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Time to Clinical Benefit of Dapagliflozin in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction

A Prespecified Secondary Analysis of the DELIVER Randomized Clinical Trial

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IMPORTANCE Dapagliflozin was recently shown to reduce cardiovascular death or worsening heart failure (HF) events in patients with HF with mildly reduced or preserved ejection fraction in the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial.

OBJECTIVE To evaluate the time course of benefits of dapagliflozin on clinically relevant outcomes in this population.

DESIGN, SETTING, AND PARTICIPANTS The DELIVER trial was a global phase 3 clinical trial that randomized patients with HF with mildly reduced or preserved ejection fraction to dapagliflozin or matching placebo. Inclusion criteria included symptomatic HF, left ventricular ejection fraction greater than 40%, elevated natriuretic peptide levels, and evidence of structural heart disease. In this prespecified secondary analysis of the DELIVER trial, to examine the timeline to onset of clinical benefit with dapagliflozin, hazard ratios (HR) and 95% CIs were iteratively estimated for the primary composite end point and worsening HF events alone with truncated data at every day postrandomization. Time to first and sustained statistical significance of dapagliflozin for these end points were then examined. Participants were enrolled from August 2018 to December 2020, and for this secondary analysis, data were analyzed from April to September 2022.

INTERVENTIONS Dapagliflozin, 10 mg, once daily or matching placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first occurrence of cardiovascular death or worsening HF (hospitalization for HF or urgent HF visit requiring intravenous HF therapies).

RESULTS Overall, 6263 patients were randomized across 350 centers in 20 countries. Of 6263 included patients, 2747 (43.9%) were women, and the mean (SD) age was 71.7 (9.6) years. During a median (IQR) of 2.3 (1.7-2.8) years' follow-up, 1122 primary end point events occurred, with an incidence rate per 100 patient-years of 8.7 (95% CI, 8.2-9.2). Time to first nominal statistical significance for the primary end point was 13 days (HR, 0.45; 95% CI, 0.20-0.99; $P = .046$), and significance was sustained from day 15 onwards. First and sustained statistical significance was reached for worsening HF events (HR, 0.45; 95% CI, 0.21-0.96; $P = .04$) by day 16 after randomization. Significant benefits for the primary end point and worsening HF events were sustained at 30 days, 90 days, 6 months, 1 year, 2 years, and final follow-up (primary end point: HR, 0.82; 95% CI, 0.73-0.92; worsening HF events: HR, 0.79; 95% CI, 0.69-0.91).

CONCLUSIONS AND RELEVANCE In the DELIVER trial, dapagliflozin led to early and sustained reductions in clinical events in patients with HF with mildly reduced or preserved ejection fraction with statistically significant reductions observed within 2 weeks of treatment initiation.

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Supplemental content

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In the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial, the sodium glucose cotransporter 2 (SGLT-2) inhibitor dapagliflozin was shown to reduce cardiovascular death or worsening heart failure (HF) events in patients with HF with mildly reduced or preserved ejection fraction.[1] These data are highly complementary to findings from the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial[2] and are anticipated to strengthen current treatment recommendations supporting the use of the SGLT-2 inhibitors in this patient population.[3,4] Worsening HF is a marker of disease progression, and its prevention is a recognized priority in the comprehensive management of this population.[5] However, worsening HF events may occur over an uncertain time horizon, and in implementing SGLT-2 inhibitors in care, patients and clinicians may be interested in the expected time course to disease stabilization and clinical improvement. In this prespecified analysis of the DELIVER trial, we evaluated the time course of benefits of dapagliflozin on clinically relevant outcomes in patients with HF with mildly reduced or preserved ejection fraction.

Key Points

Question When are the clinical benefits of the sodium glucose cotransporter 2 inhibitor dapagliflozin first apparent among patients with heart failure with mildly reduced or preserved ejection fraction?

Findings In this prespecified secondary analysis of the DELIVER trial including 6263 patients, dapagliflozin resulted in rapid and substantial reductions in the primary end point of cardiovascular death or worsening heart failure, with first statistical significance attained within 2 weeks of randomization; these benefits were sustained until final trial follow-up.

Meaning In this study, dapagliflozin led to early and sustained reductions in clinical events in patients with heart failure with mildly reduced or preserved ejection fraction.

Methods

The DELIVER trial was a global, event-driven phase 3 clinical trial that randomized patients with HF with mildly reduced or preserved ejection fraction to dapagliflozin, 10 mg, once daily or matching placebo.[6] Randomization was stratified by type 2 diabetes status. Key inclusion criteria included symptomatic HF (New York Heart Association class II to IV), left ventricular ejection fraction greater than 40%, elevated natriuretic peptide levels, and evidence of structural heart disease. Participants could be enrolled irrespective of care setting (ambulatory care or during hospitalization). Race was captured on a dedicated demographics case report form and included the following categories: Asian, Black or African American, White, or other race designation (including Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native). The primary outcome was time to first occurrence of cardiovascular death, hospitalization for HF, or urgent HF visit requiring intravenous HF therapies. To examine the timeline to onset of clinical benefit with dapagliflozin, we iteratively estimated hazard ratios (HRs) and 95% CIs for the primary composite end point with truncated data at every day postrandomization. All time-to-event data were analyzed using Kaplan-Meier curves and Cox proportional hazards models stratified by type 2 diabetes status. Early postrandomization data were smoothed by applying a locally weighted scatterplot smoothing procedure. We report time to first nominally statistically significant reduction in the primary composite end point, worsening HF event alone, and HF hospitalization alone. Additionally, we examine the time to sustained statistical significance, ie, the time point in which the upper bounds of the treatment CI remained below unity for the remainder of the trial. Effect sizes at multiple time points until final follow-up were also estimated. All end points were adjudicated by Clinical Endpoints Committees (Brigham and Women's Hospital, Boston Massachusetts, and University of Glasgow, Glasgow, Scotland, UK). The study protocol was approved by local ethics committees or institutional review boards at each participating site, and each patient provided written informed consent. The DELIVER trial was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The trial protocol can be found in Supplement 1.

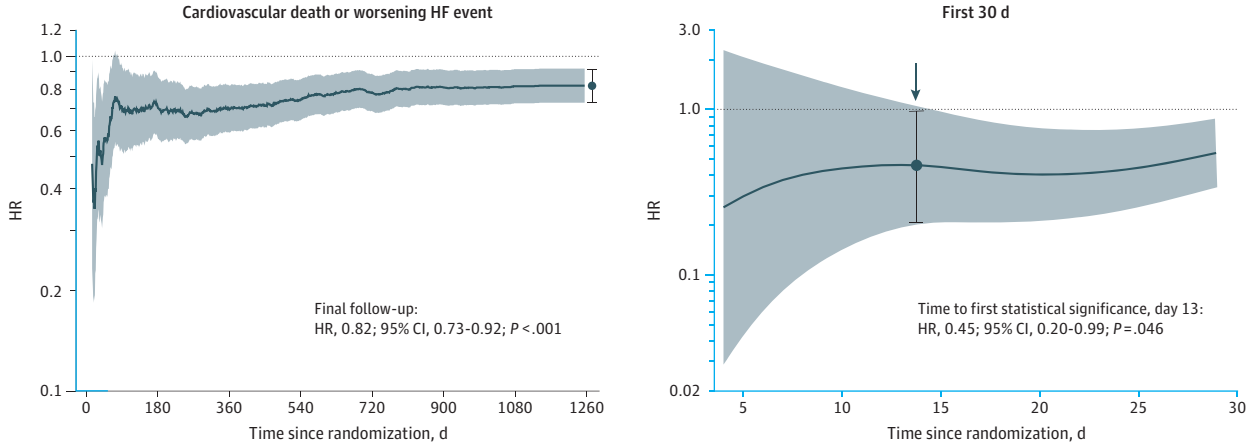
Statistical analyses were performed using Stata version 17 (StataCorp). Two-sided *P* values less than .05 were considered statistically significant.

Results

Between August 2018 and December 2020, 6263 patients were randomized across 350 centers in 20 countries (eFigure in Supplement 2). The mean (SD) age was 71.7 (9.6) years, 2747 (43.9%) were women, 1274 (20.3%) were Asian, 159 (2.5%) were Black, 4439 (70.9%) were White, and 391 (6.2%) were of another race designation. A total of 4713 patients (75.3%) had New York Heart Association functional class II symptoms, and 654 (10.4%) were randomized during HF hospitalization or within 30 days of discharge. Over a median (IQR) of 2.3 (1.7-2.8) years' follow-up, 1122 primary end point events (incidence rate per 100 patient-years, 8.7; 95% CI, 8.2-9.2), 823 first worsening HF events (incidence rate per 100 patient-years, 6.4; 95% CI, 6.0-6.8), and 747 first HF hospitalizations (incidence rate per 100 patient-years, 5.7; 95% CI, 5.3-6.2) occurred.

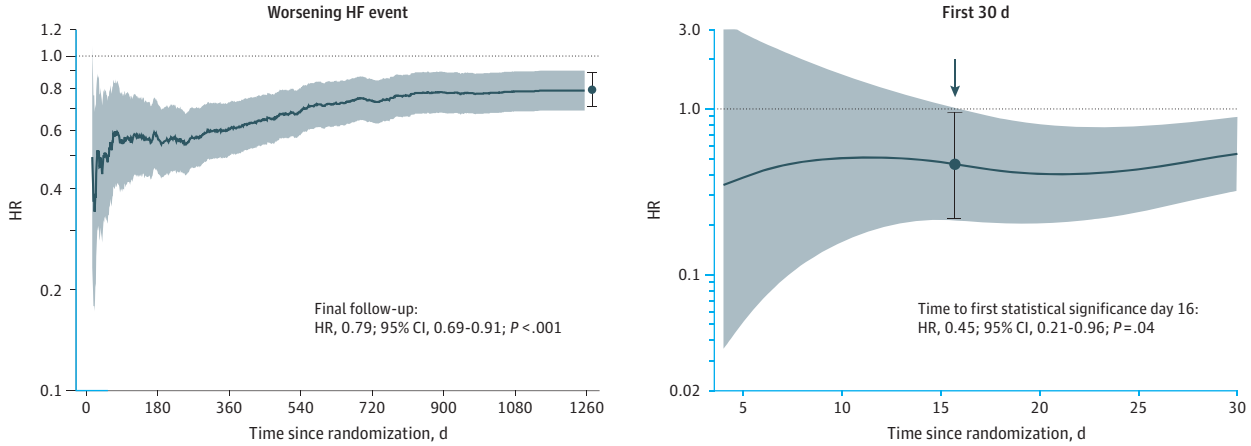
Figure 1 displays the time course of clinical benefit with dapagliflozin on the primary composite end point. Time to first nominal statistical significance for the primary end point was 13 days (HR, 0.45; 95% CI, 0.20-0.99; *P* = .046), and statistical significance was sustained from day 15 onwards. First nominal statistical significance for worsening HF events (HR, 0.45; 95% CI, 0.21-0.96; *P* = .04) was reached and sustained at day 16 after randomization (**Figure 2**). Similarly, time to first nominal statistical significance for HF hospitalizations alone (HR, 0.42; 95% CI, 0.18-0.96; *P* = .04) was observed and sustained after day 16. Significant benefits for the primary end point (**Figure 3**A) and worsening HF events (Figure 3B) were sustained at 30 days, 90 days, 6 months, 1 year, and 2 years. At final follow-up, compared with placebo, dapagliflozin significantly reduced the primary end point by 18% (HR, 0.82; 95% CI,

Figure 1. Time to Clinical Benefit for the Primary End Point in the DELIVER Trial



Hazard ratios (HRs) and 95% CIs by day postrandomization for the primary end point (cardiovascular death or worsening heart failure [HF] event) in the DELIVER trial, with a magnified view of the first 30 days postrandomization (smoothed by applying a locally weighted scatterplot smoothing procedure).

Figure 2. Time to Clinical Benefit for Worsening Heart Failure (HF) Events in the DELIVER Trial



Hazard ratios (HRs) and 95% CIs by day postrandomization for worsening HF (defined as hospitalization for HF or urgent visit for HF requiring intravenous HF therapies) in the DELIVER trial, with a magnified view of the first 30 days postrandomization (smoothed by applying a locally weighted scatterplot smoothing procedure).

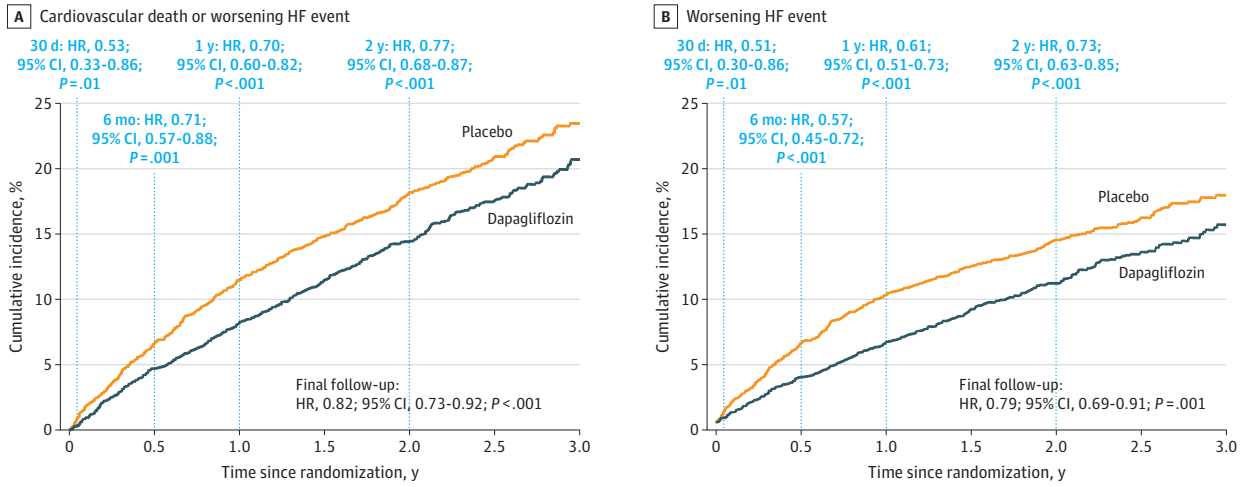
0.73-0.92; $P < .001$) and worsening HF events by 21% (HR, 0.79; 95% CI, 0.69-0.91; $P = .001$).

Discussion

This prespecified analysis of the DELIVER trial demonstrated early and sustained reductions in clinical events with dapagliflozin in patients with HF with mildly reduced or preserved ejection fraction, with statistically significant reductions in the primary end point observed within 2 weeks of randomization. Notably, visual inspection of the event curves showed almost immediate clinical benefits soon after treatment initiation, but a short period of time was needed to observe a sufficient number of events to detect statistical significance. This timeline of clinical benefit was highly consistent with similar observations from the EMPEROR-Preserved trial in which the nominal significance was first reached at day 18 after randomization[7] and in trials of SGLT-2 inhibitors in patients with HF with reduced ejection fraction (12 to 28 days).[8,9] Furthermore, these data align with rapid improvements in symptoms, physical limitations, and quality of life seen with SGLT-2 inhibition as early as 2 to 4 weeks.[7,10,11]

The time course of clinical benefits may be expected to vary based on the clinical end points of interest. SGLT-2 inhibitors appear to alter key biological pathways and confer rapid diuretic and hemodynamic effects in patients with HF. Indeed, natriuresis[12] and intracardiac filling pressures[13] are favorably modified within days of treatment initiation. These posited early biological mechanisms, together with the high burden of worsening HF in this population, may explain the early benefits observed in preventing or postponing hospitalizations or urgent visits for HF. For less frequent events in HF with mildly reduced or preserved ejection

Figure 3. Treatment Effects at Multiple Time Points in the DELIVER Trial



Treatment effects on the primary end point (A) and worsening heart failure (HF; defined as hospitalization for HF or urgent visit for HF requiring intravenous HF therapies) (B) in the DELIVER trial at multiple time points to final follow-up. Treatment effects summarized as hazard ratios (HRs) and 95% CIs.

fraction, such as cardiovascular death or kidney disease progression, the anticipated timeline to clinical benefit and duration necessary to demonstrate statistical significance may be longer.

Beyond these early benefits, sustained therapeutic efficacy through the duration of the trial was observed for multiple clinically relevant end points, supporting long-term continuation of dapagliflozin in clinical practice. Notably, there was violation of the proportional hazards assumption in the DELIVER trial, potentially suggesting differential early vs late treatment effects. However, examination of log-log survival plots demonstrated no substantial convergence and point estimates for benefit remained robust late into follow-up suggesting sustained clinical benefit over time.[1]

Limitations

Key limitations of this approach should be acknowledged. Evaluating timing of clinical benefit on discrete events, such as deaths and hospitalizations, is challenging. While time to first statistical significance is driven in part by the magnitude of the early therapeutic effect size, it is also strongly influenced by relative number of accrued events. In light of phenotypic heterogeneity in this population, there is high interest in understanding if certain subpopulations may respond more quickly or more favorably to therapeutic interventions. However, as these methodologies are highly sensitive to sample size, time to statistical significance is best assessed in the overall trial population rather than in individual subgroups.

Conclusions

Implementation of effective therapies in patients with HF with mildly reduced or preserved ejection fraction may be delayed or deferred, in part related to clinical inertia or lower perceived clinical risk of this cohort. Patients themselves may be reluctant to initiate a new therapy as the promise to avert downstream clinical events may be over an uncertain time horizon. This therapeutic hesitancy may be especially prevalent among patients who otherwise appear clinically stable with relatively mild symptoms (a population well-represented in the DELIVER trial). However, these data from the DELIVER trial underscore the rapid clinical benefits observed with the SGLT-2 inhibitor dapagliflozin and highlight key opportunities for the early identification and prompt management of this patient population without delay.

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