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Dapagliflozin and Mode of Death in Heart Failure With Improved Ejection Fraction
A Post Hoc Analysis of the DELIVER Trial

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IMPORTANCE Heart failure with improved ejection fraction (HFimpEF), defined as prior left ventricular ejection fraction (LVEF) 40% or lower that has increased to greater than 40%, is understudied.

OBJECTIVE To examine mode of death and the association of dapagliflozin with reductions in cause-specific death in patients with HFimpEF.

DESIGN, SETTING, AND PARTICIPANTS This was a post hoc analysis from the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) randomized clinical trial, conducted from August 2018 to December 2020. The trial randomly assigned patients with HF with LVEF greater than 40%, New York Heart Association class II to IV symptoms, and elevated natriuretic peptides to treatment with dapagliflozin (10 mg, once daily) or placebo. The presence of HFimpEF was captured through study case report forms. The primary outcome was a composite of worsening HF events (hospitalization or urgent HF visits) or cardiovascular death. Clinical outcomes were adjudicated by a blinded clinical end points committee. Data were analyzed from May 2022 to August 2023.

INTERVENTION Dapagliflozin vs placebo.

MAIN OUTCOMES AND MEASURES The mode of death in relation to HFimpEF status was examined, as well as the association of randomized treatment with cause-specific death in Cox regression models.

RESULTS Of 1151 patients with HFimpEF in DELIVER, 190 (16.5%) died, compared with 833 patients (16.3%) of 5112 with LVEF consistently greater than 40%. The overall distribution of mode of death was similar in those with HFimpEF compared with those with LVEF consistently greater than 40% (noncardiovascular death: 103 of 190 [54%] vs 428 of 833 [51%]; cardiovascular death: 87 of 190 [46%] vs 405 of 833 [49%], respectively). Most deaths in individuals with HFimpEF were noncardiovascular (103 of 180 [54%]). For cardiovascular deaths, sudden deaths were most common (36 of 190 events [19%]), followed by HF-related (29 of 190 events [15%]). Among patients with HFimpEF, treatment with dapagliflozin was associated with lower rates of cardiovascular death relative to placebo, a difference primarily due to lower rates of sudden death (hazard ratio, 0.38; 95% CI, 0.18-0.79; *P* for interaction = .01).

CONCLUSIONS AND RELEVANCE The findings in this study support current guideline recommendations for use of sodium-glucose transport protein 2 inhibitor therapy, and further suggest that the addition of a sodium-glucose transport protein 2 inhibitor therapy to other guideline-directed medical therapies may help reduce cardiovascular mortality in patients with HFimpEF.

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Supplemental content

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Patients with heart failure with improved ejection fraction (HFimpEF), defined as prior left ventricular ejection fraction (LVEF) 40% or lower that has increased to greater than 40%, represent an understudied group. These patients experience similar rates of adverse nonfatal clinical outcomes as those with HF with mildly reduced or preserved ejection fraction (HFpEF).[1-3] Little is known regarding the potential benefit of initiating new therapies in those with LVEF that has improved to greater than 40%. In the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) randomized clinical trial, dapagliflozin reduced worsening HF or cardiovascular death in patients with HFimpEF to a similar extent as in those with LVEF consistently greater than 40%.[1] In this post hoc report, we evaluated the mode of death of patients with HFimpEF compared to those with LVEF consistently greater than 40% and assessed the association of dapagliflozin with reductions in cause-specific death in patients with HFimpEF.

Key Points

Question What is the mode of death and the association of dapagliflozin with cause-specific death in patients with heart failure with improved ejection fraction (HFimpEF)?

Findings In this post hoc analysis of the DELIVER trial including 6263 participants, 1151 participants had HFimpEF. The distribution of mode of death was similar in those with HFimpEF compared with those with LVEF consistently greater than 40%, and dapagliflozin was associated with less cardiovascular death relative to placebo in HFimpEF, primarily due to lower rates of sudden death.

Meaning The findings indicate that sodium-glucose transport protein 2 inhibitor therapy may help reduce cardiovascular mortality in patients with HFimpEF.

Methods

From August 2018 to December 2020, DELIVER randomized patients aged 40 years and older with symptomatic HF, LVEF greater than 40% with evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy), and elevated natriuretic peptide concentrations to dapagliflozin, 10 mg daily once daily, or placebo.[4] Additional details of the study design, protocol (Supplement 1), and primary study results have been previously published.[5] In this analysis focused on the HFimpEF cohort, patients were identified via study case report forms if they previously had LVEF 40% or lower but had LVEF greater than 40% on their qualifying echocardiogram. Exact LVEF values prior to enrollment were not available. Study end points, including death, were adjudicated by an independent clinical end point committee blinded to study drug assignment. Deaths were classified as cardiovascular (related to HF, sudden cardiac death, or other), noncardiovascular, or unknown (eAppendix in Supplement 2). 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.

Baseline characteristics of participants with HFimpEF who died vs did not die were summarized as means and standard deviations (SD), medians and interquartile ranges, or percentages and compared by χ^2 test for categorical variables and Wilcoxon test and 2-sample *t* test for nonnormal and normally distributed continuous variables, respectively. Mode of death was compared between participants with HFimpEF and those with LVEF consistently greater than 40%. Among those with HFimpEF, time-to-event data for death (cardiovascular and noncardiovascular) by treatment allocation were evaluated using Cox proportional hazards models stratified by diabetes status at randomization. A sensitivity analysis was performed using the European Society of Cardiology definition of HFimpEF (patients with a history of overtly reduced LVEF [≤40%] who later present with LVEF 50% or higher).[6] All analyses were performed in Stata version 17 (Statacorp). *P* values less than .05 were considered statistically significant. Data were analyzed from May 2022 to August 2023.

Results

Of 6263 participants enrolled in DELIVER, 1151 (18%) had HFimpEF (572 assigned to dapagliflozin and 579 to placebo), 190 of whom (16.5%) died compared with 833 patients (16.3%) of 5112 patients with LVEF consistently greater than 40%. Individuals with HFimpEF who died, compared to those who did not die, were older, had a longer duration of HF, history of prior hospitalization for HF, were more likely NYHA functional class III (vs II), had higher N-terminal prohormone of brain natriuretic peptide levels, had lower estimated glomerular filtration rates, and were more likely to be taking loop diuretics and to have pacemakers (**Table**; eTable 1 in Supplement 2). Similar patterns were observed among patients who died who had LVEF consistently greater than 40% (eTable 2 in Supplement 2). Among those with HFimpEF, baseline characteristics were well balanced between those allocated to dapagliflozin vs placebo.

The distribution of mode of death was similar in those with HFimpEF and those with LVEF consistently greater than 40% (noncardiovascular death: 103 of 190 [54%] vs 428 of 833 [51%]; cardiovascular death: 87 of 190 [46%] vs 405 of 833 [49%], respectively) (**Figure**). For cardiovascular deaths, sudden deaths were most common (36 of 190 events [19%] in HFimpEF and 199 of 833 events [24%] in LVEF consistently >40%), followed by those related to HF (29 of 190 events [15%] in HFimpEF and 135 of 833 events [16%] in LVEF consistently >40%). In patients with HFimpEF, dapagliflozin was associated with a reduction in cardiovascular death relative to placebo (34 vs 53 events; hazard ratio [HR], 0.62; 95% CI, 0.41-0.96), which was not observed in those with LVEF consistently greater than 40% (197 vs 208

Table. Baseline Characteristics by All-Cause Death Among Individuals With Heart Failure With Improved Ejection Fraction (HFimpEF)

Characteristic	No. (%)		*P* value
	HFimpEF living (n = 961)	HFimpEF died (n = 190)	
Age, mean (SD), y	69.5 (9.9)	73.0 (10.1)	<.001
Sex			
Female	320 (33.3)	57 (30.0)	.38
Male	641 (66.7)	133 (70.0)	
Race[a]			
Asian	254 (26.4)	36 (18.9)	
Black or African American	29 (3.0)	7 (3.7)	
American Indian or Alaska Native	18 (1.9)	3 (1.6)	
White	635 (66.1)	139 (73.2)	.29
Other[b]	25 (2.6)	5 (2.6)	
Geographic region			
Europe and Saudi Arabia	398 (41.4)	84 (44.2)	.04
Asia	252 (26.2)	32 (16.8)	
Latin America	162 (16.9)	36 (18.9)	
North America	149 (15.5)	38 (20.0)	
History			
AFF	483 (50.3)	110 (57.9)	.050
Stroke	77 (8.0)	19 (10.0)	.37
Dyslipidemia	641 (66.7)	127 (66.8)	.97
Type 2 diabetes	435 (45.3)	94 (49.5)	.29
Chronic obstructive pulmonary disease	116 (12.1)	34 (17.9)	.03
Myocardial infarction	339 (35.3)	61 (32.1)	.40
Hypertension	807 (84.0)	172 (90.5)	.02
Heart failure hospitalization	453 (47.1)	107 (56.3)	.02
Any coronary artery disease	570 (59.3)	110 (57.9)	.72
Any atherosclerotic cardiovascular disease	612 (63.7)	120 (63.2)	.89
Smoking status			
Current	102 (10.6)	16 (8.4)	.43
Former	423 (44.0)	79 (41.6)	
Never	436 (45.4)	95 (50.0)	
Baseline body mass index, mean (SD)[c]	29.5 (5.9)	29.1 (6.5)	.49
Time from diagnosis of heart failure to baseline			
0-3 mo	48 (5.0)	13 (6.8)	.05
>3-6 mo	66 (6.9)	4 (2.1)	
>6-12 mo	94 (9.8)	20 (10.5)	
>1-2 y	132 (13.7)	17 (8.9)	
>2-5 y	288 (30.0)	62 (32.6)	
>5 y	333 (34.7)	74 (38.9)	
NYHA class at baseline			
II	787 (81.9)	131 (68.9)	<.001
III	171 (17.8)	58 (30.5)	
IV	3 (0.3)	1 (0.5)	
Baseline LVEF, mean (SD), %	50.6 (8.2)	50.0 (8.8)	.34
LVEF group, %			
≤40	1 (0.1)	0 (0.0)	.08
≥41-49	507 (52.8)	116 (61.1)	
50-59	288 (30.0)	40 (21.1)	
≥60	165 (17.2)	34 (17.9)	

(continued)

Table. Baseline Characteristics by All-Cause Death Among Individuals With Heart Failure With Improved Ejection Fraction (HFimpEF) (continued)

Characteristic	No. (%)		*P* value
	HFimpEF living (n = 961)	HFimpEF died (n = 190)	
Baseline NT-proBNP, median (IQR), ng/L	953 (597-1528)	1554 (908-2875)	<.001
NT-proBNP in AFF (ECG), median (IQR)	1307 (967-2030)	2048 (1286-3375)	<.001
NT-proBNP when no AFF (ECG), median (IQR)	704 (477-1190)	1140 (641-2362)	<.001
Baseline ECG atrial fibrillation/flutter	344 (35.8)	80 (42.1)	.10
Baseline systolic blood pressure, mean (SD), mm Hg	127.2 (16.4)	127.4 (17.7)	.89
Baseline diastolic blood pressure, mean (SD), mm Hg	73.7 (10.7)	72.3 (10.3)	.11
Baseline pulse, mean (SD), beats/min	70.6 (12.1)	71.6 (12.2)	.30
Baseline HbA_{1c}, mean (SD), %	6.6 (1.4)	6.8 (1.5)	.08
Baseline creatinine, mean (SD), umol/L	103.1 (31.0)	114.4 (33.4)	<.001
Baseline eGFR, mean (SD), mL/min/1.73 m^2	63.1 (19.0)	55.4 (18.9)	<.001
Loop diuretic	724 (75.3)	159 (83.7)	.01
ACE inhibitor	376 (39.1)	82 (43.2)	.30
Angiotensin receptor blocker	286 (29.8)	51 (26.8)	.42
Angiotensin receptor blocker neprilysin inhibitor	125 (13.0)	27 (14.2)	.65
β-Blocker	834 (86.8)	157 (82.6)	.13
Mineralocorticoid receptor antagonist	493 (51.3)	87 (45.8)	.17
Pacemaker	89 (9.3)	30 (15.8)	.007
Implantable cardioverter defibrillators	48 (5.0)	11 (5.8)	.65

Abbreviations: ACE, angiotensin-converting-enzyme; AFF, atrial fibrillation or flutter; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

[a] Race data were collected via self-report and summarized to allow assessment of generalizability of the study cohort.

[b] Other included Native Hawaiian or Pacific Islander or race not otherwise specified by patients or investigators. These groups were consolidated due to small sample size.

[c] Calculated as weight in kilograms divided by height in meters squared.

events; HR, 0.95; 95% CI, 0.78-1.15; *P* for interaction = .09). This was largely driven by a relatively greater reduction in sudden deaths (HFimpEF dapagliflozin vs placebo: 10 vs 26 events; HR, 0.38; 95% CI, 0.18-0.79; LVEF consistently >40%: 99 vs 100 events; HR, 0.99; 95% CI, 0.75-1.31; *P* for interaction = .01). The observed reduction in sudden cardiac death in dapagliflozin compared with placebo was apparent regardless of achieved LVEF (EF ≥50%: 1 vs 8; EF <50%: 9 vs 18).

Discussion

In this secondary analysis of patients with HFimpEF enrolled in the DELIVER trial, overall rates of death were similar among those with HFimpEF as those with LVEF consistently greater than 40%. Cardiovascular deaths were comprised primarily of sudden deaths, followed by deaths due to HF, with similar proportions in both groups. Dapagliflozin was associated with a reduced risk of cardiovascular death among patients with HFimpEF compared to placebo, primarily driven by significantly reduced sudden deaths.

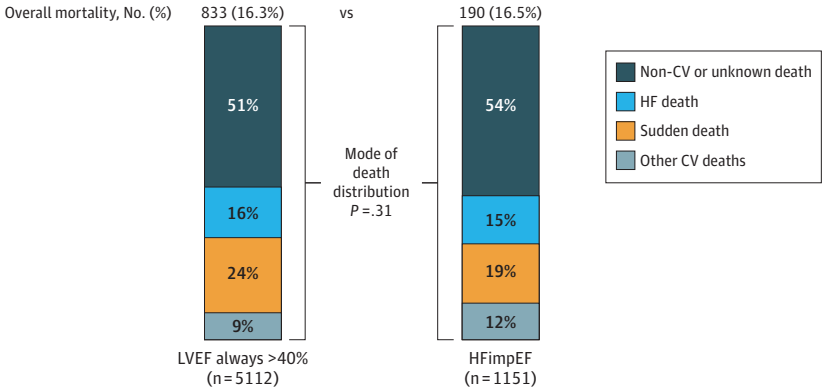
Prior analyses[7] from registries that included patients with different HF phenotypes observed lower rates of death among patients with HFimpEF compared to patients with heart failure with reduced ejection fraction (HFrEF) and HFpEF with LVEF consistently above 40%. In a cohort study[8] of 2166 outpatients with HF, age- and sex-adjusted mortality rates were 4.8% after 3 years in patients with HFimpEF compared with 13.2% in those with HFpEF and 16.3% in those with HFrEF. Our observation of similar rates of all modes of death for those with HFimpEF and individuals with LVEF consistently greater than 40% (while other studies found lower rates among patients with HFimpEF compared to other HF phenotypes) likely reflects different patient characteristics between study cohorts, such as more ischemic history for those in DELIVER, which has been associated with higher risk for sudden death compared to a nonischemic etiology of HF.[9] Patients enrolled in DELIVER were required to exhibit persistent HF symptoms and elevated natriuretic peptide levels, which could have further increased mortality risk.

The observed benefit with dapagliflozin, relative to placebo, in reduced risk of cardiovascular death was predominantly attributable to a significantly lower risk for sudden death. While the mechanism for sudden death is often ascribed to arrhythmia in patients with HFrEF,[10] the mechanism for sudden death in those with HFimpEF is less clear. Importantly, dapagliflozin was shown to be associated with a reduction in cardiovascular deaths, including sudden deaths, compared to placebo in a pooled analysis[11] from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and DELIVER trials, encompassing patients across the range of ejection fraction. The association of reduced risk of sudden death with dapagliflozin compared with placebo was consistent across LVEF values. The apparent greater magnitude of the dapagliflozin mortality benefit in patients with HFimpEF should be considered hypothesis generating.

Our data support prior evidence suggesting persistent arrhythmic risk among patients with HFimpEF. Thus, in those with implantable cardioverter defibrillators, improvement in LVEF should not be used as a rationale to defer implantable cardioverter defibrillator generator placement. These data sug-

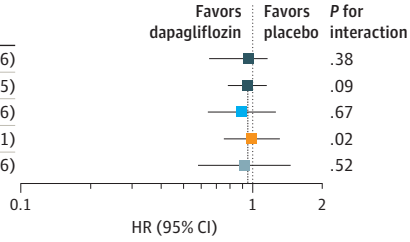
Figure. Mode of Death Comparing Individuals With Heart Failure With Improved Ejection Fraction (HFimpEF) to Those With Left Ventricular Ejection Fraction (LVEF) Consistently Over 40%

A Mode of death comparing HFimpEF with those with LVEF >40%



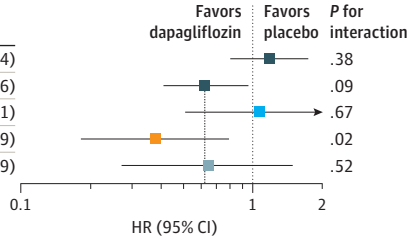
B Treatment effects of dapagliflozin on cause-specific death in patients with LVEF >40%

Outcome	Deaths, No. Dapagliflozin	Placebo	HR (95% CI)	P for interaction
Non-CV death	210	218	0.96 (0.80-1.16)	.38
CV death	197	208	0.95 (0.78-1.15)	.09
HF death	64	71	0.90 (0.64-1.26)	.67
Sudden death	99	100	0.99 (0.75-1.31)	.02
Other CV deaths	34	37	0.92 (0.58-1.46)	.52



C Treatment effects of dapagliflozin in patients with HFimpEF

Outcome	Deaths, No. Dapagliflozin	Placebo	HR (95% CI)	P for interaction
Non-CV death	56	47	1.18 (0.80-1.74)	.38
CV death	34	53	0.62 (0.41-0.96)	.09
HF death	15	14	1.07 (0.51-2.21)	.67
Sudden death	10	26	0.38 (0.18-0.79)	.02
Other CV deaths	9	13	0.64 (0.27-1.49)	.52



CV indicates cardiovascular.

gest that the risk for sudden death may be modifiable with sodium-glucose transport protein 2 inhibitor (SGLT2i) therapy in addition to other HF treatments known to reduce cardiovascular death.

Limitations

Several limitations of this post hoc study should be considered. The number of sudden death events were small, and we cannot discount the possibility that the association of dapagliflozin with lower risk of sudden death was due to chance. Classification of HFimpEF was based on a question of prior LVEF 40% or lower on a case report form, and the exact nadir of LVEF, time course, and magnitude of improvement were not collected. Thus, we were unable to examine some other definitions of HFimpEF,[6,12] although our findings were similar in a sensitivity analysis that used the European Society of Cardiology definition of HFimpEF and were similar regardless of achieved LVEF.[6]

Conclusions

In summary, patients with HFimpEF enrolled in the DELIVER trial carried a similar risk of death as those who had LVEF consistently over 40%. Dapagliflozin was associated with a reduction in cardiovascular death among those with HFimpEF, which appeared primarily driven by a lower residual risk of sudden death. These data support current guideline recommendations for use of SGLT2i across the spectrum of LVEF, and further suggest that the new addition of a SGLT2i to other guideline-directed medical therapies may help reduce cardiovascular mortality in patients with HFimpEF.

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Author Contributions: Drs Vardeny 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.
Concept and design: Vardeny, Desai, Hernandez, Kosiborod, Lam, Shah, Vaduganathan, Solomon.
Acquisition, analysis, or interpretation of data: Vardeny, Desai, Jhund, Fang, Claggett, de Boer, Hernandez, Inzucchi, Kosiborod, Lam, Martinez, Shah, McCausland, Petrie, Vaduganathan, McMurray.
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Supervision: Claggett, Kosiborod, Martinez, Petrie, Solomon.

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