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RESEARCH ARTICLE

Influence of background medical therapy on efficacy and safety of dapagliflozin in patients with heart failure with improved ejection fraction in the DELIVER trial

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Aims

The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial demonstrated the sodium–glucose cotransporter 2 inhibitor dapagliflozin to be beneficial in patients with symptomatic heart failure (HF) with improved ejection fraction (HFimpEF; those with prior left ventricular ejection fraction ≤40% that had improved to >40% by enrolment). Whether this benefit differs by background medical therapy is unclear. The current study aims to determine the efficacy and safety of dapagliflozin among patients with HFimpEF by background medical therapy.

Methods and results

Treatment effects on the primary endpoint (worsening HF or cardiovascular death) were assessed by number of background HF medical therapies (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor, evidence-based beta-blocker, and mineralocorticoid receptor antagonist). Among the 6263 patients randomized in DELIVER, 1151 (18%) had HFimpEF. Of those, 21% of patients were on 0–1 therapies, 44% were on two therapies, and 35% were on three therapies. During 2.3 years of median follow-up, the incidence rate of the primary outcome was 9.7, 8.8, and 8.4 per 100 person-years for patients on 0–1, 2 and 3 HF medications at baseline, respectively. Treatment effects with dapagliflozin on the primary outcome may be greater in patients with HFimpEF on 0–1 therapies at baseline ($p_{interaction} = 0.09$), driven mostly by a significant interaction for HF hospitalization ($p_{interaction} = 0.023$) with no evidence of effect modification for cardiovascular death ($p_{interaction} = 0.65$). Treatment effects of dapagliflozin on the primary outcome were, however, consistent when assessed across the modified Heart Failure Collaboratory Medical Therapy Score integrating both therapeutic use and dosing ($p_{interaction} = 0.39$). The use of dapagliflozin was not associated with changes in use or doses of background HF therapies, and among patients on three HF medications at baseline, the addition of dapagliflozin did not lead to higher adverse events.

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Conclusions In patients with HFimpEF, the safety and efficacy of dapagliflozin were largely similar by background use and dosing of HF medical therapies. The benefit of dapagliflozin in reducing HF events tended to be greater in those patients on 0-1 medications at baseline. Among patients already on three HF medical therapies, the addition of dapagliflozin was safe without requiring de-escalation of other therapies.

Keywords Heart failure • HFimpEF • Medical therapy • Sodium–glucose cotransporter 2 inhibitors

Introduction

As the management of heart failure with reduced ejection fraction (HFrEF) advances, more patients are exhibiting improvements in left ventricular ejection fraction (LVEF). As such, the population of patients with HF with improved ejection fraction (HFimpEF, defined as HF with a baseline LVEF ≤40%, and a second measurement of LVEF >40%)[1] continues to grow.

The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines for the management of heart failure (HF) recommend continuing medical therapy that facilitated improvement in patients with HFimpEF to prevent relapse of their left ventricular dysfunction, as cardiac function does not fully normalize in many patients and some face persistent risk of adverse cardiovascular outcomes. Unfortunately, high-quality data on the ongoing medical optimization of patients with HFimpEF are limited as this population has been largely excluded from major clinical trials.[2]

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have shown benefits across the spectrum of HF.[3–7] The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial was the first large, randomized outcome study that included patients with HFimpEF, testing the incremental effects of initiation of medical therapy.[7] In this trial, dapagliflozin reduced the primary outcome of cardiovascular death and worsening HF compared to placebo in the subset with HFimpEF.[8] Whether this treatment effect is consistent irrespective of background medical therapy, including those who are already treated with traditional HFrEF medical therapies, is unclear. In this analysis, we investigated the efficacy and safety of dapagliflozin in patients with HFimpEF by HF medical therapy at baseline.

Methods

DELIVER was a randomized, double-blind, placebo-controlled trial in patients with HF and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), who were allocated to receive either dapagliflozin 10 mg daily or placebo, in addition to other recommended therapies. The details of the study design, inclusion/exclusion criteria, and primary results have been previously published.[9] Briefly, DELIVER was conducted at 353 sites in 20 countries, and included adults (≥40 years) with symptomatic HF with New York Heart Association class II–IV functional limitations, LVEF >40%, structural heart disease (left atrial enlargement or left ventricular hypertrophy), and elevated natriuretic peptide levels. Unlike prior trials in HFmrEF/HFpEF, patients were eligible if they had a history of LVEF ≤40%, if they fulfilled study entry criteria. The protocol was approved by the local ethics committees at each site and an independent monitoring committee reviewed the trial. Data from patients with HFimpEF were included in this analysis.

Exposure and outcomes

Background number of HF medical therapies were collected at each study visit. Number of medications were counted (angiotensin-converting enzyme inhibitor [ACEi], angiotensin receptor blocker [ARB], or angiotensin receptor–neprilysin inhibitor, evidence-based beta-blocker [BB], and mineralocorticoid receptor antagonist [MRA]). As such, the number of HF medical therapies could range from 0 (no therapies) to 3 (triple therapy with renin–angiotensin system inhibitor or ARNI, BB, and MRA). Dosing of background HF medications was analysed at baseline and during follow-up, except for ARNI, as dosing information was not consistently available. Additional analysis of background HF therapies was conducted using a modified version of the Heart Failure Collaboratory Medical Therapy Score.[10] The primary study outcome was a composite of time to cardiovascular death or worsening HF (defined as either unplanned hospitalization or an urgent non-hospitalized HF visit requiring intravenous therapy). Secondary outcomes included total HF events, cardiovascular death, and death from any cause. Clinical outcomes were adjudicated by an independent, blinded endpoint committee.

Statistical analysis

Baseline characteristics by number of background HF medical therapies were compared using counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, and medians and interquartile ranges for non-normally distributed continuous variables. To compare differences between groups we used a test for trend, using linear regression, Chi-squared trend tests and Cuzick's non-parametric trend test. Outcomes by number of background HF medical therapies were compared using Cox proportional hazards models stratified by geographic region and adjusted for the following covariates: age, sex, treatment arm, region, diabetes history, estimated glomerular filtration rate (eGFR), history of myocardial infarction, baseline LVEF, Kansas City Cardiomyopathy Questionnaire total symptom score, N-terminal pro-B-type natriuretic peptide, and systolic blood pressure. Selection of covariates for adjustment in our model was guided by both clinical relevance and statistically significant differences detected when comparing baseline characteristics. The treatment effect of dapagliflozin compared to placebo as a function of the number of background HF medical therapies was evaluated using Cox regression, with an interaction term between the number of background HF medical therapies and treatment group. In terms of medication analysis, patients who either died or were lost to follow-up at each study visit were also excluded. Post-randomization concomitant medication use was analysed using logistic regression, adjusted for baseline medication use. Reported concomitant medication doses

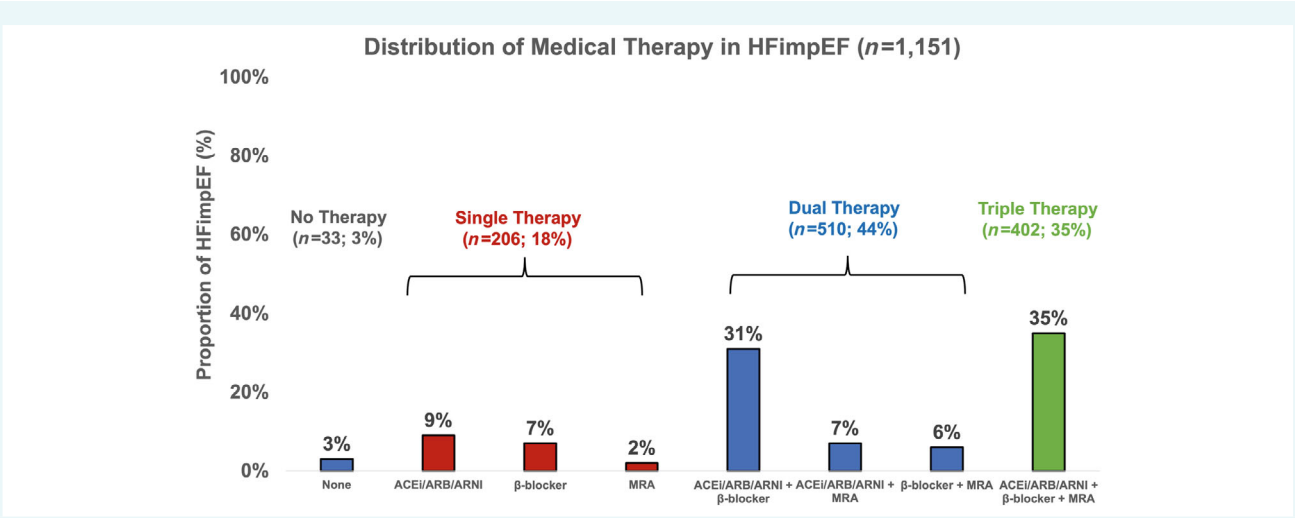

Figure 1 Distribution of medical therapy in heart failure with improved ejection fraction (HFimpEF) participants in DELIVER. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

were converted into equivalent doses of carvedilol, enalapril, losartan, and spironolactone for BBs, ACEi, ARBs, and MRAs, respectively (online supplementary *Table S1*), and then subsequently converted into percentages of the target dose for each class of medications. Values reported to be greater than 500% of the target dose were considered data entry errors and excluded from analysis. Post-randomization changes in these doses were analysed using linear regression, adjusting for the corresponding baseline dose. Safety and tolerability data were summarized using descriptive statistics. Statistical analyses were performed using STATA 16.1 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics

A total of 6263 patients were randomized to either dapagliflozin or placebo in the DELIVER trial. Of these, 1151 patients (18.0%) had HFimpEF. Among patients with HFimpEF, 572 were randomized to dapagliflozin and 579 to placebo. There were 239 patients (21%) receiving no or single therapy, 510 (44%) patients receiving two therapies, and 402 patients (35%) on triple therapy at baseline (*Figure 1*). Those on higher number of HF medical therapies tended to be younger, were more likely to be men, and less likely to have diabetes. Participants on higher number of HF medical therapies also tended to have a history of myocardial infarction, a lower ejection fraction, systolic blood pressure, and higher eGFR at baseline, and were more likely to have been treated with an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT). Among the patients who were taking BBs at the beginning of the study, 46% of them were prescribed doses that were ≥50% of the recommended target dose. For ACEi, this percentage was 21%, 54% in the case of ARBs and 97% in the case of MRAs (*Table 1*).

Baseline number of heart failure therapies, clinical event rates, and treatment effect

During a median follow-up of 2.3 years, the incidence rate for the primary outcome was 9.7 per 100 person-years among those on 0–1 background HF therapies, 8.8 per 100 person-years for those on two therapies, and 8.4 per 100 person-years among patients on three therapies. There were no significant differences in the primary or secondary outcomes across background HF medical therapy categories following covariate adjustment (*Table 2*). There was a marginal interaction between randomized treatment group and number of background HF therapies for the primary outcome ($p_{interaction} = 0.09$), and a significant interaction for the secondary outcome of HF event ($p_{interaction} = 0.023$) without evidence of effect modification for cardiovascular death ($p_{interaction} = 0.65$) (*Figure 2*). The treatment effect of dapagliflozin was greater in the subgroup of patients receiving 0–1 therapies at baseline (primary endpoint: hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.25–0.84) and worsening HF event: HR 0.41, 95% CI 0.20–0.81) (*Figure 2*). Relative effects of dapagliflozin on all-cause mortality were not significantly modified by the number of HF therapies at baseline ($p_{interaction} = 0.85$). Benefits of dapagliflozin were not modified by baseline doses of background medical therapy (online supplementary *Figure S1*). Treatment effects of dapagliflozin on the primary outcome were however consistent, when assessed across the modified Heart Failure Collaboratory Medical Therapy Score ($p_{interaction} = 0.39$) (online supplementary *Table S2*, *S3* and *Figure S2*).

Continuation of background heart failure therapies during follow-up

Among patients with HFimpEF treated with dapagliflozin there was no significant change in the proportion of patients receiving BBs,

Table 1 Baseline characteristics of heart failure with improved ejection fraction participants in the DELIVER trial by number of background heart failure medical therapies

Characteristic	Number of background HF medical therapies			
	0–1	2	3	*p*-value
n (%)	239 (21)	510 (44)	402 (35)	
Age, years	71.9 ± 10.1	70.8 ± 9.8	68.2 ± 10.0	<0.001
Male sex	133 (55.6)	356 (69.8)	285 (70.9)	<0.001
Race or ethnic group[a]				0.10
White	172 (72.0)	339 (66.5)	263 (65.4)	
Asian	44 (18.4)	133 (26.1)	113 (28.1)	
Black	7 (2.9)	20 (3.9)	9 (2.2)	
American Indian or Alaska native	7 (2.9)	9 (1.8)	5 (1.2)	
Other	9 (3.8)	9 (1.8)	12 (3.0)	
Region				<0.001
Europe and Saudi Arabia	91 (38.1)	212 (41.6)	179 (44.5)	
Asia	43 (18.0)	128 (25.1)	113 (28.1)	
Latin America	49 (20.5)	84 (16.5)	65 (16.2)	
North America	56 (23.4)	86 (16.9)	45 (11.2)	
Clinical features				
Atrial fibrillation or flutter	126 (52.7)	260 (51.0)	189 (47.0)	0.14
Type 2 diabetes mellitus	119 (49.8)	253 (49.6)	157 (39.1)	0.003
History of myocardial infarction	65 (27.2)	170 (33.3)	165 (41.0)	<0.001
History of dyslipidemia	168 (70.3)	342 (67.1)	258 (64.2)	0.11
History of coronary artery disease	83 (34.7)	197 (38.6)	151 (37.6)	0.56
Body mass index, kg/m^2	29.5 ± 6.1	29.1 ± 6.0	29.7 ± 5.9	0.51
Baseline left ventricular ejection fraction, %	53.6 ± 8.7	50.7 ± 8.4	48.5 ± 7.3	<0.001
NT-proBNP at baseline, pg/ml	925.0 [590.0–1660.0]	1010.5 [645.0–1811.0]	1046.0 [615.0–1700.0]	0.33
NYHA class				0.73
II	192 (80.3)	407 (79.8)	319 (79.4)	
III	47 (19.7)	102 (20.0)	80 (19.9)	
IV	0 (0.0)	1 (0.2)	3 (0.7)	
Median total symptom score on KCCQ	75.0 [56.2–89.6]	77.1 [58.3–93.8]	76.0 [60.4–91.7]	0.41
Systolic blood pressure, mmHg	130.2 ± 16.5	127.6 ± 16.4	125.0 ± 16.8	<0.001
Heart rate, bpm	72.0 ± 12.5	70.6 ± 12.5	70.3 ± 11.2	0.11
Baseline eGFR, ml/min/1.73 m^2	60.4 ± 19.6	60.8 ± 18.8	64.0 ± 19.2	0.011
HF therapy, *n* (%)				
ACEi or ARB	92 (38.5)	376 (73.7)	319 (79.4)	<0.001
MRA	27 (11.3)	151 (29.6)	402 (100.0)	<0.001
Beta-blocker	78 (32.6)	433 (84.9)	402 (100.0)	<0.001
Sacubitril/valsartan	9 (3.8)	60 (11.8)	83 (20.6)	<0.001
ICD or CRT	7 (2.9)	46 (9.0)	31 (7.7)	0.011
Doses of HF therapy ≥50% of target dose[b]				
Beta-blocker	45 (45.9)	220 (51.4)	216 (56.4)	0.041
ACEi	8 (21.1)	40 (20.2)	45 (23.2)	0.55
ARB	27 (54.0)	72 (46.5)	49 (45.4)	0.37
MRA	29 (96.7)	156 (98.1)	362 (95.8)	0.29

Values are given as *n* (%), mean ± standard deviation, or median [interquartile range].

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, Implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire.

[a]Race or ethnic group was reported by the patients.

[b]Target dose defined as equivalent total daily doses of 50 mg of carvedilol, 40 mg of enalapril, 150 mg of losartan and 25 mg of spironolactone. Only those receiving at least one medication at baseline were included in *Table 1*.

Table 2 Adjusted primary and secondary outcomes by number of background heart failure medical therapies[a]

Outcome	Number of background HF medical therapies						*p*-value
	0–1 (*n* = 239)		2 (*n* = 510)		3 (Ref.) (*n* = 402)		
	Incidence rates	HR	Incidence rates	HR	Incidence rates	HR	
Primary composite (CV death or worsening HF)	47 events [9.7/100py]	1.07 (0.70–1.64)	93 events [8.8/100py]	1.09 (0.78–1.52)	71 events [8.4/100py]	Ref.	0.71
CV death	18 events [3.4/100py]	1.16 (0.59–1.90)	40 events [3.5/100py]	1.10 (0.68–1.77)	29 events [3.2/100py]	Ref.	0.33
HF events	36 events [7.4/100py]	1.15 (0.76–1.76)	71 events [6.7/100py]	1.04 (0.73–1.5)	54 events [6.4/100py]	Ref.	0.92
HF hospitalization	33 events [6.7/100py]	1.29 (0.76–1.85)	63 events [5.9/100py]	1.04 (0.72–1.52)	48 events [5.6/100py]	Ref.	0.98
All-cause death	38 events [7.1/100py]	1.10 (0.73–1.64)	93 events [8.2/100py]	1.25 (0.90–1.73)	59 events [6.5/100py]	Ref.	0.82

CV, cardiovascular; HF, heart failure; HR, hazard ratio; py, person-years.

[a]All hazard ratios (HR) were adjusted by treatment, age, sex, region, diabetes, estimated glomerular filtration rate, history of myocardial infarction, left ventricular ejection fraction, Kansas City Cardiomyopathy Questionnaire total symptom score, N-terminal pro-B-type natriuretic peptide and systolic blood pressure.

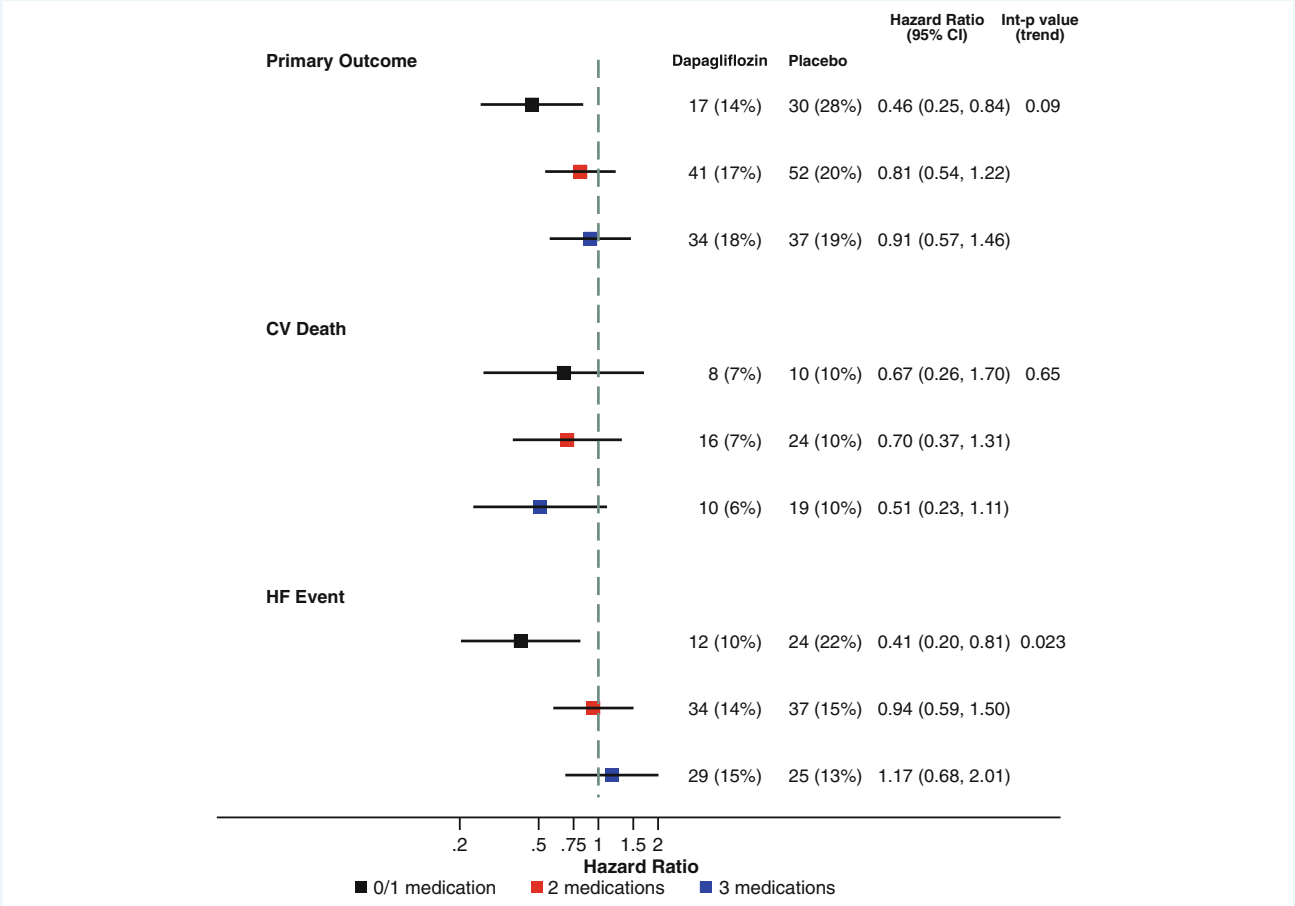

Figure 2 Treatment effect of dapagliflozin by number of background heart failure (HF) medical therapies. CI, confidence interval; CV, cardiovascular.

ACEi, ARBs, ARNI or MRAs during follow-up at 4, 8 and 12 months (*Figure 3*). Similarly, HFimpEF participants treated with dapagliflozin did not have a significant change in the percentage of target dose of BBs, ACEi, ARBs or MRAs used during follow-up at 4, 8, and 12 months (online supplementary *Table S4*). Doses of ARNI were not consistently available for analysis.

Adverse outcomes

Patients treated with dapagliflozin did not experience higher rates of adverse outcomes than those treated with placebo, irrespective of background number of HF therapies. Specifically, there were no significant differences in serious adverse events, study medication discontinuation or interruption, amputation, probable or definite

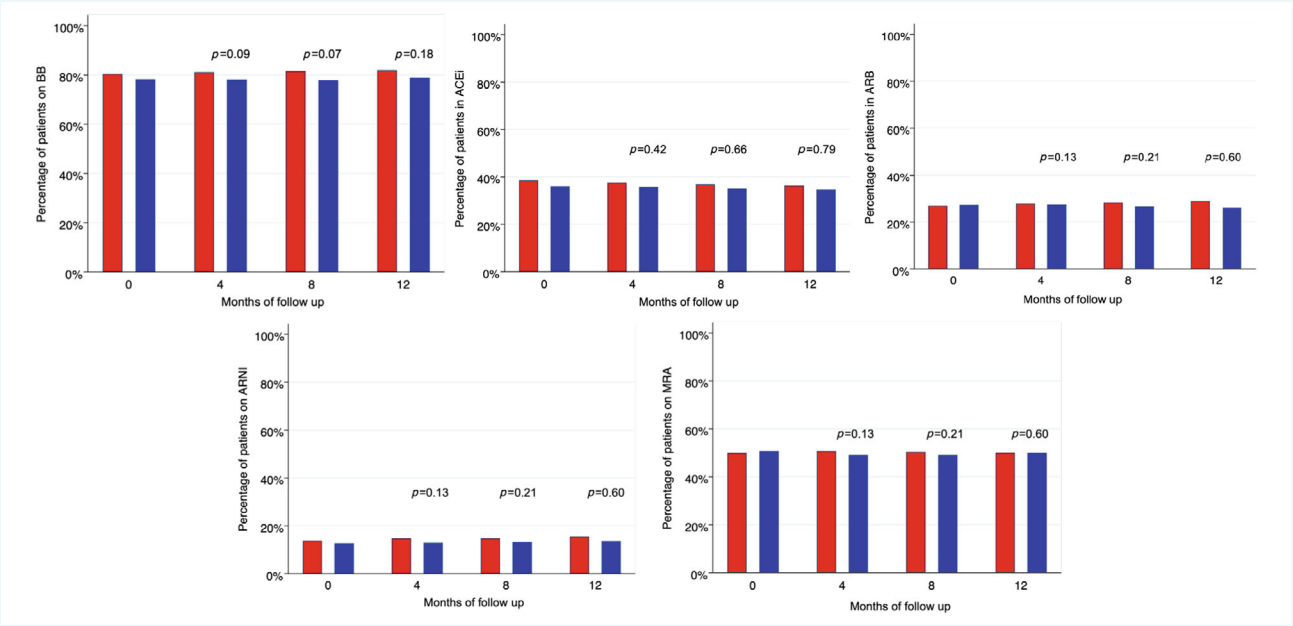

Figure 3 Continuation of background medications among participants with heart failure with improved ejection fraction (HFimpEF) in DELIVER during follow-up. ACEi, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist. *p-values represent differences between month of follow-up and baseline (0 months).

diabetic ketoacidosis, any major hypoglycaemic event, renal serious adverse event, or any serious adverse event leading to study drug discontinuation suggestive of volume depletion, including among those already on three HF therapies at baseline (all p-values >0.05) (*Table 3*).

Discussion

In this post-hoc analysis of the DELIVER trial, patients with HFimpEF were treated with widely variable intensity of background HF medical therapies. The clinical benefits of dapagliflozin on the primary outcome appear consistent regardless of the number of background HF therapies; however, those patients on 0–1 medications at baseline may derive greater benefit in preventing worsening HF events. Furthermore, treatment with dapagliflozin was well tolerated and did not lead to significant changes in the use or dosing of background HF therapies during follow-up, or higher rates of adverse outcomes, including those already on triple therapy.

Patients with HFimpEF are less likely to experience adverse cardiovascular events compared to those with HFrEF.[2,11,12] However, these patients are still at high risk for adverse clinical events; we and others have shown that nearly 20% of patients with HFimpEF experience cardiovascular death or need for advanced HF therapies and are at similar risk for HF hospitalization as those with HFpEF.[8,11,12] These findings differ from those from prior observational studies, which have reported double the risk of cardiovascular death and HF hospitalization in HFpEF patients compared to HFimpEF patients,[11,13–15] which might be attributed to the selective enrolment criteria in DELIVER of HFimpEF patients exhibiting persistent symptoms and elevated natriuretic peptides, potentially representing a higher-risk subset of the HFimpEF population.

Indeed, current guidelines recommend continuing HF medical therapies in patients with HFimpEF to prevent HF relapse or left ventricular dysfunction, even when asymptomatic.[16,17] This is largely based on the TRED-HF trial, which investigated the withdrawal of HF medical therapies in asymptomatic HFimpEF patients with dilated cardiomyopathy, where 40% of patients whose treatment was withdrawn had a relapse of their cardiomyopathy within 6 months.[18] However, TRED-HF was a relatively small trial that included only a subset of HFimpEF patients with a single cardiomyopathy aetiology. We found that patients with HFimpEF at baseline in DELIVER were on widely variable treatment regimens, which might in part be related to the requisite HF medical therapies required to facilitate or scaffold left ventricular improvement.

There are significant gaps in evidence regarding management strategies and therapies for the HFimpEF population, besides the use of SGLT2 inhibitors. No previous trial performed in patients with an LVEF >40% (including those evaluating candesartan, spironolactone, sacubitril/valsartan and empagliflozin) has included HFimpEF patients.[19] Given the previous heterogeneity in HFimpEF definition, it is possible that a substantial proportion of patients with HFmrEF have HFimpEF.[17] This might account for the observed benefit of sustained neurohormonal blockade in these patients, even after ejection fraction recovery.[17] Further investigations are warranted to determine the optimal medical therapy for HFimpEF patients definitively.

In our study, patients with HFimpEF who were treated with three HF medical therapies were younger and had higher eGFR, which

Table 3 Adverse events in heart failure with improved ejection fraction patients by number of background heart failure medical therapies

Variable	0–2 HF medical therapies			3–4 HF medical therapies		*p*-value
	Dapagliflozin (*n* = 346)	Placebo (*n* = 342)	*p*-value	Dapagliflozin (*n* = 226)	Placebo (*n* = 235)	
Safety outcomes						
Any serious adverse event	149 (43%)	168 (49%)	0.11	98 (43%)	105 (45%)	0.77
Discontinuation because of adverse event	25 (7%)	22 (6%)	0.68	11 (5%)	16 (7%)	0.37
Any adverse event leading to interruption of IP	45 (13%)	57 (17%)	0.18	34 (15%)	35 (15%)	0.96
Any amputation	4 (1%)	4 (1%)	0.99	1 (0.4%)	3 (1%)	0.33
Any potential risk factor adverse event for amputation affecting lower limbs	26 (8%)	32 (9%)	0.38	12 (5%)	24 (10%)	0.04
Any definite or probable diabetic ketoacidosis	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	–
Any major hypoglycaemic event	1 (0.3%)	1 (0.3%)	0.99	0 (0%)	0 (0%)	–
Any serious adverse event or adverse event leading to study drug discontinuation suggestive of volume depletion	5 (1%)	3 (1%)	0.49	5 (2%)	5 (2%)	0.95
Any renal serious adverse event or adverse event leading to study drug discontinuation	8 (2%)	9 (3%)	0.79	6 (3%)	7 (3%)	0.83

HF, heart failure; IP, investigational product.

might have allowed these patients to tolerate more. However, these patients also had lower baseline ejection fraction and were more likely to have received an ICD or CRT, indicating that they likely had severe left ventricular dysfunction in the past that required device therapy and higher use of pharmacological therapy. Reassuringly, our analysis demonstrated that the addition of dapagliflozin did not lead to significant changes in the use or dosing of background HF therapies. Also, the addition of dapagliflozin did not increase the risk of adverse outcomes in these patients with HFimpEF, irrespective of background intensity of HF medical therapies.

Prior secondary analyses of DAPA-HF and EMPEROR-Reduced trials have shown that dapagliflozin and empagliflozin, respectively, reduce the risk of cardiovascular death and worsening HF in HFrEF patients, regardless of background medical therapy.[20–22] Our study shows that patients with HFimpEF on no or single HF medical therapy at baseline may derive relatively greater benefits from dapagliflozin, especially in preventing worsening HF events. We cannot rule out the possibility of attenuation of benefits of dapagliflozin with increasing number of HF therapies at baseline; however, these findings must be interpreted with caution due to statistical fragility as our subgroups may be underpowered to detect effect modification adequately. In addition, patients receiving dual or triple therapy at baseline, appear to continue to derive protection from other outcomes like cardiovascular death. Moreover, the present study did not reveal any significant interaction when quantifying the baseline HF therapies using the integrative Heart Failure Collaboratory Medical Therapy Score. Future larger studies are needed to determine the additive potential of dapagliflozin in HFimpEF patients receiving various HF medications.

Several limitations of this analysis should be considered. Firstly, the analysis was post-hoc, and patients with HFimpEF represented only 18% of the participants enrolled in DELIVER, which limits the statistical power to detect differences between background therapy groups. Additionally, data on prior LVEF, aetiology of cardiomyopathy, and duration of prior medical therapy and devices were not collected, which may limit the interpretation of the results. Moreover, we cannot determine the reasons underlying use or non-use of medical therapies and did not have information on prior therapeutic trials. Also, dosing of ARNI at baseline and during follow-up was not documented systematically for the majority of patients, precluding dosing analysis after the addition of dapagliflozin.

Among patients with HFimpEF in a large, global clinical trial, the addition of dapagliflozin was safe and did not lead to a higher risk of adverse events among those with HFimpEF, including those treated with a BB, MRA and ACEi/ARB/ARNI at baseline. Patients on 0–1 HF medications at baseline tended to derive greater benefit of dapagliflozin in reducing the risk of worsening HF event, but the effects of dapagliflozin on other outcomes such as cardiovascular death were consistent irrespective of background HF therapies. Furthermore, when both background therapy use and dosing were integrated, treatment benefits of dapagliflozin

on the primary outcome were consistently observed across a range of the Heart Failure Collaboratory Medical Therapy Score. Taken together, these data from DELIVER support the safety and efficacy of addition of the SGLT2 inhibitor dapagliflozin for further medical optimization in HFimpEF, irrespective of their background HF medical regimen.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

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