserved ejection fraction (HFpEF) are obese, especially women and younger patients. What was the influence of body mass index (BMI) on symptoms and outcomes in the DELIVER trial and did it affect the benefits of dapagliflozin?

**Key Finding**
Obesity (BMI >30.0 kg/m²) was common (45%) and associated with a higher risk of the primary composite outcome (worsening heart failure or cardiovascular death), although not mortality. The effect of dapagliflozin on the primary outcome was consistent across BMI categories (p interaction = 0.82), with a larger absolute effect in obese patients. KCCQ-TSS improved, and weight fell in all BMI categories; both effects were greater in more obese patients.

**Take Home Message**
Obesity is very common in contemporary patients with HFpEF. The efficacy and safety of dapagliflozin is consistent across the spectrum of BMI, with substantial absolute benefits in patients with obesity.

**Introduction**
Obesity is a risk factor for the development of heart failure (HF), especially HF with preserved ejection fraction (HFpEF), more so in women than men. Consequently, many patients with HF are obese and obesity is more often a concomitant problem in patients with HFpEF. Indeed, in the USA, >80% of patients with HFpEF are overweight or obese and in contemporary clinical trials, the proportion of HF patients with severe obesity [World Health Organization (WHO) Class III] is almost 20%. Obese patients generally have worse symptoms and greater functional limitations than their non-obese counterparts. Recent studies have highlighted several potential explanations for this, including a variety of...
systemic effects of inflammatory cytokines and other mediators secreted by adipose tissue, direct cardiac consequences such as pericardial restraint due to local deposition of adipose tissue, greater concentric left-ventricular remodelling and right-ventricular dilatation and dysfunction, and even renal dysfunction due to excess adipose tissue in and around the kidney.4,8–13 Consequently, finding treatments that are efficacious in HFrEF patients with concomitant obesity are important. Sodium-glucose cotransporter 2 (SGLT2) inhibitors may be a particularly attractive treatment in these patients, especially as obesity is part of a common triad which includes dysglycaemia and hypertension and SGLT2 inhibitors lead to modest reductions in weight, glycated haemoglobin, and blood pressure, in addition to their benefits on HF symptoms and outcomes.14–20

Therefore, the effect of SGLT2 inhibition was examined according to body mass index (BMI) in the Dapagliflozin Evaluation to Improve the LIVES of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial.19,21,22 DELIVER included 6263 patients with HF and mildly reduced and preserved ejection fraction and showed that dapagliflozin, compared with placebo, reduced the risk of worsening HF events or cardiovascular death, and improved symptoms.19,21

Methods

The DELIVER was a double-blind, placebo-controlled trial which examined the efficacy and safety of dapagliflozin 10 mg once daily compared with matched placebo in patients with HF and mildly reduced and preserved ejection fraction. Randomization was stratified by the presence or absence of Type 2 diabetes. The design, baseline characteristics, and primary results are published.19,21,22 The protocol was approved by an Ethics Committee at each participating centre and all patients provided written informed consent.

Study patients

Key inclusion criteria included age ≥40 years, HF diagnosis ≥6 weeks, and a requirement for treatment with at least intermittent diuretic, New York Heart Association (NYHA) functional Classes II–IV, left-ventricular ejection fraction (LVEF) >40%, evidence of structural heart disease (either left-atrial enlargement or left-ventricular hypertrophy), and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥300 pg/mL (≥600 pg/mL if atrial fibrillation/flutter on the electrocardiogram at enrolment). Patients could be enrolled in both the outpatient and inpatient setting. Patients were excluded if BMI was >50 kg/m². Other key exclusion criteria included Type 1 diabetes; estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m²; and systolic blood pressure <95 mmHg. A complete list of inclusion and exclusion criteria is provided in the design paper.21

Body mass index

Body mass index was calculated as weight in kilograms divided by height in meters squared, using measurements made at the trial enrolment visit. Patients categorized using WHO definitions, i.e. underweight (<18.5 kg/m²); normal weight (18.5–24.9 kg/m²); overweight (25.0–29.9 kg/m²); obesity Class I (30.0–34.9 kg/m²); obesity Class II (35.0–39.9 kg/m²), and obesity Class III (≥40 kg/m²).23

Outcomes

The primary outcome in DELIVER was the composite of time to the first occurrence of a worsening HF event (HF hospitalization or urgent outpatient HF visit requiring intravenous diuretic therapy) or cardiovascular death. The primary outcome was assessed in the full population and patients with an ejection fraction of <60% in a dual primary analysis. Secondary outcomes included in this analysis were the total number of worsening HF events (including first and recurrent events) and cardiovascular deaths; change in self-reported severity of HF symptoms at 8 months based on the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); worsening HF events, cardiovascular death, and all-cause death.

Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment, and selected adverse events, including volume depletion, renal adverse events, amputation, major hypoglycaemia, and diabetic ketoacidosis for consistency across reporting in trials. These analyses included only patients who had taken at least one dose of study medication.

Statistical analyses

Baseline characteristics are reported for each BMI category as means ± standard deviation (SD), median with interquartile range (IQR; Q1–Q3) and proportions, as appropriate. The Cochran–Armitage test was used to test-for-trend across groups for binary variables and the Jonckheere–Terpstra test for continuous variables.

The association between BMI category and each outcome, adjusted for randomized treatment, was compared between BMI groups in a Cox regression model with overweight as the reference. This was repeated with additional adjustments for age, sex, race, region, heart rate, systolic blood pressure, glycated haemoglobin (HbA1c), creatinine, history of HF hospitalization, NYHA class, LVEF, atrial fibrillation/flutter, hypertension, myocardial infarction, coronary artery bypass graft, stroke, and (log-transformed) NT-proBNP. The associations between BMI, as a continuous variable, and outcomes were modelled using restricted cubic splines with adjustment for randomized treatment with median population BMI as reference. The 5 knots were placed at default positions according to percentiles of BMI (5, 27.5, 50, 72.5, and 95 centile). This was repeated with the additional adjustments listed above, in both the whole population and in males and females separately.

The efficacy of dapagliflozin, compared with placebo, in each BMI category, was examined using Kaplan–Meier estimates and Cox regression models. Event rates per 100 person-years and hazard ratios (HRs) are reported for each BMI category (these and all other models were stratified by diabetes status). The presence of an interaction between BMI category and treatment on the occurrence of each outcome was examined using a likelihood ratio test. The effect of randomized treatment across baseline BMI as a continuous variable was modelled flexibly using restricted cubic splines with 3 knots (at 10th, 50th, and 90th percentile of BMI), in the whole population and subgroups of interest (males and females; LVEF <60 and ≥60; presence or absence of diabetes; and patients of White and Asian race). Analysis of recurrent events was by the Lin, Wei, Ying, and Yang method, a semi-parametric proportional-rates model.24 Mean change in KCCQ-TSS at 8 months was calculated using a mixed model for repeated measurements including all time points within each BMI category. A three-way interaction between treatment, time, and BMI was assessed in the mixed model at 8-month follow up.

A mixed model for repeated measurement was used to examine change in weight over time according to baseline BMI (adjusted for baseline values, randomized treatment, and interaction of treatment and visit, with a random intercept and slope per patient). A three-way interaction between treatment, time, and BMI was assessed at 12-month follow up.

The interaction between BMI category and randomized treatment on the occurrence of the safety outcomes was tested in a logistic regression model. All analyses were conducted using STATA version 17.0 (College Station, TX, USA).

Results

Of the 6263 patients randomized in DELIVER, 6 had missing data for BMI (Structured Graphical Abstract). Body mass index ranged from 15.2 to 50 kg/m² with a mean value of 29.8 (SD ± 6.1) kg/m² and a median value of 29.1 (Q1–Q3 25.4–33.4) kg/m² and an approximately normal
Table 1  Baseline characteristics according to body mass index category

|                         | Normal weight n = 1343 | Overweight n = 2073 | Obesity Class I n = 1574 | Obesity Class II n = 798 | Obesity Class III n = 415 | P-value |
|-------------------------|------------------------|---------------------|--------------------------|--------------------------|---------------------------|---------|
| **Age (years)**         | 73.3 ± 10.0            | 72.4 ± 9.5          | 71.4 ± 9.0               | 69.3 ± 9.1               | 67.8 ± 9.0                | <0.001  |
| **Female sex**          | 578 (43.0)             | 828 (39.9)          | 676 (42.9)               | 380 (47.6)               | 255 (61.4)                | <0.001  |
| **Race**                |                        |                     |                          |                          |                           | <0.001  |
| White                   | 587 (43.7)             | 1427 (68.8)         | 1333 (84.7)              | 711 (89.1)               | 362 (87.2)                |         |
| Asian                   | 633 (47.1)             | 453 (21.9)          | 119 (7.6)                | 24 (3.0)                 | 8 (1.9)                   |         |
| Black or African American| 24 (1.8)               | 47 (2.3)            | 32 (2.0)                 | 30 (3.8)                 | 25 (6.0)                  |         |
| Other                   | 99 (7.4)               | 146 (7.0)           | 90 (5.7)                 | 33 (4.1)                 | 20 (4.8)                  |         |
| **Smoking status**      |                        |                     |                          |                          |                           | 0.58    |
| Current                 | 115 (8.6)              | 158 (7.6)           | 116 (7.4)                | 65 (8.1)                 | 21 (5.1)                  |         |
| Former                  | 475 (35.4)             | 750 (36.2)          | 579 (36.8)               | 281 (35.2)               | 158 (38.1)                |         |
| Never                   | 753 (56.1)             | 1165 (56.2)         | 879 (55.8)               | 452 (56.6)               | 236 (56.9)                |         |
| **Vital signs**         |                        |                     |                          |                          |                           |         |
| Pulse (beats/min)       | 71.2 ± 12.1            | 70.9 ± 11.8         | 71.7 ± 11.2              | 72.4 ± 11.7              | 72.8 ± 12.0               | <0.001  |
| SBP (mmHg)              | 124.9 ± 15.6           | 127.8 ± 14.7        | 130.1 ± 14.7             | 130.6 ± 15.9             | 130.6 ± 16.1              | <0.001  |
| DBP (mmHg)              | 72.1 ± 10.4            | 73.5 ± 9.8          | 75.1 ± 10.1              | 75.6 ± 10.3              | 75.4 ± 11.9               | <0.001  |
| **Laboratory values**   |                        |                     |                          |                          |                           |         |
| HbA1c (%)               | 6.0 (5.6–6.5)          | 6.1 (5.7–6.8)       | 6.2 (5.8–7.1)            | 6.4 (5.9–7.6)            | 6.5 (5.9–7.7)             | <0.001  |
| Creatinine (μmol/L)     | 100.0 ± 30.4           | 102.4 ± 30.5        | 103.8 ± 31.4             | 105.1 ± 32.7             | 100.3 ± 30.8              | 0.01    |
| eGFR (mL/min/1.73 m²)    | 62.1 ± 19.4            | 61.2 ± 19.0         | 60.2 ± 18.5              | 60.0 ± 19.4              | 62.0 ± 20.6               | 0.03    |
| eGFR < 60 mL/min/1.73 m² (%) | 643 (47.9)          | 1004 (48.4)         | 786 (49.9)               | 405 (50.8)               | 201 (48.4)                | 0.28    |
| NT-proBNP (ng/L)        | 1155.0 (667.0–2055.0)  | 1014.0 (623.0–1764.0)| 981.0 (616.0–1690.0)    | 934.5 (601.0–1524.0)     | 862.0 (539.0–1311.0)      | <0.001  |
| NT-proBNP (ng/L) if baseline ECG in AF/flutter | 1606.0 (1100.0–2573.0) | 1447.0 (996.0–2311.0)| 1404.5 (956.0–2155.0)    | 1242.0 (865.0–1974.0)     | 1108.0 (865.0–1616.0)     | <0.001  |
| NT-proBNP (ng/L) if baseline ECG not in AF/flutter | 810.0 (497.0–1580.0) | 757.0 (492.0–1308.0)| 663.0 (447.0–1182.0)    | 627.0 (433.5–1154.0)     | 612.0 (426.0–936.0)      | <0.001  |
| **Heart failure characteristics** |                      |                     |                          |                          |                           |         |
| Prior HF hospitalization | 586 (43.6)             | 817 (39.4)          | 625 (39.7)               | 309 (38.7)               | 173 (41.7)                | 0.10    |
| NYHA class              |                        |                     |                          |                          |                           | <0.001  |
| II                      | 1064 (79.2)            | 1633 (78.8)         | 1160 (73.7)              | 560 (70.2)               | 245 (59.0)                |         |
| IIVIV                   | 279 (20.8)             | 439 (21.2)          | 414 (26.3)               | 238 (29.8)               | 170 (41.0)                |         |

Continued
|               | Normal weight | Overweight | Obesity Class I | Obesity Class II | Obesity Class III | P-value |
|---------------|---------------|------------|----------------|------------------|-------------------|---------|
| n = 1343      |               | n = 2073   | n = 1574       | n = 798          | n = 415           |         |
| KCCQ-TSS      | 80.2 (62.5–93.8) | 75.0 (59.4–89.6) | 69.8 (54.2–84.4) | 66.7 (50.0–83.3) | 58.3 (38.5–72.9) | <0.001  |
| Baseline LVEF (%) | 53.0 (46.0–60.0) | 53.0 (46.0–60.0) | 54.0 (47.0–60.0) | 55.0 (47.0–60.0) | 55.0 (49.0–60.0) | 0.02    |

**Clinical history**

|                   | Normal weight | Overweight | Obesity Class I | Obesity Class II | Obesity Class III | P-value |
|-------------------|---------------|------------|----------------|------------------|-------------------|---------|
| T2DM              | 421 (31.3)    | 885 (42.7) | 782 (49.7)     | 463 (58.0)       | 240 (57.8)        | <0.001  |
| Atrial fibrillation | 720 (53.6)   | 1060 (51.1) | 929 (59.0)   | 486 (60.9)       | 235 (56.6)        | <0.001  |
| Hypertension      | 1071 (79.7)   | 1812 (87.4) | 1474 (93.6)  | 750 (94.0)       | 398 (95.9)        | <0.001  |
| Myocardial infarction | 344 (25.6) | 635 (30.6) | 398 (25.3) | 180 (22.6) | 71 (17.1) | <0.001 |
| CABG              | 126 (9.4)     | 283 (13.7)  | 207 (13.2)    | 89 (11.2)        | 37 (8.9)          | 0.97    |
| Stroke            | 147 (10.9)    | 220 (10.6)  | 140 (8.9)     | 66 (8.3)         | 22 (5.3)          | <0.001  |

**Medical therapy**

|                   | Normal weight | Overweight | Obesity Class I | Obesity Class II | Obesity Class III | P-value |
|-------------------|---------------|------------|----------------|------------------|-------------------|---------|
| Beta-blocker      | 1033 (77.0)   | 1694 (81.7) | 1353 (86.0)   | 699 (87.6)       | 352 (84.8)        | <0.001  |
| Calcium channel blockers | 353 (26.3) | 594 (28.7) | 491 (31.2) | 313 (39.2) | 150 (36.1) | <0.001 |
| ACEi, ARB, or ARNI | 941 (70.2)    | 1594 (76.9) | 1289 (81.9)  | 644 (80.7)       | 329 (79.3)        | <0.001  |
| Mineralocorticoid receptor antagonist | 618 (46.1) | 869 (41.9) | 679 (43.1) | 308 (38.6) | 167 (40.2) | 0.004  |
| Loop diuretics    | 980 (73.1)    | 1513 (73.0) | 1227 (78.0)  | 674 (84.5)       | 373 (89.9)        | <0.001  |
| Other (non-loop) diuretics | 243 (18.1) | 448 (21.6) | 356 (22.6) | 189 (23.7) | 95 (22.9) | 0.003  |

Data are presented as mean±SD or median (IQR) for continuous measures, and n (%) for categorical measures.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire—Total Symptom Score; LVEF, left-ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2DM, Type 2 diabetes mellitus.
distribution (see Supplementary material online, Figure S1). In total, 54 (0.9%) patients were classified as underweight, 1343 (21.5%) as normal weight, 2073 (33.1%) as overweight, 1574 (25.2%) as Class I obesity, 798 (12.8%) as Class II obesity, and 415 (6.6%) as Class III obesity. Due to the small number of patients in the underweight category, these participants were not included in the main results but are presented in the Supplementary material online, Tables S1–S4.

Patient characteristics
Baseline characteristics according to BMI class are presented in Table 1. Compared with patients with normal BMI, those with obesity were younger, more often female and more likely to be white (and less likely to be of Asian race). They had higher systolic and diastolic blood pressure, a higher HbA1c and were more likely to have a diagnosis of Type 2 diabetes than patients with a normal weight. There was an inverse association between BMI and NT-proBNP with the lowest level of NT-proBNP in Class III obesity—862 (IQR 539–1311) ng/L compared with 1155 (IQR 667–2055) ng/L in patients in the normal weight category. A higher proportion of patients with obesity were in NYHA Class III or IV and patients with obesity had lower (worse) KCCQ-TSS. Patients with higher BMI had a higher mean LVEF compared with those with normal weight. Patients with greater obesity had more hypertension but less coronary heart disease. Patients with obesity were more often treated with a beta-blocker, renin–angiotensin system blocker, calcium channel blocker, and a loop diuretic, but were less often treated with a mineralocorticoid receptor antagonist.

Outcomes according to body mass index
There was a J-shaped relationship between BMI categories and the crude (unadjusted) incidence of the primary outcome and worsening HF events.

### Table 2  Outcomes according to body mass index category

|                          | Normal weight (n = 1343) | Overweight (n = 2073) | Obesity Class I (n = 1574) | Obesity Class II (n = 798) | Obesity Class III (n = 415) |
|--------------------------|-------------------------|-----------------------|---------------------------|---------------------------|----------------------------|
| Primary outcome          |                         |                       |                           |                           |                            |
| N (%)                    | 233 (17.4)              | 331 (16.0)            | 298 (18.9)                | 154 (19.3)                | 92 (22.2)                  |
| Rate (95% CI)            | 8.7 (7.6–9.9)           | 7.7 (6.9–8.6)         | 9.1 (8.1–10.2)            | 9.2 (7.9–10.8)            | 11.0 (9.0–13.6)            |
| Unadjusted (95% CI)*     | 1.17 (0.99–1.38)        | REF                   | 1.16 (0.99–1.36)          | 1.15 (0.95–1.39)          | 1.37 (1.09–1.73)           |
| Additional adjustmentb (95% CI) | 1.12 (0.94–1.34)   | REF                   | 1.21 (1.03–1.43)          | 1.26 (1.03–1.54)          | 1.68 (1.32–2.15)           |
| Worsening heart failure event |                       |                       |                           |                           |                            |
| N (%)                    | 163 (12.1)              | 227 (11.0)            | 234 (14.9)                | 122 (15.3)                | 72 (17.4)                  |
| Rate (95% CI)            | 6.1 (5.2–7.1)           | 5.3 (4.6–6.0)         | 7.1 (6.3–8.1)             | 7.3 (6.1–8.7)             | 8.6 (6.9–10.9)             |
| Unadjusted (95% CI)*     | 1.19 (0.97–1.45)        | REF                   | 1.33 (1.11–1.60)          | 1.34 (1.07–1.67)          | 1.57 (1.20–2.04)           |
| Additional adjustmentb (95% CI) | 1.07 (0.86–1.32)   | REF                   | 1.42 (1.17–1.71)          | 1.48 (1.18–1.87)          | 1.94 (1.47–2.57)           |
| Cardiovascular death     |                         |                       |                           |                           |                            |
| N (%)                    | 125 (9.3)               | 149 (7.2)             | 110 (7.0)                 | 67 (8.4)                  | 29 (7.0)                   |
| Rate (95% CI)            | 4.4 (3.7–5.2)           | 3.3 (2.8–3.8)         | 3.1 (2.6–3.7)             | 3.7 (2.9–4.7)             | 3.1 (2.2–4.5)              |
| Unadjusted (95% CI)*     | 1.39 (1.09–1.76)        | REF                   | 0.93 (0.72–1.19)          | 1.09 (0.81–1.45)          | 0.92 (0.62–1.38)           |
| Additional adjustmentb (95% CI) | 1.48 (1.15–1.90)   | REF                   | 0.98 (0.76–1.26)          | 1.27 (0.94–1.71)          | 1.25 (0.82–1.89)           |
| All-cause death          |                         |                       |                           |                           |                            |
| N (%)                    | 239 (17.8)              | 325 (15.7)            | 255 (16.2)                | 125 (15.7)                | 63 (15.2)                  |
| Rate (95% CI)            | 8.4 (7.4–9.5)           | 7.1 (6.4–7.9)         | 7.2 (6.3–8.1)             | 6.8 (5.7–8.2)             | 6.8 (5.3–8.7)              |
| Unadjusted (95% CI)*     | 1.29 (1.02–1.43)        | REF                   | 0.99 (0.84–1.16)          | 0.93 (0.75–1.14)          | 0.92 (0.70–1.20)           |
| Additional adjustmentb (95% CI) | 1.29 (1.08–1.54)   | REF                   | 1.03 (0.87–1.21)          | 1.05 (0.85–1.30)          | 1.21 (0.92–1.61)           |
| Total heart failure hospitalizations and cardiovascular deaths |                      |                       |                           |                           |                            |
| No                       | 385                     | 511                   | 514                        | 283                       | 155                        |
| Rate (95% CI)            | 13.6 (11.7–15.8)        | 11.2 (9.9–12.8)       | 14.5 (12.6–16.8)          | 15.6 (12.9–18.9)          | 16.8 (13.4–21.3)           |
| Unadjusted (95% CI)*     | 1.25 (1.02–1.53)        | REF                   | 1.26 (1.04–1.53)          | 1.33 (1.05–1.67)          | 1.42 (1.09–1.85)           |
| Additional adjustmentb (95% CI) | 1.14 (0.94–1.39)   | REF                   | 1.35 (1.11–1.64)          | 1.52 (1.21–1.91)          | 1.83 (1.38–2.41)           |

Rates are given per 100 patient-years.

*Baseline model adjusted for randomized treatment and stratified by diabetes status.

Age, sex, race, region, heart rate, systolic blood pressure, HbA1c, creatinine, history of heart failure hospitalization, NYHA class, LV ejection fraction, atrial fibrillation, hypertension, MI, CABG, stroke, NT-proBNP (log-transformed).
The crude incidence of both outcomes was lowest in the overweight category and increased with increasing BMI category above this, driven by an increasing incidence of worsening HF events (Table 2, Figures 1 and 2). The relationship between BMI category and cardiovascular and all-cause death was different, with the lowest crude rates among patients with Class III obesity (Table 2, Figures 1 and 2). Examination of BMI as a continuous variable confirmed these patterns.

Adjustment for prognostically important variables, including NT-proBNP, did not fundamentally alter the patterns observed in the unadjusted categorical or continuous analyses described above (Table 2 and Figure 2).

Repeating this analysis in males and females separately showed the nadir in risk for the primary endpoint and HF hospitalization occurred at a slightly lower BMI in men compared with women (see Supplementary material online, Figure S2). There was no difference between sexes for mortality outcomes.

**Effects of dapagliflozin on clinical outcomes according to body mass index**

The HR for the primary outcome was 0.82 [95% confidence interval (CI) 0.73–0.92] in the full population and 0.83 (95% CI 0.73–0.95) in the <60% ejection fraction subgroup. Dapagliflozin reduced the risk of the primary outcome to a similar extent across BMI categories: HR (95% CI) 0.89 (0.69–1.15) for normal weight, 0.87 (0.70–1.08) for overweight; 0.74 (0.58–0.93) for obesity Class I, 0.78 (0.57–1.08) for obesity Class II, and 0.72 (0.47–1.08) for obesity Class III (P-interaction = 0.82; Table 3). Examined as a continuous variable, there was no significant interaction between BMI and randomized treatment on the primary outcome (P-interaction = 0.68; Figure 3). Results in the subgroup of patients with ejection fraction <60% were consistent with that of the full population (see Supplementary material online, Table S5 and Figure S3).

The effects of dapagliflozin on the other outcomes (cardiovascular death, a worsening HF event, all-cause mortality, total HF events, and cardiovascular death) were also consistent across BMI categories (P for interaction for all outcomes ≥0.4; Table 3). The results were also consistent when BMI was modelled as a continuous variable (P for interaction all ≥0.2; Figure 3). There was no treatment-by-sex-by-BMI interaction (P = 0.76 for the primary endpoint). The effect of treatment in men and women separately is shown in Supplementary material online, Figure S4 and of other subgroups of interest in Supplementary material online, Figure S5, with no significant variation of treatment effect by BMI in these subgroups.
Change in KCCQ-TSS according to baseline body mass index

Overall, 5,792 patients (93%) had KCCQ-TSS recorded at baseline, and 4,485 (71.7%) had a measurement at 8 months (219 missing due to death). The improvement in KCCQ-TSS at 8 months with dapagliflozin, compared with placebo, was greater in patients with higher BMI: placebo-corrected change 0.9 (−1.1, 2.8), 2.5 (0.8, 4.1), 1.9 (−0.1, 3.8), 2.7 (−0.5, 5.8), and 8.6 (4.0, 13.2) points, in normal weight, overweight, Class I obesity, Class II obesity, and Class III obesity, respectively (P-interaction = 0.03; Table 3 and Structured Graphical Abstract).

Change in weight according to baseline body mass index

Patients with a higher baseline BMI lost a greater amount of weight (at 12 months) with dapagliflozin. The placebo-corrected weight loss with dapagliflozin was: normal weight −0.88 (−1.28, −0.47) kg; overweight −0.65 (−1.04, −0.26) kg; Class I obesity −1.42 (−1.89, −0.94) kg; Class II obesity −1.17 (−1.94, −0.40) kg; and Class III obesity −2.5 (−4.4, −0.64) kg (P for interaction = 0.002).

Safety analyses

There was no significant interaction between BMI categories and the occurrence of adverse events according to randomized treatment (Table 4).

Discussion

The key finding of this study was that dapagliflozin was equally efficacious in reducing the primary composite outcome of worsening HF or cardiovascular death across the spectrum of BMI in DELIVER, including among participants who were obese. Treatment with dapagliflozin also led to an improvement in symptoms measured with the KCCQ-TSS and which was greater in patients with a higher BMI. In addition, dapagliflozin treatment led to a modest but significantly larger reduction in weight in more obese patients than others.

In keeping with epidemiological observations, 45% of participants in this study were found to be obese and 78% were obese or overweight, despite the exclusion of patients with a BMI >50 kg/m². As expected, the prevalence of diabetes and history of hypertension were higher (as was blood pressure) in patients with obesity. Participants with obesity had less evidence of coronary disease, which might also appear paradoxical but has been described previously and may reflect their younger age and the higher proportion of women. The association between higher BMI and lower NT-proBNP was confirmed and LVEF tended to be higher in participants with a higher BMI. Notably, patients with obesity had worse NYHA class, with almost twice as many in functional Class III or IV compared with participants with a normal weight. This was mirrored in self-reported symptoms and health-related quality of
life, with a striking difference of over 20 points between patients with Class III obesity, compared with a normal weight, at baseline.

Regarding clinical outcomes during follow up, a ‘U-’ or ‘J-shaped’ relationship was found between BMI and mortality in patients with HFpEF (as in HF with reduced ejection fraction) with the nadir in crude risk among patients with Class I obesity (BMI range 30.0–34.9 kg/m²) and the highest risk of death in patients who were normal or underweight (although there were very few patients in the latter category).

Interestingly, the pattern was different for worsening HF, where risk increased with increasing obesity, and was highest in patients with Class II/III obesity. Why the relationships between BMI and fatal, compared with non-fatal, outcomes diverged in this way is uncertain. The well-known, but poorly understood association between higher BMI and lower natriuretic peptides is a confounding factor relevant to these findings and in a fully adjusted analysis, including NT-proBNP, the association of obesity with lower mortality was eliminated. By contrast, the association with higher rates of worsening HF were not, possibly because the relationship between natriuretic peptides and plasma volume in patients with obesity may be different than in non-obese patients (obesity, unusually, is associated with low natriuretic peptide levels despite a greater expansion of plasma volume and higher filling pressures, especially during exercise).28

Dapagliflozin reduced the risk of the primary composite endpoint (worsening HF or cardiovascular death), with no interaction between the effect of treatment and BMI, examined as either a categorical or continuous variable, for this or any other outcome. Conservatively, applying the HR for the trial overall to each BMI category gave an NNT for the primary outcome in patients with Class III obesity of only 22 (over the median DELIVER follow up of 2.3 years), compared with 31 in patients with a normal weight, indicating a greater absolute benefit in obese individuals because of their higher absolute risk of this outcome.

As described above, patients with greater obesity had markedly worse health status at baseline and, importantly, this was improved following randomization to dapagliflozin. Indeed, the improvement in KCCQ-TSS was greatest in patients with the highest BMI. This finding is consistent with the hypothesis that the results of the PRESERVED-HF were more positive than EMPERIAL-Preserved because of the much higher prevalence of obesity in the former trial.29,30

While the main reason to use SGLT2 inhibitors in HFpEF is to improve symptoms and reduce worsening HF, their modest weight-reducing effect may be a useful additional attribute in patients with obesity. By increasing urinary excretion of glucose and calories, these agents have been shown to reduce weight in a range of patient populations, including patients with HF.14,15,27 The overall weight reduction at 12 months in DELIVER was just over 1 kg, slightly larger than in dapagliflozin and prevention of adverse outcomes in heart failure (DAPA-HF).27 The reduction in DELIVER was greater in patients with a higher BMI; the most obese participants with nearly three times the loss of those who had a normal weight (2.5 vs. 0.88 kg). Although modest, this additional benefit of SGLT2 inhibition may augment other strategies to reduce weight in HFpEF patients with obesity. One example is caloric restriction and aerobic exercise training which was shown to lead to a larger decrease in weight, and improvement in peak oxygen consumption but no consistent improvement in health-related quality of life.31,32 Glucagon-like peptide-1 receptor agonists and related treatments are currently under investigation as weight-loss treatments in HFpEF patients with obesity (www.ClinicalTrials.gov, NCT04788511, NCT04847557, and NCT04916470).

As with similar reports, our study had some limitations. Body mass index does not take into account the location of body fat or its amount,
| Table 3  | Effect of randomized treatment on outcomes according to body mass index category |
|----------|--------------------------------------------------------------------------------|
| Overall (n = 6263) | Normal weight (n = 1343) | Overweight (n = 2073) | Obesity Class I (n = 1574) | Obesity Class II (n = 798) | Obesity Class III (n = 415) | P-int |
| | Placebo | Dapagliflozin | Placebo | Dapagliflozin | Placebo | Dapagliflozin | Placebo | Dapagliflozin | Placebo | Dapagliflozin | Placebo | Dapagliflozin | Placebo | Dapagliflozin |
| n | 3132 | 3131 | 670 | 673 | 1048 | 1025 | 802 | 772 | 386 | 412 | 204 | 211 |
| Primary endpoint | | | | | | | | | | | | | | | |
| N (%) | 610 (19.5) | 512 (16.4) | 122 (18.2) | 111 (16.5) | 176 (16.8) | 155 (15.1) | 172 (21.5) | 126 (16.3) | 84 (21.8) | 70 (17.0) | 32 (25.5) | 40 (19.0) |
| Rate (95% CI) | 9.6 (8.9–10.4) | 7.8 (7.2–8.5) | 9.2 (7.7–11.0) | 8.2 (6.8–9.9) | 8.2 (7.1–9.5) | 7.2 (6.1–8.4) | 10.5 (9.0–12.2) | 7.7 (6.5–9.2) | 10.3 (8.3–12.8) | 8.2 (6.5–10.3) | 13.2 (10.0–17.3) | 9.1 (6.7–12.5) |
| HR | 0.82 (0.73–0.92) | 0.89 (0.69–1.15) | 0.87 (0.70–1.08) | 0.74 (0.58–0.93) | 0.78 (0.57–1.08) | 0.72 (0.47–1.08) | 0.82 (0.73–0.92) | 0.89 (0.69–1.15) | 0.87 (0.70–1.08) | 0.74 (0.58–0.93) | 0.78 (0.57–1.08) | 0.72 (0.47–1.08) |
| Worsening heart failure event | | | | | | | | | | | | | | | |
| N (%) | 455 (14.5) | 368 (11.8) | 83 (12.4) | 80 (11.9) | 126 (12.0) | 101 (9.9) | 136 (17.0) | 98 (12.7) | 66 (17.1) | 56 (13.6) | 43 (21.1) | 29 (13.7) |
| Rate (95% CI) | 7.2 (6.5–7.8) | 5.6 (5.1–6.2) | 6.3 (5.0–7.8) | 5.9 (4.7–7.3) | 5.9 (5.0–7.0) | 4.7 (3.8–5.7) | 8.3 (7.0–9.8) | 6.0 (4.9–7.3) | 8.1 (6.4–10.3) | 6.5 (5.0–8.5) | 10.9 (8.1–14.7) | 6.6 (4.6–9.5) |
| HR | 0.79 (0.69–0.91) | 0.94 (0.69–1.28) | 0.79 (0.61–1.03) | 0.72 (0.56–0.94) | 0.80 (0.56–1.14) | 0.63 (0.39–1.00) | 0.66 (0.56–0.74) | 0.88 (0.74–1.05) | 0.88 (0.62–1.25) | 0.84 (0.61–1.16) | 0.75 (0.52–1.10) | 1.00 (0.62–1.61) |
| Cardiovascular death | | | | | | | | | | | | | | | |
| N (%) | 261 (8.3) | 231 (7.4) | 66 (9.9) | 59 (8.8) | 81 (7.7) | 68 (6.6) | 64 (8.0) | 46 (6.0) | 33 (8.6) | 34 (8.3) | 13 (6.4) | 16 (7.6) |
| Rate (95% CI) | 3.8 (3.3–4.3) | 3.3 (2.9–3.8) | 4.1 (3.2–5.3) | 3.5 (2.8–4.4) | 3.0 (2.4–3.8) | 3.5 (2.8–4.5) | 2.6 (2.0–3.5) | 3.7 (2.6–5.1) | 3.7 (2.6–5.1) | 2.9 (1.7–5.0) | 3.3 (2.0–5.5) |
| HR | 0.79 (0.69–0.91) | 0.94 (0.69–1.28) | 0.79 (0.61–1.03) | 0.72 (0.56–0.94) | 0.80 (0.56–1.14) | 0.63 (0.39–1.00) | 0.66 (0.56–0.74) |
| All-cause death | | | | | | | | | | | | | | | |
| N (%) | 526 (16.8) | 497 (15.9) | 126 (18.8) | 113 (16.8) | 171 (16.3) | 154 (15.0) | 134 (16.7) | 121 (15.7) | 58 (15.0) | 67 (16.3) | 31 (15.2) | 32 (15.2) |
| Rate (95% CI) | 7.6 (9.7–8.3) | 7.2 (6.6–7.8) | 8.9 (7.5–10.6) | 7.9 (6.5–9.5) | 7.4 (6.4–8.6) | 6.8 (5.8–8.0) | 7.4 (6.2–8.7) | 6.9 (5.8–8.3) | 6.4 (5.0–8.3) | 7.2 (5.7–9.2) | 6.8 (4.8–7.9) |
| HR | 0.94 (0.83–1.07) | 0.88 (0.69–1.14) | 0.91 (0.73–1.13) | 0.94 (0.74–1.20) | 1.00 (0.79–1.60) | 0.97 (0.59–1.60) |
| Total heart failure hospitalizations and cardiovascular deaths | | | | | | | | | | | | | | | |
| N (%) | 1057 | 815 | 198 | 187 | 288 | 223 | 323 | 191 | 154 | 129 | 89 | 66 |
| Rate (95% CI) | 15.3 (13.9–16.9) | 11.8 (10.7–13.1) | 14.0 (11.4–17.5) | 13.1 (10.6–16.3) | 126 (10.6–15.1) | 99 (82–12.0) | 178 (14.6–21.9) | 110 (9.1–13.4) | 172 (13.5–22.2) | 140 (10.5–19.1) | 19.8 (14.8–27.1) | 13.9 (9.8–20.4) |
| Rate ratio | 0.77 (0.67–0.89) | 0.93 (0.69–1.25) | 0.78 (0.60–1.01) | 0.62 (0.47–0.82) | 0.80 (0.55–1.18) | 0.71 (0.45–1.12) |
| KCCQ-TSS | | | | | | | | | | | | | | | |
| Mean change in KCCQ at 8 m | 5.6 | 7.9 (7.2–8.6) | 3.9 | 4.8 (3.5–6.2) | 5.6 (4.4–6.7) | 8.0 (6.9–9.2) | 6.1 (4.7–7.5) | 8.0 (6.6–9.4) | 7.2 (5.0–9.5) | 9.9 (7.7–12.1) | 5.9 (2.6–9.1) |
| Placebo-corrected change at 8 m | 2.4 (1.4, 3.4) | 0.9 (−1.1, 2.8) | 2.5 (0.8, 4.1) | 1.9 (−0.1, 3.8) | 2.7 (−0.5, 5.8) | 8.6 (4.0, 13.2) |

Rates are given per 100 patient-years.

Full trial population, including the six patients with missing BMI at baseline.

Mixed-effect models for repeated measurements adjusted for baseline value, visit (Months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.
Therefore, the conventional definition of obesity based on this metric may not account for these differences across populations, although our models were adjusted for race and region. Patients with extreme obesity (a BMI >50 kg/m²) were excluded and only 54 patients who were ‘underweight’ were enrolled, precluding any meaningful analysis, although this is a rare group of patients, at least in most countries.

### Conclusion

In conclusion, the benefit of dapagliflozin on clinical outcomes was consistent across the spectrum of BMI in DELIVER, without any safety concerns. Treatment with dapagliflozin led to an improvement in symptoms and a modest reduction in weight, both of which were amplified in patients with a higher BMI.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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### Conflict of interest

T.K. received speaker fees from Abbott, Ono Pharma, Otsuka Pharma, Novartis, AstraZeneca, Bristol-Myers Squibb, and Abiomed. P.S.J.’s employer the University of Glasgow has been remunerated by AstraZeneca for working on the DAPA-HF and DELIVER trials, personal fees from Novartis and Cytokinetics, and grants from Boehringer Ingelheim. R.A.B.’s institution, the UMCG, has received research grants and fees (outside the submitted work) from AstraZeneca, Abbott, Boehringer Ingelheim, Cardio Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc, Novo Nordisk, and Roche. R.A.B. has received speaker fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche (outside the submitted work). J.W.C.H., W.A.H., and P.N.V. received either personal or institutional research support for DELIVER from AstraZeneca. B.C. has received consulting fees from Boehringer Ingelheim. A.S.D. has received grants and personal fees from AstraZeneca during the conduct of the study; personal fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, Corvidia, DalCor Pharma, Relypsa, Regeneron, and Merck; and personal and grant fees from Alnylam and Novartis; and personal fees from Amgen, outside the submitted work. M.A.A.G. has received personal fees from Saner, Roche, Amgen, Asofarma, Sanofi, AstraZeneca, Eli Lilly, Boehringer, Bristol Myers Squibb, Bayer, Pfizer, Merck, Abbott, Silanes, Servier, Jansen Cilag, Medtronic, and Boston Scientific. A.F.H. has received research support from American Regent, AstraZeneca, Boehringer Ingelheim, Merck, Novartis, and Verily; and has served as a consultant on the Advisory Board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Myokardia, Merck, Novartis, and Vifor. S.E.I. has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion; and has given lectures sponsored by AstraZeneca and Boehringer Ingelheim. M.N.K. has received research grant support from AstraZeneca, and Boehringer Ingelheim; has served as a consultant or on an advisory board for Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Merck (Diabetes and Cardiovascular), Novo Nordisk, Sanofi, and Vifor Pharma; has received other research support from AstraZeneca; and has received honorarium from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical
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Data availability
The data sharing policy of the DELIVER trial sponsor, AstraZeneca, is described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Description.

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