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.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03619213
In the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DE-\textsc{LIVER}) 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. 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 and are anticipated to strengthen current treatment recommendations supporting the use of the SGLT-2 inhibitors in this patient population. Worsening HF is a marker of disease progression, and its prevention is a recognized priority in the comprehensive management of this population. 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 \textsc{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.

**Methods**

The \textsc{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. 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 \textsc{Deliver} trial was reported in accordance with the Consolidated Standards of Reporting Trials (\textsc{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 (\textsc{Figure 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.

\textsc{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 (\textsc{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 (\textsc{Figure 3A}) and worsening HF events (\textsc{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,
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 and in trials of SGLT-2 inhibitors in patients with HF with reduced ejection fraction (12 to 28 days). 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.

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 and intracardiac filling pressures 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 fraction, a longer period may be needed to observe statistical significance.
Figure 3. Treatment Effects at Multiple Time Points in the DELIVER Trial

A. Cardiovascular death or worsening HF event

- 30 d: HR, 0.51; 95% CI, 0.33-0.86; P = .01
- 1 y: HR, 0.70; 95% CI, 0.60-0.82; P < .001
- 2 y: HR, 0.77; 95% CI, 0.68-0.87; P < .001

- 6 mo: HR, 0.71; 95% CI, 0.57-0.88; P = .001

Cumulative incidence, %

Time since randomization, y

B. Worsening HF event

- 30 d: HR, 0.51; 95% CI, 0.30-0.86; P = .01
- 1 y: HR, 0.51-0.73; 95% CI, 0.63-0.85; P < .001
- 2 y: HR, 0.73; 95% CI, 0.63-0.85; P < .001

- 6 mo: HR, 0.57; 95% CI, 0.45-0.72; P < .001

Cumulative incidence, %

Time since randomization, y

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.4

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.

ARTICLE INFORMATION

Accepted for Publication: September 7, 2022.
Published Online: October 3, 2022
Open Access: This is an open access article distributed under the terms of the CC-BY-NC-ND License. © 2022 Vaduganathan M et al. JAMA Cardiology.

Author Affiliations: Cardiovascular Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts (Vaduganathan, Claggett, Desai, Hegde, Solomon); British Heart Foundation, University of Glasgow, Glasgow, Scotland (Jhund, McMurray); University of Groningen, Groningen, the Netherlands (de Boer); Duke University Medical Center, Durham, North Carolina (Hernandez); Associate Editor, JAMA Cardiology (Hernandez); Yale School of Medicine, New Haven, Connecticut (Inzucchi); Saint Luke’s Mid America Heart Institute, Kansas City, Missouri (Kosiborod); University of Missouri–Kansas City, Kansas City, Missouri (Kosiborod); National Heart Centre Singapore, Duke–National University of Singapore, Singapore (Lam); Universidad Nacional de Córdoba, Córdoba, Argentina (Martinez); Northwestern University Feinberg School of Medicine, Chicago, Illinois (Shah); AstraZeneca, Gothenburg, Sweden (Lindholm, Peterson, Langkilde).

Author Contributions: Drs Vaduganathan and Solomon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Vaduganathan, Hernandez, Kosiborod, Lam, Shah, Desai, Peterson, Langkilde, Solomon. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Vaduganathan, Claggett, Desai. Critical revision of the manuscript for important intellectual content: Vaduganathan, Jhund, de Boer, Hernandez, Inzucchi, Kosiborod, Lam, Martinez, Shah, Desai, Hegde, Lindholm, Petersson, Langkilde, McMurray, Solomon.
Conflict of Interest Disclosures: Dr Vaduganathan has received personal fees from Amgen, AstraZeneca, Baxter HealthCare, Bayer, Boehringer Ingelheim, CytokineRx, Relypsa, American Regent, Novartis, Roche Diagnostics, Lexicon Pharmaceuticals, Galmed, Oclutech, Impulse Dynamics, Pharmacosmos, Sanofi, and Tricofrog Health outside the submitted work. Dr Claggett has received personal fees from Boehringer Ingelheim, Cardurion, Corvia, and Novartis outside the submitted work. Dr Jhund has received grants from the British Heart Foundation and research support from AstraZeneca paid to his employer during the conduct of the study; research support from Novartis, Bayer, and Novo Nordisk paid to his employer; and personal fees from Boehringer Ingelheim outside the submitted work. Dr Boer has received personal fees from Abbott, AstraZeneca, Boehringer Ingelheim, Caridor Pharmaceuticals, Ionis Pharmaceuticals, Novo Nordisk, and Roche paid to his institution and personal fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche during the conduct of the study. Dr Hernandez has received personal fees from AstraZeneca during the conduct of the study; grants from AstraZeneca, American Regent, and Verily; and personal fees from Amgen, Bayer, Boehringer Ingelheim, Boston Scientific, Biofourmis, Cytokinetics, Merck, Bristol Myers Squibb, Somologie, Novo Nordisk, and Novartis outside the submitted work. Dr Inuzuka has received personal fees from AstraZeneca during the conduct of the study; personal fees from AstraZeneca, Novo Nordisk, Lexicon, vTv Therapeutics, Merck/Pfizer, Esperion, and Abbott; and nonfinancial support from Boehringer Ingelheim outside the submitted work. Dr Kosiborod has received grants from AstraZeneca and Boehringer Ingelheim as well as personal fees from AstraZeneca, Boehringer Ingelheim, Alynlam, Amgen, Applied Therapeutics, Bayer, Cytokinetics, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck, Novo Nordisk, Pharmacosmos, Sanofi, and Vifor outside the submitted work. Dr Lam has received grants from National Medical Research Council of Singapore, Bayer, and Roche Diagnostics as well as personal fees from Abbott, Actelion, Alveignant Medical, Albyssa Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Danma, EchoNous, Eli Lilly, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development, Medscape/WebMD Global, Merck, Novartis, Novo Nordisk, Proscentio, Radcliffe Group, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai outside the submitted work; has patented PCT/SG/2016/052017 pending and patent PCT/SG/2017/02247 issued; and is co-founder and a director of Us2.ai. Dr Martinez has received personal fees from AstraZeneca during the conduct of the study as well as grants from Novartis and personal fees from Bayer, Gado, and Bago outside the submitted work. Dr Shah has received personal fees from AstraZeneca during the conduct of the study as well as grants from the National Institutes of Health, Actelion, AstraZeneca, Corvia, Novartis, and Pfizer and personal fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, British Science Foundation, Bristol Myers Squibb, Cardiora, CytRx, Cyvion, Cytokinetics, Edwards Lifesciences, Eisai, Elstar, Impulse Dynamics, Intellia, Ionis, Ironwood, Lilly, Merck, Myokardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Shifamed, Tenax, Tenaya, and United Therapeutics outside the submitted work. Dr Claggett has received personal fees from Boehringer Ingelheim, Cardurion, Corvia, and Novartis outside the submitted work. Dr Jhund has received grants from the British Heart Foundation and research support from AstraZeneca paid to his institution and personal fees from AstraZeneca during the conduct of the study as well as grants from Abbott, Alynlam, Bayer, and Novartis paid to his institution and personal fees from Abbott, Alynlam, Amgen, Avidity, Bayer, Boston Scientific, Biofourmis, Avon Therapeutics, Cytokinetics, GlaxoSmithKline, Medpace, Merck, Novartis, Parexel, Regeneron, Roche, Verily, and NewAmsterdam outside the submitted work. Dr Hegde has received research payments paid to her institution from Bristol Myers Squibb outside the submitted work. Dr McMurray has received consulting fees from AstraZeneca paid to his institution during the conduct of the study as well as consulting fees from Bayer, Aymen, Servier, Theracos, Dalcour, GloxolSmithKline, Bristol Myers Squibb, Alynlam, Ionis Pharmaceuticals, Cardurion, Boehringer Ingelheim, and Novartis paid to his institution and personal fees from Abbott, Alkem Metabolics, Eis Lifesciences, Ikiha, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, and Cortex outside the submitted work. Dr Solomon has received grants from AstraZeneca paid to his institution during the conduct of the study as well as grants from Actelion, Alynlam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eis, Gilead, GloxolSmithKline, Ionis, Lilly, Mesoblast, Myokardia, the National Heart, Lung, and Blood Institute, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and Us2.ai paid to his institution and personal fees from Abbott, Action, Akros, Alynlam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiora, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GloxolSmithKline, Dalcour, Lilly, Merck, Mykardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremell, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Puretech Health outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by AstraZeneca.

Role of the Funder/Sponsor: The DELIVER trial was designed by the academic members of the executive committee in collaboration with representatives from AstraZeneca. AstraZeneca was involved in the overall design and conduct of the trial and collection, management, and interpretation of the data but had no role in the statistical analysis of the study and drafting of the manuscript; or decision to submit the manuscript for publication. Coauthors who are employees of AstraZeneca reviewed and approved the manuscript in accordance with authorship guidelines.

Disclaimer: Dr Hernandez is Associate Editor of JAMA Cardiology, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

REFERENCES