Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER

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Whether the sodium–glucose cotransporter 2 inhibitor dapagliflozin reduces the risk of a range of morbidity and mortality outcomes in patients with heart failure regardless of ejection fraction is unknown. A patient-level pooled meta-analysis of two trials testing dapagliflozin in participants with heart failure and different ranges of left ventricular ejection fraction (≤40% and >40%) was pre-specified to examine the effect of treatment on endpoints that neither trial, individually, was powered for and to test the consistency of the effect of dapagliflozin across the range of ejection fractions. The pre-specified endpoints were: death from cardiovascular causes; death from any cause; total hospital admissions for heart failure; and the composite of death from cardiovascular causes, myocardial infarction or stroke (major adverse cardiovascular events [MACEs]). A total of 11,007 participants with a mean ejection fraction of 44% (s.d. 14%) were included. Dapagliflozin reduced the risk of death from cardiovascular causes (hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.76–0.97; P = 0.01), death from any cause (HR 0.90, 95% CI 0.82–0.99; P = 0.03), total hospital admissions for heart failure (rate ratio 0.71, 95% CI 0.65–0.78; P < 0.001) and MACEs (HR 0.90, 95% CI 0.81–1.00; P = 0.045). There was no evidence that the effect of dapagliflozin differed by ejection fraction. In a patient-level pooled meta-analysis covering the full range of ejection fractions in patients with heart failure, dapagliflozin reduced the risk of death from cardiovascular causes and hospital admissions for heart failure (PROSPERO: CRD42022346524).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to be of benefit in patients with heart failure (HF), leading to significant reductions in the composite outcome of worsening HF (often leading to hospitalization) or death from cardiovascular (CV) causes.1–3 We planned a prospective, patient-level pooled meta-analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Dapagliflozin Evaluation to Improve the LivEs of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trials to provide additional data about the efficacy and safety of dapagliflozin as a treatment for patients with HF.4–6 The individual trials were powered for their primary composite endpoints6,7 and the purpose of the pooled analysis was to evaluate the key components of these endpoints and important secondary efficacy outcomes that required more power than provided by the individual trials. In particular, we pre-specified examination of the effect of dapagliflozin on mortality and the composite of death from CV causes, myocardial infarction (MI) or stroke (MACE). We also pre-specified that these outcomes would be examined in a limited number of patient subgroups to examine the consistency of the effects of dapagliflozin. One of these, left ventricular ejection fraction (LVEF), has become a key clinical question since the pooled analysis was originally conceived.8 Treatments for heart failure that work through neurohumoral pathways have their greatest benefit in patients with a reduced LVEF, that is, ≤40%. Analyses of trials testing such treatments demonstrated attenuated benefit in patients with an ejection fraction >55–60%.9–11 This pattern is considered biologically plausible because patients with lower ejection fractions exhibit greater neurohumoral activation than patients with higher ejection fractions9–11. SGLT2 inhibitors are not thought to act through neurohumoral pathways and no gradient in their effect related to ejection fraction was anticipated. However, a pooled analysis of the EMPagliflozin outcomE Trial in patients with chronic heart failure (EMPEROR) trials unexpectedly suggested a similar pattern of attenuated benefit in patients with a normal ejection fraction.12–14 If correct, this finding has major implications for the treatment of patients with HF, a large proportion of whom have a
Table 1 | Baseline characteristics of the pooled DAPA-HF and DELIVER cohort by ejection fraction category

|                      | ≤30%     | >30 and ≤37% | >37 and ≤44% | >44 and ≤51% | >51 and ≤60% | >60%    | P for trend |
|----------------------|----------|--------------|--------------|--------------|--------------|---------|------------|
|                      | N = 2,161 | N = 1,584    | N = 1,863    | N = 1,862    | N = 2,142    | N = 1,395 |            |
| LVEF (%)             | 24.9 ± 4.7 | 34.4 ± 1.8   | 40.6 ± 1.9   | 47.7 ± 2.2   | 56.4 ± 2.7   | 66.6 ± 4.6 | 0.27       |
| Randomized treatment: |          |              |              |              |              |         |            |
| Placebo              | 1,099 (50.9) | 785 (49.6)   | 900 (48.3)   | 947 (50.9)   | 1,054 (49.2) | 718 (51.5) |            |
| Dapagliflozin        | 1,062 (49.1) | 799 (50.4)   | 963 (51.7)   | 915 (49.1)   | 1,088 (50.8) | 677 (48.5) |            |
| Age (years)          | 65 ± 11    | 67 ± 11      | 69 ± 10      | 70 ± 10      | 73 ± 10      | 74 ± 10   | <0.001     |
| Sex: no. (%)         |          |              |              |              |              |         | <0.001     |
| Female               | 445 (20.6) | 379 (23.9)   | 528 (28.3)   | 667 (35.8)   | 1,053 (49.2) | 784 (56.2) |            |
| Male                 | 1,716 (79.4) | 1,205 (76.1) | 1,335 (71.7) | 1,195 (64.2) | 1,089 (50.8) | 611 (43.8) |            |
| Race: no. (%)        |          |              |              |              |              |         | <0.001     |
| White                | 1,423 (65.8) | 1,133 (71.5) | 1,387 (74.4) | 1,442 (77.4) | 1,554 (72.5) | 833 (59.7) |            |
| Asian                | 554 (25.6) | 367 (23.2)   | 379 (20.3)   | 293 (15.7)   | 404 (18.9)   | 393 (28.2) |            |
| Other                | 147 (6.8)  | 59 (3.7)     | 33 (1.8)     | 42 (2.3)     | 59 (2.8)     | 45 (3.2)  |            |
| Other                | 37 (1.7)   | 25 (1.6)     | 64 (3.4)     | 85 (4.6)     | 125 (5.8)    | 124 (8.9) | 0.047      |
| Stroke (beats min⁻¹) | 72 ± 12    | 71 ± 12      | 71 ± 11      | 72 ± 12      | 72 ± 12      | 71 ± 12   | <0.001     |
| Systolic blood pressure (mmHg) | 118 ± 15 | 124 ± 17      | 126 ± 15      | 128 ± 15      | 129 ± 15      | 129 ± 15   | <0.001     |
| Diastolic blood pressure (mmHg) | 72 ± 10 | 74 ± 11      | 75 ± 10      | 75 ± 10      | 74 ± 11      | 73 ± 10   | 0.002      |
| BMI (kg·m⁻²)         | 28 ± 6    | 28 ± 6       | 29 ± 6       | 30 ± 6       | 30 ± 6       | 30 ± 6   | <0.001     |
| Clinical history     |          |              |              |              |              |         |            |
| Hypertension: no. (%) | 1,463 (67.7) | 1,221 (77.1) | 1,565 (84.0) | 1,646 (88.4) | 1,937 (90.4) | 1,244 (89.2) | <0.001     |
| Type 2 diabetes mellitus: no. (%) | 885 (41.0) | 661 (41.7) | 838 (45.0) | 844 (45.3) | 952 (44.4) | 609 (43.7) | 0.16       |
| Stroke: no. (%)      | 207 (9.6) | 149 (9.4)   | 184 (9.9)    | 166 (8.9)    | 236 (11.0)   | 121 (8.7) | 0.39       |
| MI: no. (%)          | 940 (43.5) | 704 (44.4) | 799 (42.9) | 635 (34.1) | 449 (21.0) | 204 (14.6) | <0.001     |
| Atrial fibrillation: no. (%) | 736 (34.1) | 635 (40.1) | 811 (43.5) | 1,014 (54.5) | 1,291 (60.3) | 796 (57.1) | <0.001     |
| HF hospitalization: no. (%) | 1,063 (49.2) | 735 (46.4) | 860 (46.2) | 835 (44.8) | 843 (39.4) | 454 (32.5) | <0.001     |
| NYHA II or III/IV: no. (%) |          |              |              |              |              |         | <0.001     |
| II                   | 1,466 (67.8) | 1,065 (67.2) | 1,277 (68.5) | 1,369 (73.5) | 1,641 (76.6) | 1,098 (78.8) |            |
| III/IV               | 695 (32.2) | 519 (32.8) | 586 (31.5) | 493 (26.5) | 501 (23.4) | 296 (21.2) |            |
| KCCQ-TSS             | 78 (59–93) | 78 (59–92) | 75 (57–91) | 74 (56–90) | 71 (54–86) | 73 (54–88) | <0.001     |
| NT-proBNP (ng·l⁻¹)   | 1680 (964–3163) | 1309 (805–2362) | 1225 (714–2225) | 1089 (653–1877) | 976 (632–1631) | 903 (542–1548) | <0.001     |
| eGFR (ml per min per 1.73 m²) | 66 ± 20 | 66 ± 20      | 64 ± 19      | 62 ± 19      | 60 ± 18      | 59 ± 19   | <0.001     |
| Creatinine (µmol·l⁻¹) | 106 ± 31 | 104 ± 30      | 103 ± 30      | 103 ± 31      | 102 ± 31      | 101 ± 32   | <0.001     |
| Baseline treatment: no. (%) |          |              |              |              |              |         |            |
| Diuretics            | 1,876 (86.8) | 1,312 (82.8) | 1,565 (84.0) | 1,645 (88.3) | 1,952 (91.1) | 1,238 (88.7) | <0.001     |
| ACEI or ARB          | 1,714 (79.3) | 1,339 (84.5) | 1,516 (81.4) | 1,381 (74.2) | 1,549 (72.3) | 996 (71.4) | <0.001     |

Continued
Table 1 | Baseline characteristics of the pooled DAPA-HF and DELIVER cohort by ejection fraction category (continued)

| ≤30% | >30 and ≤37% | >37 and ≤44% | >44 and ≤51% | >51 and ≤60% | >60% | P for trend |
|------|--------------|--------------|---------------|---------------|-------|------------|
| N=2,161 | N=1,584 | N=1,863 | N=1,862 | N=2,142 | N=1,395 |
| ARNI | 306 (14.2) | 153 (9.7) | 162 (8.7) | 107 (5.7) | 60 (2.8) | 21 (1.5) | <0.001 |
| ACEI, ARB or ARNI | 2,009 (93.0) | 1,488 (93.9) | 1,671 (89.7) | 1,483 (79.6) | 1,606 (75.0) | 1,017 (72.9) | <0.001 |
| β-Blocker | 2,079 (96.2) | 1,529 (96.5) | 1,689 (90.7) | 1,617 (86.8) | 1,741 (81.3) | 1,080 (77.4) | <0.001 |
| MRA | 1,610 (74.5) | 1,124 (71.0) | 1,149 (61.7) | 853 (45.8) | 821 (38.3) | 480 (34.4) | <0.001 |
| Digitalis | 472 (21.8) | 273 (17.2) | 185 (9.9) | 89 (4.8) | 106 (4.9) | 58 (4.2) | <0.001 |
| CRT-D or CRT-P | 202 (9.3) | 104 (6.6) | 68 (3.7) | 43 (2.3) | 31 (1.4) | 6 (0.4) | 0.002 |
| CRT-D or ICD | 772 (35.7) | 329 (20.8) | 187 (10.0) | 74 (4.0) | 39 (1.8) | 9 (0.6) | <0.001 |

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CRT-D, cardiac resynchronization therapy—defibrillator; CRT-P, cardiac resynchronization therapy—pacermaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. P values are two sided and calculated from Cochrane, Armitage and Cuzick’s tests across quartiles.

Fig. 1 | Effect of dapagliflozin on key clinical outcomes in pooled DAPA-HF and DELIVER dataset. a–f. Incidence of: death from CV causes (a); death from all causes (b), the total number of hospital admissions for HF (c); time to first hospital admission for HF (d); death from CV causes, MI or stroke (e); and death from CV causes or hospital admission for HF (f), according to randomized therapy. Participants randomized to dapagliflozin are shown in blue and those randomized to placebo in red. All figures are Kaplan–Meier curves with an HR and 95% CI estimated from Cox’s model with two-sided P values except for the total number of hospital admissions for HF, which was plotted using the Gosh and Lin method accounting for death from CV causes (the RR is estimated from the joint frailty model with a two-sided P value). No adjustment for multiple comparisons was made. NNT indicates the number of patients who need to be treated over the median duration of follow-up to prevent one event (of the type in each panel). An NNT could not be calculated for the total number of hospital admissions for HF because this was an episode-based rather than a patient-based analysis (that is, patients may have had more than one hospital admission). ARR and NNTs are shown with a 95% CI.

normal ejection fraction, as well as our understanding of the pathophysiology of this syndrome and how SGLT2 inhibitors exert their benefits in HF. For this reason, before DELIVER was unblinded, we prepared an updated statistical analysis plan to pre-specify additional analyses of the effects of dapagliflozin across the full range of LVEF at baseline (Supplementary information).

Results
Patient-level pooled meta-analysis of DAPA-HF and DELIVER.
Of the 11,007 participants included in this analysis, 4,744 had an LVEF ≤40% and 6,263 an ejection fraction >40%, with 5,503 randomized to placebo and 5,504 randomized to dapagliflozin. The distributions of LVEFs in the overall population are shown in Extended Data Fig. 1. The mean LVEF was 44% (s.d. 14%) and the median 44% (interquartile range (IQR) 34–55%). The median follow-up was 22 months (IQR 17–30 months).

Baseline characteristics. Compared with participants with a lower ejection fraction, those with a higher ejection fraction were older and more likely to be a woman (Table 1). Blood pressure
HRs and the 95% CI are estimated from Cox’s model and the rate ratio (RR) and 95% CI are estimated from a joint frailty model with death from CV causes as a competing event. Dapa, dapagliflozin.

Table 2 | Clinical outcomes according to ejection fraction category and randomized therapy

|                | ≤30% | >30% and ≤37% | >37% and ≤44% | >44% and ≤51% | >51% and ≤60% | >60% | Pooled cohort |
|----------------|------|---------------|---------------|---------------|---------------|------|--------------|
| **CV death**   |      |               |               |               |               |      |              |
| Rate per 100 patient years (95% CI) | 9.9 (8.5–11.6) | 8.4 (7.0–10.0) | 6.4 (5.1–8.1) | 6.8 (5.6–8.2) | 5.2 (4.3–6.3) | 4.7 (3.9–5.8) | 4.1 (3.3–4.9) | 4.2 (3.4–5.1) | 4.3 (3.4–5.4) | 2.8 (2.1–3.8) | 5.9 (5.4–6.4) | 5.1 (4.6–5.5) |
| HR (95% CI)    | 0.85 (0.67–1.07) | 0.86 (0.61–1.20) | 0.81 (0.61–1.07) | 0.81 (0.61–1.07) | 0.91 (0.69–1.20) | 1.02 (0.77–1.34) | 0.68 (0.47–1.00) | 0.77 (0.59–1.00) | 0.91 (0.77–1.10) | 0.90 (0.72–1.11) | 0.86 (0.76–0.97) |
| **All-cause death** |      |               |               |               |               |      |              |
| Rate per 100 patient years (95% CI) | 11.1 (9.5–12.9) | 9.6 (8.2–11.3) | 8.1 (6.6–10.0) | 9.4 (8.0–11.0) | 8.0 (6.9–9.3) | 7.5 (6.4–8.8) | 6.7 (5.7–7.8) | 6.9 (5.9–8.0) | 7.2 (6.0–8.6) | 6.0 (4.9–7.4) | 8.3 (7.7–8.8) | 7.4 (6.9–8.0) |
| HR (95% CI)    | 0.87 (0.70–1.09) | 0.81 (0.60–1.09) | 0.86 (0.68–1.08) | 0.94 (0.75–1.17) | 1.02 (0.82–1.27) | 0.86 (0.65–1.13) | 0.91 (0.79–1.02) | 0.90 (0.78–0.99) |
| **Total HF hospitalizations** |      |               |               |               |               |      |              |
| Rate per 100 patient years (95% CI) | 12.8 (15.8–20.0) | 11.9 (10.3–13.8) | 11.2 (9.4–13.3) | 9.5 (7.9–11.5) | 10.9 (9.4–12.7) | 6.9 (5.8–8.38) | 10.5 (9.2–12.0) | 8.8 (7.6–10.2) | 10.6 (9.4–12.0) | 6.8 (5.8–7.9) | 8.5 (7.1–10.0) | 6.3 (5.2–7.7) | 8.2 (7.7–8.8) |
| RR (95% CI)    | 0.66 (0.54–0.80) | 0.84 (0.64–1.09) | 0.62 (0.48–0.79) | 0.84 (0.68–1.03) | 0.63 (0.51–0.77) | 0.77 (0.59–0.92) | 0.71 (0.65–0.78) |
| **HF hospitalization** |      |               |               |               |               |      |              |
| Rate per 100 patient years (95% CI) | 12.4 (10.7–14.4) | 8.2 (6.9–9.8) | 8.6 (7.0–10.5) | 6.6 (5.3–8.3) | 6.9 (5.7–8.4) | 5.4 (4.4–6.6) | 6.7 (5.7–8.0) | 5.6 (4.6–7.0) | 6.9 (5.8–8.1) | 4.6 (3.8–5.6) | 5.4 (4.4–6.8) | 4.6 (3.6–5.9) | 5.7 (5.2–6.2) |
| HR (95% CI)    | 0.66 (0.52–0.83) | 0.76 (0.56–0.93) | 0.78 (0.59–1.04) | 0.83 (0.64–1.07) | 0.66 (0.51–0.84) | 0.88 (0.64–1.22) | 0.74 (0.66–0.82) |
| **CV death, MI or stroke** |      |               |               |               |               |      |              |
| Rate per 100 patient years (95% CI) | 11.6 (10.0–13.4) | 10.3 (8.8–12.1) | 8.8 (7.2–10.7) | 7.7 (6.2–9.5) | 8.7 (7.3–10.3) | 7.4 (6.2–8.9) | 7.3 (6.3–8.6) | 6.6 (5.5–7.8) | 6.0 (5.1–7.1) | 6.4 (5.5–7.5) | 5.8 (4.7–7.2) | 7.8 (7.3–8.4) | 7.1 (6.6–7.6) |
| HR (95% CI)    | 0.90 (0.72–1.11) | 0.86 (0.65–1.15) | 0.87 (0.68–1.11) | 0.89 (0.70–1.13) | 1.07 (0.85–1.34) | 0.77 (0.56–1.06) | 0.90 (0.81–1.00) |
| **CV death or HF hospitalization** |      |               |               |               |               |      |              |
| Rate per 100 patient years (95% CI) | 18.8 (16.7–21.2) | 14.1 (12.3–16.2) | 13.0 (11.0–15.3) | 12.5 (10.8–14.4) | 9.3 (8.0–10.9) | 10.0 (8.7–11.5) | 9.0 (7.8–10.4) | 9.6 (8.4–11.0) | 7.5 (6.5–8.7) | 8.7 (7.3–10.3) | 6.4 (5.2–7.9) | 11.7 (9.2–12.1) |
| HR (95% CI)    | 0.75 (0.63–0.90) | 0.79 (0.62–1.01) | 0.75 (0.61–0.93) | 0.90 (0.73–1.10) | 0.77 (0.63–0.95) | 0.77 (0.59–1.00) | 0.78 (0.72–0.86) |
was 11 mmHg higher and body mass index (BMI) was 2 kg m$^{-2}$ higher in those with an ejection fraction $>60\%$ compared with $\leq30\%$. A history of hypertension and atrial fibrillation was more common and that of MI less common in patients with higher ejection fractions. The proportion of patients in New York Heart Association (NYHA) class III/IV was lower among those with a higher ejection fraction but patient-reported health status, measured by the Kansas City Cardiomyopathy Questionnaire—Total symptom score (KCCQ-TSS), was worse in participants with higher ejection fractions. Both N-terminal pro-brain natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR) were lower in the patients with higher ejection fraction, as was the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), sacubitril/valsartan, β-blockers, mineralocorticoid receptor antagonists (MRAs) and intracardiac devices.

**Effect of dapagliflozin on outcomes according to ejection fraction.** The rate of each pre-specified outcome was lower in the dapagliflozin group (Fig. 1). In the overall population, dapagliflozin reduced the risk of death from CV causes with an HR of 0.86 (95% CI 0.76–0.97), $P=0.01$. There was no evidence of effect modification by ejection fraction examined as either a categorical (Table 2 and Fig. 2) or a continuous variable ($P$ for interaction $=0.63$ and 0.94, respectively).

In sensitivity analyses, the results were unchanged when undetermined deaths were excluded from the definition of death from CV causes or if the definition of death from CV causes used in each trial was examined (Extended Data Fig. 2). The absolute risk reduction (ARR) was 1.5% (95% CI 0.2–2.8%) and the NNT over the median follow-up was 67 (95% CI 36–603).

![Fig. 2](image-url)  
**Fig. 2 | Effect of dapagliflozin on clinical outcomes across the range of ejection fraction.** a–f, Effect of dapagliflozin on: death from CV causes (a); death from all causes (b); the total number of hospital admissions for HF (c); time to first hospital admission for HF (d); death from CV causes, MI or stroke (e); and death from CV causes or hospital admission for HF (f), according to baseline LVEF. The horizontal blue line shows the continuous HR across the range of LVEF and the shaded area around this line represents the 95% CI from Cox’s model. The overall effect of treatment in the pooled population is shown in each panel as an HR (95% CI) with the two-sided $P$ value from Cox’s model for Wald’s test of interaction between treatment and LVEF. No adjustment for multiple comparisons was made. *Restricted cubic spline and interaction $P$ value derived from LWYY model for total HF hospitalization.
Fig. 3 | Effect of randomized treatment on CV death according to the pre-specified subgroups. Estimates are HRs with error bars representing 95% CIs from Cox’s model and a two-sided P value for interaction from Wald’s test of Cox’s model. No adjustment for multiple comparisons was made. *Not a pre-specified subgroup.

Dapagliflozin reduced the risk of total (that is, first and subsequent) hospital admissions for HF (RR 0.71 (95% CI 0.65–0.78), P < 0.001) and there was no evidence of a treatment interaction with ejection fraction, whether analyzed by category (P for interaction = 0.62) or as a continuous variable (P for interaction = 0.84). The pre-specified supportive analysis of time to first hospital admission showed a consistent benefit of dapagliflozin (HR 0.74 (95% CI 0.66–0.82); P < 0.001). The ARR was 1.3% (95% CI 0.0–2.6%) and the NNT over the median follow-up was 76 (95% CI 39–2187).

To address the possible attenuation of treatment benefit at higher ejection fractions reported in the EMPEROR trials, we examined the effect of dapagliflozin on the primary composite endpoint used in those trials, that is, time to the first occurrence of hospital admission for worsening HF or death from CV causes. Dapagliflozin reduced the risk of this outcome by 22% (HR 0.78 (95% CI 0.72–0.86); P < 0.001) (Table 2 and Fig. 2). The benefit appeared consistent across ejection fraction categories, with the test for interaction between ejection fraction and the effect of dapagliflozin giving a P value of 0.82 (Table 2). Inspection of the restricted cubic spline showed that the HR was below unity across the full range of ejection fraction, with the upper 95% CI around the HR crossing unity only at the extreme ends of the range (at around 9% and 70%, respectively), probably due to the small number of patients with either a very high or a very low ejection fraction. The P value for the test of interaction was 0.71. In sensitivity analyses, the results were unchanged if undetermined deaths were excluded from the definition of death from CV causes or if the definition from the individual trials was used (Extended Data Fig. 2).

Effect of dapagliflozin in the pre-specified subgroups. The effect of dapagliflozin on CV death was consistent across the pre-specified...
subgroups except for NYHA class, where the benefit seemed to be less in patients who were in a worse functional class (Fig. 3). To determine whether this interaction was likely to be true or to reflect the play of chance, we also examined the interaction between the KCCQ-TSS score and the effect of dapagliflozin on death from CV causes in a post-hoc subgroup analysis and found that the interaction was not significant (Fig. 3). We also conducted a post-hoc subgroup analysis using NT-proBNP as a continuous measure modeled as a restricted cubic spline and found no evidence of a difference in the effect of dapagliflozin by baseline NT-proBNP levels for any of the outcomes (Fig. 4).

**Discussion**

In a patient-level pooled meta-analysis of 11,007 participants in DAPA-HF and DELIVER\(^1,2\), compared with placebo, dapagliflozin 10 mg once daily reduced the risk of each of the pre-specified endpoints, that is, death from CV causes (by 14%), death from any cause (by 10%), total (first and repeat) hospital admissions for HF (by 29%) and the composite of death from CV causes, MI or stroke (by 10%), in patients with HF, with no evidence of heterogeneity of the benefit across the range of ejection fractions.

The original reason for planning a pooled analysis of DAPA-HF and DELIVER was to provide a more statistically robust estimate of the effect of dapagliflozin on outcomes that the individual trials had limited power to examine. Of particular interest was death from CV causes, and death from any cause, as neither trial was powered to show a modest benefit of dapagliflozin on these endpoints, which could still be clinically important. There was a significant benefit of dapagliflozin on death from CV causes in DAPA-HF (HR 0.82 (95% CI 0.69–0.98)) but the present analysis provides a more reliable and precise estimate of the effect of treatment (HR 0.86 (95% CI 0.76–0.97)). Using the pooled analysis of DAPA-HF and DELIVER, the number of patients with HF who needed to be treated (NNT) for a median of 22 months to prevent one death from CV causes was 68 (95% CI 39–281). The conclusion for death from any cause was similar, with a modest-sized benefit that was statistically significant.
The reduction in MACE was of borderline statistical significance. However, the beneficial effect on hospital admissions for HF was substantial, as was observed in the individual trials with SGLT2 inhibitors in HF. As a result, our pooled analysis demonstrates the large and generally consistent effect of dapagliflozin on this key outcome in patients with HF, irrespective of ejection fraction phenotype. Although there was a nominally significant interaction between NYHA class and the effect of dapagliflozin, NYHA class and KCCQ-TSS score were dissociated across the spectrum of LVEF at baseline and the effect of dapagliflozin was consistent across the range of KCCQ-TSS scores included.

The second and potentially more important reason to conduct the pooled analysis of DAPA-HF and DELIVER was to address the surprising findings of a pooled analysis of the EMPORER trials, which appeared to show that the size of the reduction in risk of hospital admission for worsening HF with empagliflozin declined as LVEF increased, with an apparent loss of effect in patients with an ejection fraction in the region of 60–65%. Although this attenuation of benefit with increasing ejection fraction has been shown repeatedly with treatments acting on neurohumoral pathways, it was not expected with SGLT2 inhibitors. We did not find any attenuation of the effect of dapagliflozin with increasing ejection fraction for any of the outcomes of interest, including the EMPORER primary endpoint of first hospitalization for HF or death from CV causes, with consistently nonsignificant tests of interaction between ejection fraction and the effect of treatment. We also found no interaction according to baseline NT-proBNP level as a measure of neurohumoral activation, although the minimum NT-proBNP inclusion threshold was 300 pg ml⁻¹ and some patients with HF with preserved ejection fraction (HFpEF) have levels below this.

The seemingly contrary findings of the pooled EMPORER trials and the present analysis are not explained by the distribution of ejection fraction, which was similar in each. The pooled analysis of the dapagliflozin trials included 1,289 more patients than the equivalent analysis of the empagliflozin trials. Therefore, we think that the findings of the present analysis are probably more reliable and those of the EMPORER analysis may have been spurious, given that they were unexpected and observed in a post-hoc analysis, and whether there was a significant ejection fraction-by-treatment interaction was uncertain. However, we cannot conclude that this is definitively the case and our findings cannot necessarily be generalized to other SGLT2 inhibitors. In addition, in a randomized trial testing the effect of dapagliflozin on symptoms and functional capacity in patients with HFpEF, there was no heterogeneity of treatment effect according to ejection fraction.

Our findings have clinical implications. Currently, except for diuretics, treatment for HF depends on knowledge of ejection fraction, the measurement of which may not be immediately available, especially where there are limited healthcare resources or geographical or other barriers to obtaining specialist care. The consistency of benefit of SGLT2 inhibitors across the range of ejection fraction, the rapidity with which benefit is obtained, the lack of requirement for titration of dose and the excellent safety profile suggest that this treatment could be initiated while waiting for ejection fraction to be measured. A modeling exercise suggested that first-line treatment with an SGLT2 inhibitor maximizes the benefit of evidence-based treatments in patients with reduced ejection fraction. Moreover, no other treatment for patients with mildly reduced or preserved ejection fraction has the same strength of evidence as SGLT2 inhibitors.

Our study has several limitations. LVEF was reported by investigators and was not measured in a core laboratory. As commonly found, there was digit preference in the ejection fraction measurements reported. However, we minimized this effect by examining all outcomes with ejection fraction modeled as a continuous variable and using categories that utilized mid-point ranges rather than whole numbers. We also had a minimum NT-proBNP inclusion threshold of 300 pg ml⁻¹ in DELIVER and it is known that some patients with HFpEF have an NT-proBNP level below this value. Consequently, we cannot be sure about the generalizability of our findings to these patients.

Our analysis demonstrates that, in patients with HF, dapagliflozin led to significant reductions in the risk of death from CV causes and any cause, as well as MACE, irrespective of LVEF. There was a larger reduction in total hospital admissions for HF than in death, which was also consistent across the range of ejection fractions. Most patients with HF, regardless of ejection fraction, are likely to benefit from treatment with an SGLT2 inhibitor, although the ARR is somewhat smaller in patients with higher compared with lower ejection fractions. This analysis supports a recommendation that treatment with dapagliflozin can be initiated in patients with a clinical diagnosis of HF and no contraindications, even if a measurement of ejection fraction is awaited.

Online content
Any methods, additional references, Nature Research reporting summaries, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-022-01971-4.

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References
1. McMurray, J. J. V. et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N. Engl. J. Med. 381, 1995–2008 (2019).
2. Solomon S. D. et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. (2022). https://doi.org/10.1056/NEJMoa2206286
3. Packer, M. et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N. Engl. J. Med. 383, 1413–1424 (2020).
4. Anker, S. D. et al. Empagliflozin in heart failure with a preserved ejection fraction. N. Engl. J. Med. 385, 1451–1461 (2021).
5. Bhatt, D. L. et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N. Engl. J. Med. 384, 117–128 (2021).
6. McMurray, J. J. V. et al. A trial to evaluate the effect of the sodium–glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail. 21, 665–675 (2019).
7. Solomon, S. D. et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 23, 1217–1225 (2021).
8. Kondo, T. & McMurray, J. J. V. Re-emergence of heart failure with a normal ejection fraction? Eur Heart J 43, 427–429 (2022).
9. Solomon, S. D. et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 37, 455–462 (2016).
10. Lund, L. H. et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 20, 1230–1239 (2018).
11. Solomon, S. D. et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation 141, 352–361 (2020).
12. Butler, J. et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. Eur Heart J 43, 416–426 (2022).
13. Verbrugge, F. H. et al. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. Eur Heart J 43, 1941–1951 (2022).
14. Nassif, M. E. et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. N. Engl. J. Med. 381, 1995–2008 (2019).
15. Berg, D. D. et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. JAMA Cardiol. 6, 499–507 (2021).
16. Butler, J. et al. Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPORER-Preserved trial. Eur. J. Heart Fail. 24, 245–248 (2022).
17. Shen, L. et al. Accelerated and personalized therapy for heart failure with reduced ejection fraction. Eur Heart J 43, 2573–2587 (2022).
18. Heidenreich, P. A. et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* **145**, e895–e1032 (2022).

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Baseline characteristics were summarized as means (s.d.), median (IQRs) or percentages and described across groups according to ejection fraction. Ejection fraction was normally distributed but demonstrated digit preference and, to account for this, sextiles were used to describe the distribution of baseline characteristics. Cochran, Armitage and Cuzick's tests were used to examine trends across ejection fraction quantiles. Rates were calculated using the total number of events divided by the person-years of follow-up and expressed as a rate per 100 person-years. Cox's models included randomized therapy and were stratified by diabetes status at enrollment and trial (DAPA-HF or DELIVER). To account for the clustering within trials, a variable denoting the trial was used as a stratification variable in the model, to indicate that different trial populations are exposed to different baseline risks. The effect of therapy according to ejection fraction was tested in Cox's models by entering an interaction term between randomized therapy and ejection fraction as a continuous variable modeled as a restricted cubic spline. Three knots were chosen (ejection fraction of 6%, 45% and 84%) after examining the Akaike information criterion (AIC) for different numbers of knots, and the spline with the lowest AIC was chosen. All models used the full range of ejection fraction values. The interaction was represented graphically showing the HR for the effect of dapagliflozin against placebo across the range of ejection fraction. Total HF hospitalizations were analyzed by a joint frailty model with CV death treated as a competing risk. The model included the treatment term and adjustment for previous hospital admission for HF, diabetes status at enrollment and trial (DAPA-HF or DELIVER). The nonparametric estimates of the marginal mean of the cumulative number of total hospital admissions for HF over time were calculated allowing for death as a terminal event, and the estimates were plotted according to the approach of Ghosh and Lin. To examine the interaction between the effect of dapagliflozin on each CV death and total hospital admissions for HF, a spline term for ejection fraction, as outlined above, was entered into an extension of the proportional hazards model for recurrent events as described by the Lin–Wei–Yiang–Ying (LWY') and Lin–Wei–Yiang–Ying–Cho parameter which is a semiparametric proportional rates model. The continuous RR interaction term was then plotted. All analyses were conducted using Stata v.17.0 and SAS v.9.4. There were no missing data for the variables used in the models and missing follow-up data were handled by censoring at the time of the assessment for potential endpoints. Few patients in either trial had an incomplete follow-up. A P < 0.05 was considered statistically significant.

Data availability

Data underlying the findings described in this manuscript may be obtained following AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

References

19. Munda, M. & Legrand, C. Adjusting for centre heterogeneity in multicentre clinical trials with a time-to-event outcome. Pharm. Stat. 13, 145–152 (2014).
20. Rogers, J. K., Yaroshinsky, A., Pocock, S. J., Stokar, D. & Pogoda, J. Analysis of recurrent events with an associated informative dropout time: application of the joint frailty model. Stat. Med. 35, 2195–2205 (2016).
21. Ghosh, D. & Lin, D. Nonparametric analysis of recurrent events and death. Biometrika 56, 554–562 (2000).
22. Lin, D. Y., Wei, L. J., Yang, I. & Ying, Z. Semiparametric regression for the mean and rate functions of recurrent events. J. R. Statist. Soc. B 62, 711–730 (2000).

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Author contributions
PS.1, S.D.S. and J.J.V.M conceived the study, PS.1, S.D.S, J.J.V.M, O.B., S.B.G. and B.L.C. developed the methodology for data analysis. PS.1, T.K. J.B., K.F.D., O.B., S.B.G. and B.L.C. analyzed the data. P.S.1 and J.J.V.M interpreted the data and prepared the first draft of the manuscript, which was reviewed and edited by all of the authors. All authors approved the final version.

Competing interests
PS.1’s employer, the University of Glasgow, has been remunerated by AstraZeneca for working on the DAPA-HF and DELIVER trials and by Bayer and Novo Nordisk for work on clinical trials; he has received speakers and consulting fees from Novartis and Boehringer Ingelheim, and grants from AstraZeneca and Boehringer Ingelheim. T.K. received speaker fees from Abbott, Ono Pharma, Otsuka Pharma, Novartis, AstraZeneca, Bristol Myers Squibb and Abiomed. J.B. reports advisory board honoraria from Bayer. K.F.D reports receiving honoraria from AstraZeneca and a research grant to his institution from Boehringer Ingelheim. B.L.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; and personal fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, Corvidia, DaiCor Pharma, Reelypsa, Regeneron and Merck; grants and personal fees from Alnylam and Novartis; and personal fees from Amgen, outside the submitted work. M.V. has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacomm, Relypsa, Roche Diagnostics, Sanofi and Tricog Health; speaker engagements with AstraZeneca, Novartis and Roche Diagnostics and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech and Impulse Dynamics. S.B.G., O.B., D.L., M.P. and A.L. are employees and shareholders of AstraZeneca. 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Additional information
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Extended Data Fig. 1 | Distribution of LVEF in pooled DAPA-HF and DELIVER dataset complete. Distribution of left ventricular ejection fraction (LVEF) in the total population in DAPA-HF and DELIVER.
Extended Data Fig. 2 | Effect of dapagliflozin on clinical outcomes across the range of NT-proBNP. Effect of dapagliflozin on death from cardiovascular causes (CV death) and CV death or hospitalisation for heart failure (HF hospitalisation) where the definition of CV death used excluded undetermined deaths from the definition of CV death (top two panels) and according to the original trial definitions (that is, including undetermined deaths in DAPA-HF and excluding undetermined deaths in DELIVER) (bottom two panels). The horizontal blue line shows the continuous hazard ratio (HR) across the range of left ventricular ejection fraction (LVEF) and the shaded area around this line represents the 95% confidence interval (95%CI) estimated from a Cox model. The overall effect of treatment in the pooled population is shown in each panel as a HR (95%CI) with the two-sided p-value estimated from a Cox model for the Wald test of interaction between treatment and LVEF. No adjustment for multiple comparisons was made.
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| Sample size | Sample size was 11007, 4744 from DAPA-HF and 6263 from DELIVER. The sample size and power calculations are described in the following:

1: Solomon SD, de 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 Jul;23(7):1217-1225. doi: 10.1002/ejhf.2249.

2: 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, Ljungman CEA, Merkely B, Nicolau JC, O’Meara E, Petrie MC, Vinh PN, Schou M, Tereschenko 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 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoA1911303. |

Data exclusions None.

Replication Prospectively designed clinical trials.

Randomization Both were double blind placebo controlled prospective randomized trials.

Blinding Both trials were double blind.

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Human research participants

Policy information about studies involving human research participants

Population characteristics

Each enrolled patients with a diagnosis of heart failure, functional limitation, and elevated natriuretic peptides. The principal difference between the two trials was that patients with an ejection fraction of 40% or less were randomized in DAPA-HF and those with an ejection fraction greater than 40% in DELIVER. In both trials, patients were randomized to dapagliflozin at a dose of 10 mg once daily, or a matching placebo, in addition to standard care. The full characteristics of each trial have been described in detail in the following publications:

1: Solomon SD, de 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 Jul;23(7):1217-1225. doi: 10.1002/ejhf.2249.

2: 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,
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Clinical trial registration
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Study protocol
Statistical plans have been submitted with manuscript. See also,

1: Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Lindholm D, Wilderång U, Öhrn F, Claggett B, Langkilde AM, Petersson M, McMurray JIV. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 2021 Jul;23(7):1217-1225. doi: 10.1002/ejhf.2249.

2: McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez F, Shah SJ, Lindholm D, Wilderång U, Öhrn F, Claggett B, Langkilde AM, Petersson M, McMurray JIV. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 2021 Jul;23(7):1217-1225. doi: 10.1002/ejhf.2249.

Data collection
Data were collected at study sites by investigators and by AstraZeneca during each trial, but were analyzed independently at the University of Glasgow. The DAPA-HF trial randomized patients between 5 February 2017 and 17 August 2018, with patients enrolled in 410 sites in 20 countries. Enrollment in DELIVER began on 27 August 2018 and the last patient was randomized on 18 January 2021, with patients enrolled at 353 sites, in 20 countries. See also

1: Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Lindholm D, Wilderång U, Öhrn F, Claggett B, Langkilde AM, Petersson M, McMurray JIV. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 2021 Jul;23(7):1217-1225. doi: 10.1002/ejhf.2249.

2: McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD; DAPA-HF Committees and Investigators. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail. 2019 Nov;21(11):1402-1411. doi: 10.1002/ejhf.1548. Epub 2019 Jul 15.

Outcomes
Both trials were event-driven and had the same primary endpoint which was a composite of the time to the first occurrence of worsening heart failure or death from a cardiovascular cause. Worsening heart failure was defined as unplanned hospital admission for heart failure or an urgent visit for worsening heart failure resulting in the administration of an intravenous diuretic. In the original "regulatory" statistical analysis plan for the meta-analysis (dated 2 August 2019), a pre-specified hierarchy of endpoints was provided with control of alpha (see statistical analysis below). The endpoints were: death from cardiovascular causes; death from any cause; total (i.e., first and repeat) hospital admissions for heart failure (with an additional supportive analysis of time to the first occurrence of hospital admissions for heart failure, outside alpha control); and the composite of death from cardiovascular causes, myocardial infarction, or stroke ("major adverse cardiovascular events" [MACE]). Because of the possible attenuation of the benefit of SGLT2 inhibition at higher ejection fractions reported in the EMPEROR trials(8) (as described in the introduction), we also examined the composite outcome used in the EMPEROR trials i.e., time to the first occurrence of hospital admission for worsening heart failure or death from cardiovascular causes in our analyses. In both trials an independent Cardiovascular Endpoint Committee (CEC), blinded to treatment allocation, adjudicated all deaths and non-fatal cardiovascular events submitted by investigators (or otherwise identified) as possible endpoints using a charter reflecting the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials developed by the Standardized Data Collection for Cardiovascular Trials Initiative

1. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Hai MT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJ, Tcheng JE, Steinhübel SR, Burton P, Mauri L, O’Connor CM, Pfeffer MA, Hung HM, Stockbridge NL, Chaitman BR, Temple RJ; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) . 2017 Cardiovascular and stroke endpoint definitions for clinical trials. Circulation 2018;137:961-972

Please see statistical plans submitted.