Signed, sealed and DELIVERed

While current guidelines recommend the use of SGLT2 inhibitors in people with chronic heart failure and a reduced ejection fraction, several gaps remain in the evidence. The DELIVER trial aimed to establish the effectiveness of dapagliflozin in those with a higher left-ventricular ejection fraction (LVEF). Participants with an LVEF 40% were randomised to receive dapagliflozin (10 mg once daily) or placebo, in addition to usual therapy, and followed for 2.3 years. The primary endpoint of a composite of worsening heart failure or cardiovascular death was significantly reduced with dapagliflozin, driven by a reduction in worsening heart failure. The benefits were not affected by diabetes status. A separate analysis found a consistent benefit of dapagliflozin across all frailty statuses, with early improvements in quality of life. These findings establish the fundamental role of SGLT2 inhibitors in heart failure therapy, regardless of ejection fraction or diabetes status.

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The present trial, DELIVER, explored the effect of dapagliflozin in people living with mildly reduced or preserved ejection fraction, irrespective of diabetes status (Solomon et al, 2022). It recruited 6263 individuals with an ejection fraction >40% to receive either dapagliflozin 10 mg or placebo. Of note, individuals with improved ejection fraction were also included (i.e. individuals whose ejection fraction was below 40% but subsequently rose above 40% at time of recruitment). This a previously understudied group.

Mean ejection fraction of the whole population was 54%. Overall, 43.6% of participants were women who, it has been well established, carry a higher burden of heart failure with preserved ejection fraction (HFpEF). Non-white ethnicities, however, comprised only 30% of participants, so were under-represented. The primary endpoint was a composite of worsening heart failure (unplanned hospitalisation for heart failure or an urgent visit for heart failure) or cardiovascular death.

After a median follow-up of 2.3 years, the primary endpoint was significantly reduced by 18% with dapagliflozin compared to placebo (absolute risk reduction, 3.1%; number needed to treat, 32). This was driven by a significant reduction in worsening heart failure. There was no statistically significant reduction in cardiovascular or all-cause death. Total events and symptom burden were lower in the dapagliflozin group.

These benefits were observed irrespective of diabetes status. Importantly, results were similar in those with left-ventricular ejection fraction ≥60% and <60%. This suggests no decline in benefit even in those with an ejection fraction in the normal range, which has been observed in previous HFpEF studies.

The incidence of adverse events did not differ significantly between the dapagliflozin and placebo groups.

Helpfully, given our ageing population, a pre-specified *post hoc* analysis of the DELIVER trial investigated the efficacy and tolerability of dapagliflozin according to frailty status in people living with mildly reduced or preserved ejection fraction (Butt et al, 2022). Unsurprisingly, frailty was found to be common in those with heart failure and was associated with worse outcomes. Reassuringly, the benefit of dapagliflozin was consistent across all frailty statuses, and improvements in quality of life occurred early and were particularly apparent in those with more severe frailty. Age and functional status **should not**, therefore, be a barrier to consideration of SGLT2 inhibitor therapy and, as always, we should assess goals of heart failure management and risk/benefit ratios on an individual basis.

DELIVER has sealed the role of SGLT2 inhibitors as a fundamental pillar of heart failure

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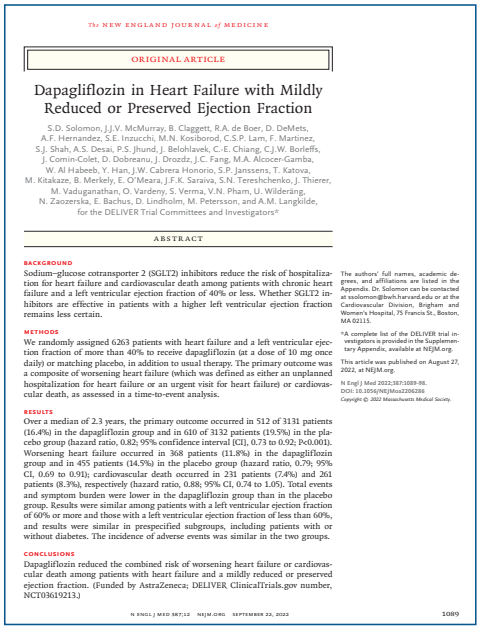
"DELIVER has sealed the role of SGLT2 inhibitors as a fundamental pillar of heart failure therapy and a new standard of care, irrespective of ejection fraction or diabetes status."

therapy and a new standard of care, irrespective of ejection fraction or diabetes status. The challenge now is to translate this seminal trial data into a change in practice in primary and secondary care. ■

Kevin Fernando's previous *Diabetes Distilled* article, "The EMPEROR really does have new clothes", provides an overview of the effect of empagliflozin in people living with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial.

Butt JH, Jhund PS, Belohlávek J et al (2022) Efficacy and safety of dapagliflozin according to frailty in patients with heart failure: a prespecified analysis of the deliver trial. *Circulation* 27 Aug [Epub ahead of print]; https://doi.org/10.1161/CIRCULATIONAHA.122.061754

Solomon SD, McMurray JJV, Claggett B et al; DELIVER Trial Committees and Investigators (2022) Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* **387**: 1089–98; https://doi.org/10.1056/NEJMoa2206286



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

METHODS

We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

RESULTS

Over a median of 2.3 years, the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.)

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*A complete list of the DELIVER trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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