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ORIGINAL INVESTIGATIONS

Estimated Long-Term Benefit of Dapagliflozin in Patients With Heart Failure

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ABSTRACT

BACKGROUND Recent guidelines support consideration of sodium-glucose cotransporter-2 inhibitors in the long-term management of heart failure (HF) with mildly reduced or preserved ejection fraction. Patients and clinicians may be interested in the expected lifetime benefits of sodium-glucose cotransporter-2 inhibitors in this population.

OBJECTIVES This study aimed to estimate event-free survival gains from long-term use of dapagliflozin in patients with HF with mildly reduced or preserved ejection fraction overall and in clinically relevant subgroups.

METHODS In this prespecified analysis of DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), we applied validated nonparametric age-based methods to extrapolate potential gains in survival free from the primary endpoint (cardiovascular death or worsening HF event) from long-term use of dapagliflozin. Eligible participants had symptomatic HF, left ventricular ejection fraction >40%, elevated natriuretic peptide levels, and structural heart disease. For every year between the ages of 55 and 85 years, we estimated event-free survival using age at randomization rather than time from randomization as the time horizon. Residual lifespan free from a primary endpoint was estimated based on area under the survival curve in each arm.

RESULTS Among 6,263 participants, mean survival free from the primary endpoint for a 65-year-old participant was 12.1 years (95% CI: 11.0-13.2 years) with dapagliflozin and 9.7 years (95% CI: 8.8-10.7 years) with placebo, representing a 2.3-year (95% CI: 0.9-3.8 years) event-free survival gain ($P = 0.002$). Treatment gains in survival free from the primary endpoint ranged from 2.0 years (95% CI: -0.6 to 4.6 years) in a 55-year-old to 1.2 years (95% CI: -0.1 to 2.4 years) in a 75-year-old patient. Mean event-free survival was greater with dapagliflozin than with placebo across all 14 subgroups.

CONCLUSIONS Treatment with dapagliflozin is projected to extend event-free survival by up to 2.0 to 2.5 years among middle-aged and older individuals with HF with mildly reduced or preserved ejection fraction. (DELIVER [Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure]; NCT03619213) (J Am Coll Cardiol 2022;80:1775-1784) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction

SGLT = sodium-glucose cotransporter

Heart failure with preserved ejection fraction (HFpEF) is a chronic disease punctuated by worsening heart failure (HF) events and decrements in health status.[1] Despite improvements in care and treatment options for comorbidities, an older person hospitalized for HFpEF has a life expectancy that is up to 15 years shorter than what may be expected for a similarly aged person without HF in the United States.[2] As such, extending meaningful survival free from these clinical events remains a central treatment priority in the management of HFpEF. Until recently, however, there have been no disease-modifying therapies available for the treatment of HFpEF, and management has largely focused on amelioration of symptoms of congestion over a near-term time horizon.

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Two large-scale randomized clinical trials of sodium-glucose cotransporter-2 (SGLT-2) inhibitors have now shown reductions in composite cardiovascular death or worsening HF events in patients with HF with mildly reduced or preserved ejection fraction with median follow-up of 2.0 to 2.5 years.[3,4] Recent clinical practice guidelines now support consideration of SGLT-2 inhibitors in the long-term treatment of patients with HF across the spectrum of left ventricular ejection fraction (LVEF), including those with mildly reduced or preserved ejection fraction (Class IIa).[5] In light of this new therapeutic application of SGLT-2 inhibitors, clinicians may be interested in the expected benefits with long-term use of these therapies in patients with HF with mildly reduced or preserved ejection fraction, and in a metric of benefit that patients can easily understand. In this prespecified analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial, using previously validated actuarial methods, we extrapolated the potential gains in event-free survival from long-term use of dapagliflozin in patients with HF with mildly reduced or preserved ejection fraction overall and in 14 clinically relevant subgroups.[6]

METHODS

DELIVER TRIAL DESIGN. The design, baseline characteristics, and primary results of the DELIVER trial have been previously published.[3,7,8] In brief, DELIVER was a phase 3, global, randomized double-blind place-controlled clinical trial of dapagliflozin in patients with HF with mildly reduced or preserved ejection fraction. The trial enrolled adults aged 40 years or older, with symptomatic HF (New York Heart Association functional class II-IV), LVEF >40%, elevated levels of N-terminal pro-B-type natriuretic peptide (at least 300 pg/mL in those without atrial fibrillation or flutter or at least 600 pg/mL in those in atrial fibrillation or flutter), and evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy). Patients with or without type 2 diabetes and those in ambulatory care or hospitalized settings were enrolled in DELIVER. Patients with HF with previously reduced, but since improved ejection fraction >40% were permitted to be enrolled. Key exclusion criteria included alternative etiologies other than HF for functionally limiting symptoms, SGLT-2 inhibitor use within 4 weeks, intolerance or allergy to SGLT-2 inhibitors, type 1 diabetes, estimated glomerular filtration rate <25 mL/min/1.73 m^2, systolic blood pressure <95 mm Hg or ≥180 mm Hg (or ≥160 mm Hg unless using ≥3 blood pressure-lowering therapies), active malignancy requiring treatment, severe acute or chronic liver disease, and life expectancy <2 years due to a noncardiovascular condition. Eligible participants were randomized 1:1 to dapagliflozin 10 mg once daily or matching placebo and randomization was stratified by type 2 diabetes status. Local ethics committees or Institutional Review Boards at each participating site approved the study protocol, and each patient provided written informed consent before participation.

PRIMARY ENDPOINT. The primary endpoint of the DELIVER trial was time to first occurrence of the composite of death from cardiovascular causes or worsening HF event (which included unplanned hospitalization for HF or urgent HF visit requiring intravenous HF therapies). Unknown or undetermined deaths where insufficient information was available to assign a specific cause of death were not assumed to be cardiovascular deaths in DELIVER. All deaths and potential worsening HF events were adjudicated by a Clinical Endpoints Committee (Brigham and Women's Hospital, Boston, Massachusetts, USA, and University of Glasgow, Glasgow,

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Scotland, United Kingdom) blinded to treatment allocation.

STATISTICAL ANALYSIS. In this prespecified analysis of DELIVER, we applied previously validated nonparametric age-based methods to extrapolate potential gains in survival free from the primary endpoint from long-term use of dapagliflozin.[6] We first reshaped the time horizon from time of randomization to a clinical event to age at randomization to a clinical event. Applying restricted mean survival time methods, we estimated residual survival free from the primary endpoint at every given age separately for the dapagliflozin and placebo arms. We then constructed lifetime event-free survival curves by treatment arm using Kaplan-Meier methods and projected event-free survival was estimated as area under the survival up to maximum of 100 years. At least 1 study participant in each arm survived through age 100 years during trial follow-up. Because randomization balanced treatment allocation across the age spectrum, differences in areas under the lifetime survival curves reflected treatment response on number of years free from the primary endpoint. We next repeated this process to estimate treatment effects of residual event-free survival at every age between 55 years and 85 years. We applied a locally weighted scatterplot smoothing procedure to model event-free survival gains with dapagliflozin together with 95% CIs across the age spectrum.[9] Finally, we examined residual event-free survival in each treatment arm in 14 subgroups using a starting age of 65 years as an example and to align with prior investigations.[10] As a sensitivity analysis to address potential competing risks of noncardiovascular death, we evaluated the endpoint of death from any cause or a primary event. For descriptive purposes, clinical characteristics and baseline medications were summarized for the DELIVER trial population by treatment arm.

Analyses were conducted among all 6,263 randomized and followed intention-to-treat principles. This analysis across the lifetime horizon was prespecified in the DELIVER Academic Statistical Analysis Plan, which was developed before trial unmasking. Actuarial estimates were calculated using STATA, version 17 (StataCorp). Two-sided P values <0.05 were considered statistically significant.

RESULTS

BASELINE CLINICAL PROFILES. From September 1, 2018, to January 18, 2021, 6,263 participants with HF with mildly reduced or preserved ejection fraction were randomized in the DELIVER trial across 350 sites in 20 countries. The mean age at randomization was 72 ± 10 years. Age at randomization ranged from 40 to 99 years and no participant had missing baseline age. Supplemental Table 1 shows the baseline characteristics of DELIVER by treatment arm. Clinical profiles and baseline medication use were well balanced between randomized arms.

PRIMARY ENDPOINT EVENTS DURING FOLLOW-UP. Overall, 6,211 (99%) had complete follow-up for the primary endpoint and 3 participants were lost to follow-up. The study drug was discontinued for any reason in 886 participants during follow-up. Over a median follow-up time of 2.3 years, 1,122 primary endpoint events occurred with an incidence rate of 8.7 per 100 patient-years (95% CI: 8.2-9.2 per 100 patient-years). Of all first primary endpoints, 300 (27%) were cardiovascular deaths, 718 (64%) were hospitalizations for HF, and 104 (9%) were urgent HF visits. Overall, there were 1,023 deaths of any cause of which 492 (48%) were adjudicated as cardiovascular, 385 (38%) were noncardiovascular, and 146 (14%) were undetermined/unknown in cause.

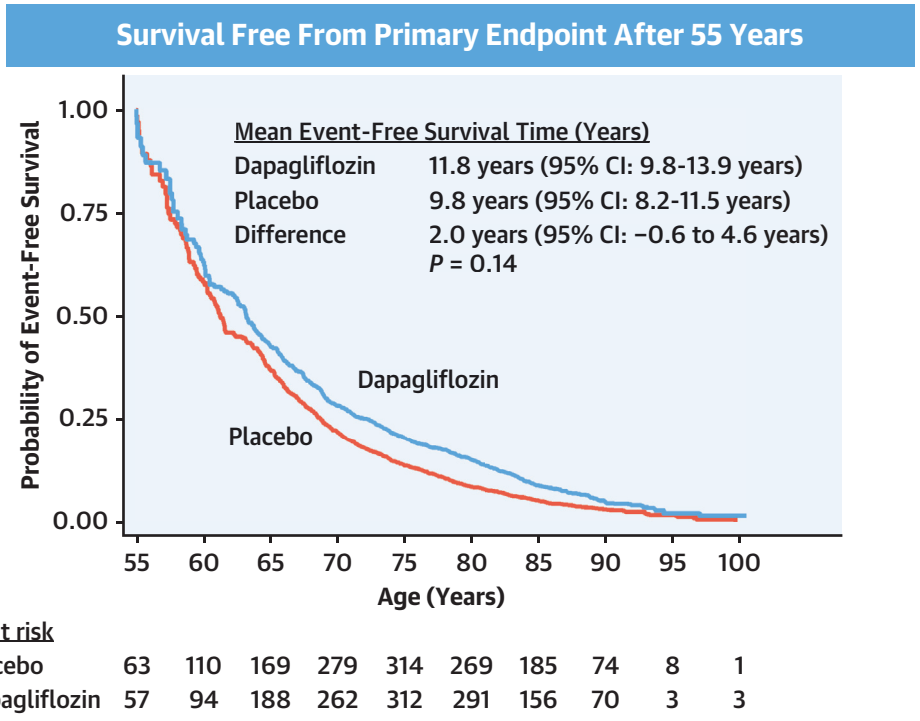
TREATMENT EFFECTS OF DAPAGLIFLOZIN. As previously reported, dapagliflozin reduced the risk of the primary endpoint by 18% compared with placebo (HR: 0.82; 95% CI: 0.73-0.92).[3] Models accounting for competing risks of noncardiovascular death yielded similar findings (subdistribution HR: 0.82; 95% CI: 0.73-0.92).[3]

There was no heterogeneity in treatment effects of dapagliflozin by age either when analyzed at the median age cutpoint or when analyzed continuously ($P_{interaction}$ >0.20 for both). Treatment effects of dapagliflozin on all-cause mortality were not statistically significant (HR: 0.94; 95% CI: 0.83-1.07).[3]

LONG-TERM EVENT-FREE SURVIVAL PROJECTIONS. At age 55 years, the estimated survival free from the primary endpoint was 11.8 years (95% CI: 9.8-13.9 years) with dapagliflozin and 9.8 years (95% CI: 8.2-11.5 years) with placebo (difference: 2.0 years [95% CI: −0.6 to 4.6 years]; $P = 0.14$) (**Central Illustration A**). At age 65 years, the estimated event-free survival was 12.1 years (95% CI: 11.0-13.2 years) with dapagliflozin and 9.7 years (95% CI: 8.8-10.7 years) with placebo (difference: 2.3 years [95% CI: 0.9-3.8 years]; $P = 0.002$) (**Central Illustration B**). At age 75 years, the estimated event-free survival was 10.6 years (95% CI: 9.7-11.5 years) with dapagliflozin and 9.4 years (95% CI: 8.6-10.3 years) with placebo (difference: 1.2 years [95% CI: −0.1 to 2.4 years]; $P = 0.063$) (**Central Illustration C**). Mean event-free survival gains with dapagliflozin vs placebo at every starting age from 55 years to 85 years are displayed

CENTRAL ILLUSTRATION **Event-Free Survival in the DELIVER Trial by Age at Randomization**

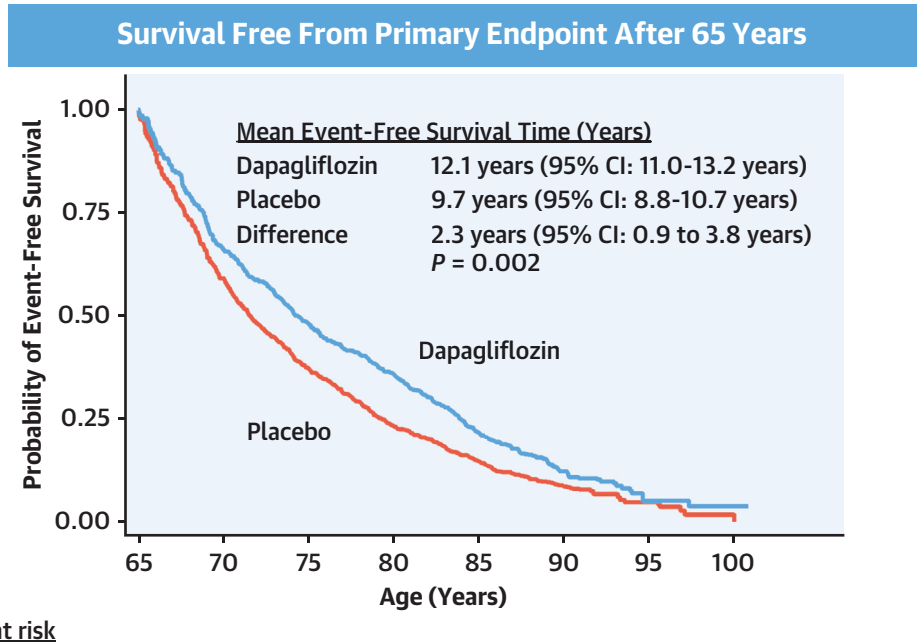
A



Number at risk

Placebo	63	110	169	279	314	269	185	74	8	1
Dapagliflozin	57	94	188	262	312	291	156	70	3	3

B



Number at risk

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Age-based Kaplan–Meier curves are displayed for patients at age 55 years **(A),** 65 years **(B),** and 75 years **(C)** for survival free from the primary endpoint (cardiovascular death or worsening heart failure event) between dapagliflozin and placebo arms. DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure.

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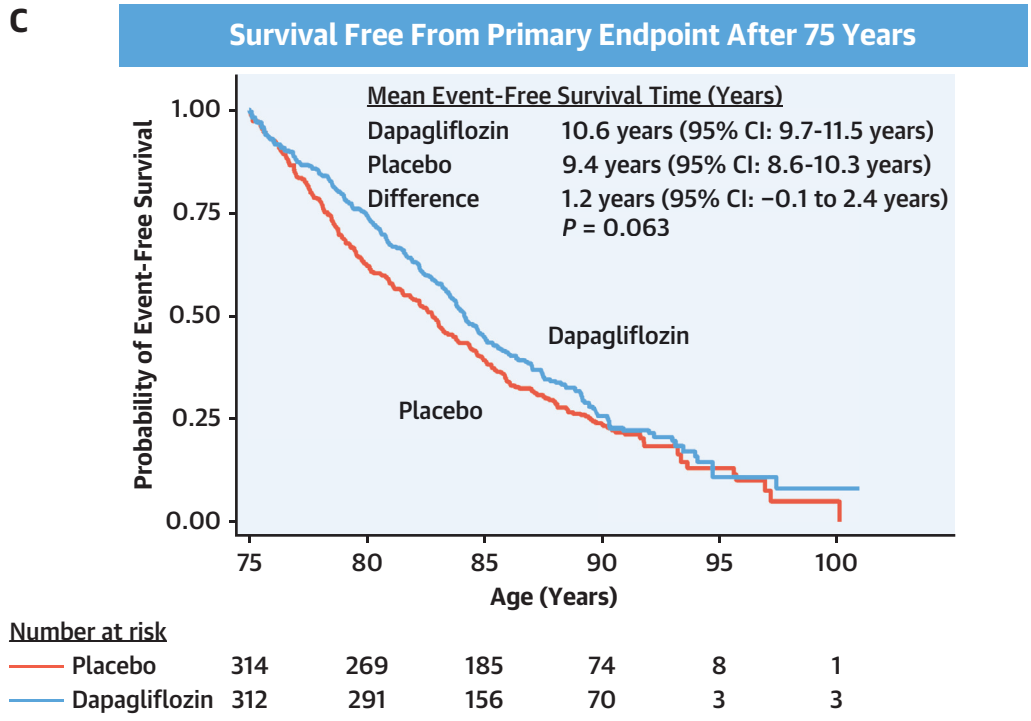
CENTRAL ILLUSTRATION Continued



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in Figure 1. Upon visual inspection, absolute benefits in event-free survival in the magnitude of ~1.0 to 2.5 years were observed across the age spectrum with attenuation after ~80 years. Using a starting age of 65 years as an example, mean event-free survival was greater with dapagliflozin compared with placebo across 14 subgroups, including those defined by LVEF, type 2 diabetes status, and concomitant use of other HF therapies (Figure 2). Mean event-free survival gains were similar among participants with HF with improved ejection fraction (2.7 years [95% CI: -0.4 to 5.9 years]) and those with LVEF always >40% (2.3 years [95% CI: 0.7 to 3.9 years]). In a sensitivity analysis analyzing the endpoint of time to death from any cause or a primary event at a starting age of 65 years, projected event-free survival would be 7.6 years (95% CI: 6.8-8.4 years) with placebo and 9.2 years (95% CI: 8.3-10.0 years) with dapagliflozin, yielding an estimated gain in event-free survival of 1.6 years (95% CI: 0.4-2.7 years) with long-term treatment.

DISCUSSION

In this prespecified analysis of the DELIVER trial, treatment with dapagliflozin is projected to extend event-free survival substantially among middle aged and older individuals with HF with mildly reduced or preserved ejection fraction. Absolute gains in event-free survival were meaningful in magnitude and were observed across a broad age range up to approximately 80 years and in clinically relevant subpopulations. These survival estimates may inform shared decision-making between patients and clinicians regarding the initiation and long-term use of dapagliflozin in this population.

Randomized trials evaluating clinical outcomes in HF have typically been conducted with 1 to 3 years of follow-up. Although these pivotal studies form the foundation of the evidence base to guide clinical decision-making, regulatory approvals, and guideline recommendations, patients and clinicians may be interested in the anticipated therapeutic effects over a longer-term horizon. Rather than time-limited trials, contemporary clinical practice guidelines put forth recommendations for medical therapies, including SGLT-2 inhibitors, for long-term use.[5,11] Furthermore, traditional clinical trial metrics for reporting (such as the HR) are intrinsically difficult to interpret and translate to individual patients.[12] Moreover, patients themselves may have limited understanding of relative and absolute risks and their

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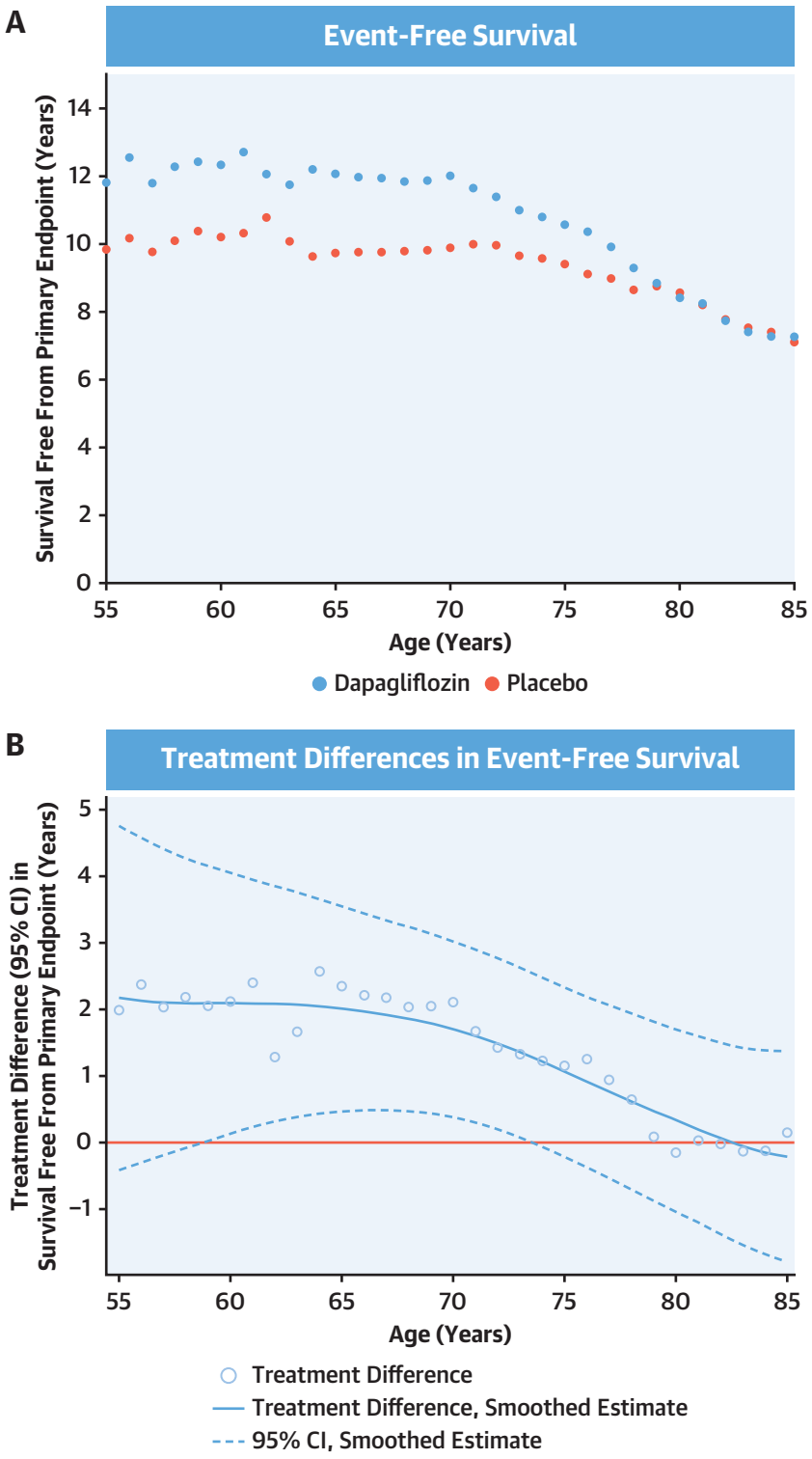
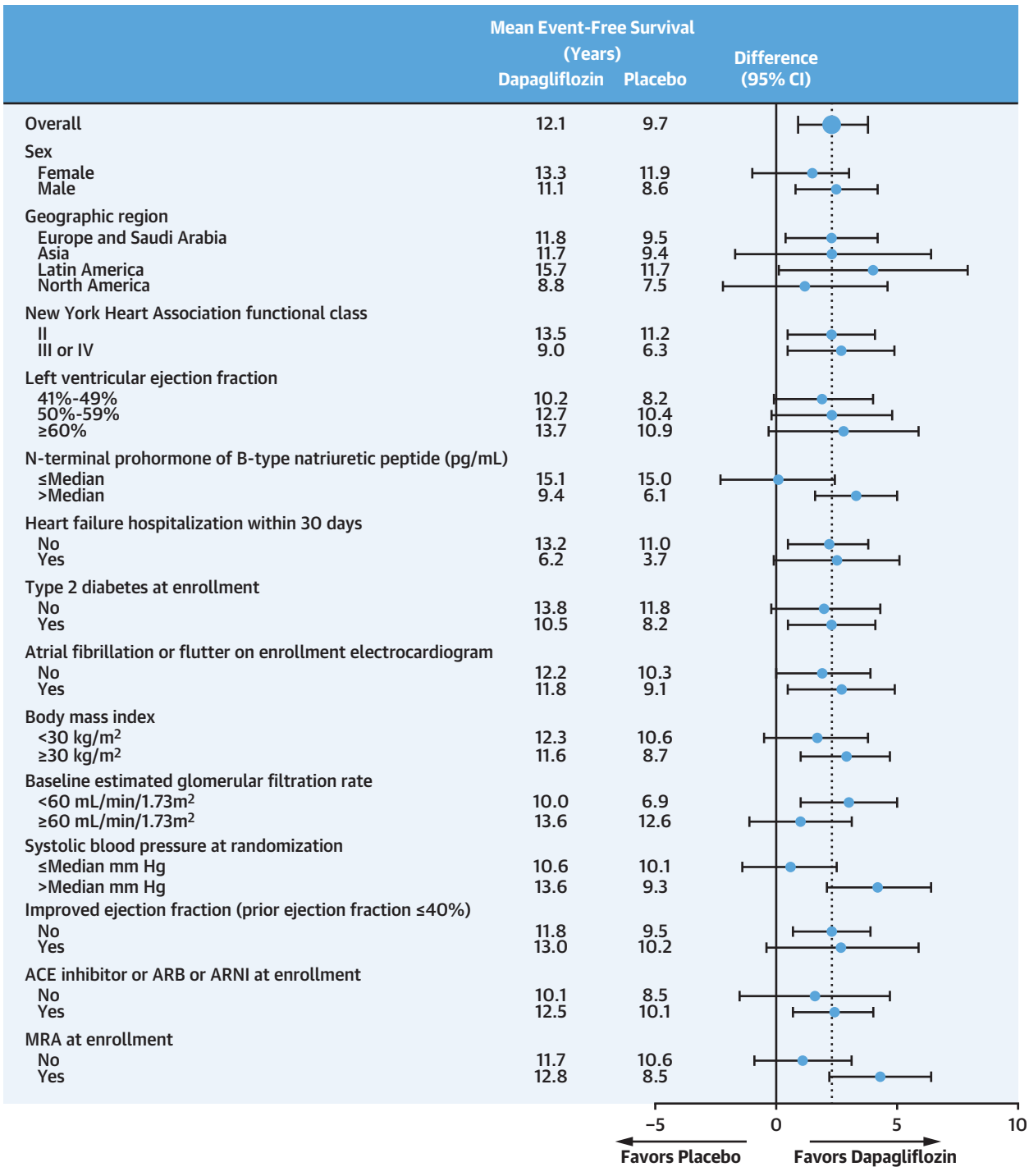
FIGURE 1 **Effect of Dapagliflozin on Residual Event-Free Survival in DELIVER**



Estimated mean event-free survival times in the dapagliflozin and placebo arms of DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) **(A)** and estimated treatment differences and 95% CIs in mean event-free survival with application of a locally weighted scatterplot smoothing procedure **(B)**. The **red line** represents null effect.

FIGURE 2 Projected Event-Free Survival Among Subgroups at Starting Age of 65 Years



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist.

distinctions. Other methods such as restricted mean survival time capture absolute treatment effects, but are still limited to the period of clinical trial follow-up, and thus are likely to underestimate the expected absolute benefits with long-term use of a therapy beyond the duration of the trial.[13]

To address these limitations of traditional clinical trials and their reporting, we developed a novel nonparametric age-based method to leverage individual patient-level data from clinical trials to extrapolate long-term survival and potential absolute gains with an intervention. These actuarial methods were previously validated in the SOLVD (Studies of Left Ventricular Dysfunction) treatment trial.[6] Using individual patient-level data from the original SOLVD treatment trial, long-term survival and life expectancy were modeled and forecasted based on within-trial data with follow-up over 3.5 years. These estimates of long-term survival with application of the actuarial methods aligned well with observed survival during extended 12-year follow-up of the SOLVD treatment trial.[14] Since initial introduction, these actuarial methods have been applied to trials of HF with reduced ejection fraction, post-myocardial infarction left ventricular dysfunction, diabetes, and hypertension.[6,10,15-19] To our knowledge, this prespecified analysis of DELIVER is the first application to HF with mildly reduced or preserved ejection fraction. These DELIVER results provide insights into the anticipated gains in life expectancy free from clinical events with long-term use of dapagliflozin. This metric may be more understandable to patients than traditional clinical trial results and informative in shared decision-making discussions regarding the initiation and long-term continuation of dapagliflozin.

DELIVER was well-represented and included patients with a broad spectrum of ages with approximately one-quarter of participants older than the age of 80 years. This facilitated stable estimates of event-free survival including among older adults in whom HFpEF is especially prevalent. Incorporating estimates of residual life expectancy free from clinical events and prognosis in discussions with patients has been challenging in HF, especially among older individuals who may have other competing clinically relevant comorbidities. However, providing estimates of timelines of meaningful event-free survival can help guide end-of-life planning, caregiver support, and shared decision-making regarding the use of a new therapy.

The absolute gains in event-free survival with dapagliflozin in DELIVER were estimated to be up to 2.0 to 2.5 years, which is in line with long-term benefits estimated with other effective therapies in HF with reduced ejection fraction.[6,10,16] In the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, long-term treatment with dapagliflozin was estimated to extend event-free survival by 2.1 years in a 65-year-old (similar to 2.3 years in DELIVER) and by 1.2 years in a 75-year old (similar to 1.2 years in DELIVER).[10] Estimated lifetime benefits of an intervention may depend on age at initiation, residual lifespan (inversely related to baseline clinical risk), and the relative risk reduction with a therapeutic intervention. As the relative benefits of dapagliflozin were largely consistent across patient subsets in DELIVER, absolute long-term gains in event-free survival for an individual patient may depend to a large degree on their age and other factors that determine their risk profile. Although some variation was observed likely as a function of baseline risk, projected event-free survival for a 65-year-old patient was longer with dapagliflozin than with placebo across all 14 subgroups examined, including those defined by LVEF, those with and without type 2 diabetes, and those already treated with other HF therapies such as mineralocorticoid receptor antagonists.

As there was no significant benefit observed in DELIVER on all-cause mortality, our modeling focused on survival free from first primary outcome events. In other diseases, such as cancer, event-free survival has been long used as a surrogate for overall survival. We postulate that this methodology may be useful to better summarize the true overall effect of a given treatment beyond effects on mortality alone. However, this event-free survival measure does not account for the burden of disease; instead it focuses on number of years gained free from a first clinical event. DELIVER has shown clinical benefits from dapagliflozin in preventing recurrent HF events and on multiple domains of health-related quality of life. As such, this extension in event-free survival is likely to be meaningful as it is accompanied by concurrent improvements in health status and lower burden of recurrent clinical events.[3] However, we observed potential attenuation in absolute benefits in event-free survival after the age of ~80 years. It is possible that the likely benefit of a cardiovascular therapy may decline with increasing age as older individuals may have other, competing nonmodifiable comorbidities. Residual survival free from clinical events is especially short among those older than 80 years, and this abbreviated clinical trajectory may be challenging to modify. In the clinical care of this older segment of the population, these actuarial estimates may be helpful in shared decision-making as initiation of dapagliflozin may not be anticipated to prolong survival but could still improve quality of life and functional status.

STUDY LIMITATIONS. Forecasting long-term event-free survival and treatment benefits based on within-trial follow-up alone relies on a number of assumptions. First, a central assumption is that the efficacy of dapagliflozin would remain relatively stable with long-term use. In DELIVER, there was a significant time-treatment interaction such that the efficacy of dapagliflozin was most apparent shortly after randomization. However, relative treatment benefits with dapagliflozin were observed throughout the 2.3-year median follow-up without apparent convergence in survival curves on visual inspection. Furthermore, application of an alternative model that is not reliant on the assumption of proportional hazards showed similar treatment effect estimates during the trial.[3] Because of the global conduct of this trial, we do not have linked records across the 20 countries to allow long-term follow-up to validate these actuarial estimates. Second, although the analysis followed intention-to-treat principles and thus accounted for within-trial treatment discontinuation, adherence to dapagliflozin in real-world settings may be different than observed among DELIVER participants during the trial. Third, this analysis did not account for interval events that occur over time, including development of comorbidities, which may alter survival estimates, the risk-benefit profile of dapagliflozin, or influence adherence or tolerability to dapagliflozin. Fourth, although this analysis was prespecified, the trial was not designed or powered to assess absolute benefits on event-free survival in individual subgroups, and no adjustment for multiplicity was performed. Finally, our estimates of residual event-free survival with dapagliflozin are only applicable to individuals similar to those enrolled in the DELIVER trial, and may not generalize to patients with HF with mildly reduced or preserved ejection fraction who were sicker with life-limiting comorbidities (who would have been excluded from the trial). Although we acknowledge that these factors may lead to overly optimistic estimated lifetime benefits with dapagliflozin, we believe these age-based methods provide ancillary information to traditional clinical trial reporting to better inform decision-making around treatment initiation and continuation in clinical care. Patients and clinicians contemplating use of dapagliflozin may consider these data on expected long-term efficacy alongside information on safety, cost, and therapeutic value.

CONCLUSIONS

Based on modeling projections from the DELIVER trial, treatment with dapagliflozin may extend event-free survival by up to 2 to 2.5 years among middle aged and older individuals with HF with mildly reduced or preserved ejection fraction. These data reinforce the primary results of the relative benefits of dapagliflozin during the DELIVER trial, and provide alternative reframing of the absolute benefits with use of dapagliflozin during the remaining lifetime of the individual.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Modeling projections from clinical trial data suggest that long-term treatment with the SGLT-2 inhibitor, dapagliflozin, extends event-free survival up to 2.5 years among middle-age and older patients who have heart failure with mildly reduced or preserved left ventricular ejection fraction.

TRANSLATIONAL OUTLOOK: Estimates of improvement in long-term event-free survival should be incorporated in shared decision-making discussions between clinicians and patients with heart failure considering initiation and long-term treatment with SGLT-2 inhibitors.

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KEY WORDS heart failure with mildly reduced ejection fraction, heart failure with preserved ejection fraction, implementation science, modeling, sodium-glucose cotransporter-2 inhibitors

APPENDIX For a supplemental table, please see the online version of this paper.