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RESEARCH ARTICLE

Dapagliflozin in patients with heart failure and previous myocardial infarction: A participant-level pooled analysis of DAPA-HF and DELIVER

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Aims Patients with heart failure (HF) and history of myocardial infarction (MI) face a higher risk of disease progression and clinical events. Whether sodium–glucose cotransporter 2 inhibitors may modify clinical trajectory in such individuals remains incompletely understood.

Methods and results The DAPA-HF and DELIVER trials compared dapagliflozin with placebo in patients with symptomatic HF with left ventricular ejection fraction (LVEF) ≤40% and > 40%, respectively. In this pooled participant-level analysis, we assessed efficacy and safety outcomes by history of MI. The primary outcome in both trials was the composite of cardiovascular death or worsening HF. Of the total of 11 007 patients, 3731 (34%) had a previous MI and were at higher risk of the primary outcome across the spectrum of LVEF in covariate-adjusted models (hazard ratio [HR] 1.12, 95% confidence interval [CI] 1.02–1.24). Dapagliflozin reduced the risk of the primary outcome to a similar extent in patients with (HR 0.83, 95% CI 0.72–0.96) and without previous MI (HR 0.76, 95% CI 0.68–0.85; $p_{interaction} = 0.36$), with consistent benefits on key secondary outcomes as well. Serious adverse events did not occur more frequently with dapagliflozin, irrespective of previous MI.

Conclusion History of MI confers increased risks of adverse cardiovascular outcomes in patients with HF across the LVEF spectrum, even among those with preserved ejection fraction. Dapagliflozin consistently and safely reduces the risk of cardiovascular death or worsening HF, regardless of previous MI.

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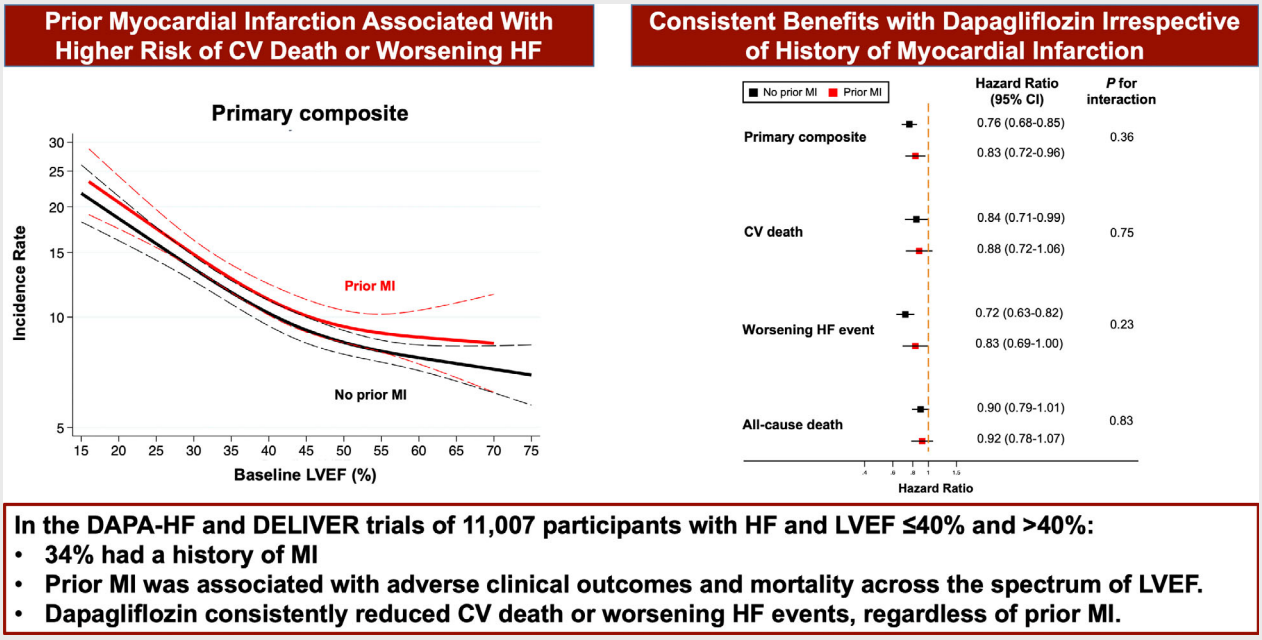
Graphical Abstract



History of myocardial infarction (MI), clinical outcomes and treatment response to dapagliflozin. Incidence rate of the primary composite outcome (first occurrence of cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent HF visit) across the spectrum of left ventricular ejection fraction (LVEF) and treatment effect of dapagliflozin compared with placebo on the primary composite outcome and key secondary outcomes according to history of MI. Ci, confidence interval.

Keywords Myocardial infarction • Heart failure with reduced ejection fraction • Heart failure with mildly reduced ejection fraction • Heart failure with preserved ejection fraction • SGLT2 inhibitors

Introduction

Coronary artery disease is highly prevalent in patients with heart failure (HF).[1,2] Indeed, in many patients, myocardial ischaemia may represent a central driver of worsening HF and disease progression. While myocardial infarction (MI) is a well-recognized pathway to incident HF with reduced ejection fraction, MI can also result in mild left ventricular dysfunction, valvular pathology, mechanical dyssynchrony, worsening diastolic function, even in the absence of large decrements in systolic function.[3,4] As such, prior MI identifies those at heightened risks for recurrent coronary events, worsening HF events, and mortality, across the spectrum of left ventricular function.[5–7] To date, targeting this high-risk intersection of HF and MI has been therapeutically challenging.[8,9] Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce cardiovascular death and HF events in a broad range of patients with HF, with evidence from meta-analyses of randomized clinical trials indicating similar benefits on these outcomes among patients with type 2 diabetes with and without atherosclerotic cardiovascular disease.[10] Although dapagliflozin was recently demonstrated to improve select cardiometabolic outcomes in the DAPA-MI trial (Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Heart Failure or Cardiovascular Death in Patients Without Diabetes With Acute Myocardial Infarction) of patients with acute MI and impaired left ventricular function without known diabetes, the low incidence of HF hospitalizations and cardiovascular death limited conclusions on its efficacy regarding these endpoints.[11] Whether SGLT2 inhibitors may modify disease trajectory in those with established HF with and without diabetes and previous MI remains incompletely understood. In this pooled analysis of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trials, we examined the efficacy and safety of dapagliflozin according to history of MI in patients with HF across the spectrum of ejection fraction.

Methods

Study design and patients

The design and primary results of the DAPA-HF and DELIVER trials have been reported previously.[12–15] In brief, DAPA-HF and

DELIVER were international, randomized, double-blind trials comparing dapagliflozin 10 mg once daily with matching placebo in patients with symptomatic HF. DAPA-HF enrolled ambulatory patients 18 years of age with New York Heart Association (NYHA) functional class II–IV, left ventricular ejection fraction (LVEF) ≤40% and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.[14] In DELIVER, patients aged >40 years with NYHA functional class II–IV, LVEF >40%, elevated NT-proBNP levels and evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy) were eligible for enrolment.[12] Key exclusion criteria in both studies included history of type 1 diabetes, symptomatic hypotension or systolic blood pressure <95 mmHg, and reduced estimated glomerular filtration rate (eGFR) (<30 ml/min/1.73 m^2 in DAPA-HF and <25 ml/min/1.73 m^2 in DELIVER). Both studies were approved by institutional review boards or ethics committees at each individual study site, and each patient provided written informed consent. The trials are registered in ClinicalTrials.gov with the identifiers NCT03036124 and NCT03619213.

History of myocardial infarction and study outcomes

In both trials, data on history of MI were assessed by the treating clinician investigator and collected using electronic case report forms. The primary outcome in both trials was the composite of worsening HF events (defined as either unplanned hospitalization or urgent HF visit requiring intravenous therapy) or cardiovascular death. This study further assessed the individual components of the primary outcome; the total number of HF events (hospitalization for HF, urgent HF visit) and cardiovascular death; the composite of MI, stroke, or cardiovascular death (major adverse cardiovascular events [MACE]); all-cause mortality; and change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS), KCCQ clinical summary score (CSS) and KCCQ overall summary score (OSS) between baseline and 8 months. In accordance with the prespecified statistical analysis plan for this pooled dataset, the definition of cardiovascular death included deaths of undetermined cause. MI and stroke were adjudicated in DAPA-HF, while serious adverse event reports were used to ascertain these outcomes in DELIVER. Prespecified safety outcomes examined in both trials included serious adverse events (AE), AEs leading to treatment discontinuation (DAE), amputation, diabetic ketoacidosis, major hypoglycaemia, and serious renal and volume depletion AEs and DAEs.

Statistical analyses

Baseline characteristics were summarized as mean ± standard deviation, median (interquartile range), or frequencies (%). Baseline characteristics between participants with and without a history of MI were compared using Student's *t*-test or Wilcoxon rank-sum test for normally and not normally distributed continuous variables, respectively, and chi-square or Fisher exact tests for categorical variables. Associations between history of MI and clinical events were assessed by Cox proportional hazards models stratified by trial with and without adjustment for randomized treatment, age, sex, geographic region, systolic blood pressure, heart rate, body mass index, duration of HF, previous HF hospitalizations, NYHA functional class, LVEF, atrial fibrillation/flutter, hypertension, stroke, chronic obstructive pulmonary disease, eGFR, and log-transformed NT-proBNP levels.[16] The association between history of MI and incidence rates of clinical events as a continuous function of LVEF was further analysed using Poisson regression models, with baseline LVEF expressed by restricted cubic splines with three knots. The effects of dapagliflozin compared with placebo were assessed by Cox proportional hazards models stratified by type 2 diabetes status at baseline and trial with interaction terms for effect modification by history of MI. Treatment effect modifications as a continuous function of LVEF were examined by Poisson regression models with baseline LVEF expressed by restricted cubic splines with three knots. Total events were examined using the semiparametric method of Lin *et al.*[17] Differences in change in KCCQ scores between baseline and 8 months by randomized treatment were estimated using linear regression models adjusted for each score's baseline value, trial, and interaction terms for randomized treatment and history of MI. Responder analyses examined the proportions of participants with clinically meaningful improvement (≥5 point increase) and deterioration (≥5 point decrease) in KCCQ scores by logistic regression models. Safety outcomes according to baseline history of MI were analysed using logistic regression models. Statistical analyses were conducted using STATA version 16.1 (StataCorp, College Station, TX, USA). *P*-values of <0.05 were considered statistically significant.

Results

Patient characteristics

Of the 11 007 patients randomized in DAPA-HF and DELIVER, 3731 (34%) had a previous MI, with a prevalence of 44% in patients with LVEF ≤40% and 26% among those with LVEF >40%. Patients with previous MI were younger, more often male, White, and enrolled at sites in Europe, had a lower body mass index, systolic blood pressure, diastolic blood pressure, heart rate, LVEF, presented less frequently in atrial fibrillation or flutter at randomization, and had higher levels of creatinine, glycated haemoglobin, and NT-proBNP (*Table 1*). NYHA functional class and KCCQ scores were similar in patients with and without previous MI. A longer duration of HF, history of stroke, dyslipidaemia, type 2 diabetes, hypertension, smoking, prior HF hospitalizations, coronary artery disease, percutaneous coronary interventions, and coronary bypass grafts were more common, and history of atrial fibrillation or flutter less common in patients with previous MI. Patients with previous MI were more likely to receive angiotensin-converting enzyme inhibitors, angiotensin receptor–neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, nitrates, antiplatelet therapies, lipid-lowering therapies, were less frequently treated with angiotensin receptor blockers and anticoagulants, had more often implantable cardioverter-defibrillator therapies, and had less frequently pacemakers.

Clinical outcomes by history of myocardial infarction

Rates for all clinical outcomes increased with decreasing LVEF in patients with and without previous MI (*Figure 1*). Patients with previous MI were at higher risk of the primary composite of worsening HF events or cardiovascular death across the spectrum of LVEF (hazard ratio [HR] 1.13, 95% confidence interval

Table 1 Baseline characteristics according to history of myocardial infarction

Characteristic	No previous myocardial infarction ($n = 7276$)	Previous myocardial infarction ($n = 3731$)	*p*-value
Age (years)	69.7 ± 10.8	68.7 ± 9.7	<0.001
Male sex, *n* (%)	4326 (59.5)	2825 (75.7)	<0.001
Race, *n* (%)			<0.001
White	4958 (68.1)	2814 (75.4)	
Asian	1707 (23.5)	683 (18.3)	
Black or African American	285 (3.9)	100 (2.7)	
American Indian or Alaska Native	125 (1.7)	68 (1.8)	
Other	201 (2.8)	66 (1.8)	
Geographic region, *n* (%)			<0.001
Europe and Saudi Arabia	3233 (44.4)	1926 (51.6)	
North America	1038 (14.3)	490 (13.1)	
South America	1349 (18.5)	649 (17.4)	
Asia/Pacific	1656 (22.8)	666 (17.9)	
Medical history, *n* (%)			
AFF	4125 (56.7)	1312 (35.2)	<0.001
Stroke	622 (8.5)	441 (11.8)	<0.001
Dyslipidaemia	4059 (55.8)	2801 (75.1)	<0.001
Type 2 diabetes mellitus	2954 (40.6)	1835 (49.2)	<0.001
Hypertension	5961 (81.9)	3114 (83.5)	0.045
Prior HF hospitalization	3135 (43.1)	1655 (44.4)	0.20
Any coronary artery disease	855 (32.2)	2092 (100.0)	N/A
Percutaneous coronary intervention	999 (13.7)	2337 (62.6)	<0.001
Coronary artery bypass graft	557 (7.7)	1019 (27.3)	<0.001
Physiologic measures			
Body mass index (kg/m^2)	29.4 ± 6.4	28.6 ± 5.5	<0.001
Systolic blood pressure (mmHg)	126.1 ± 16.4	124.3 ± 15.5	<0.001
Diastolic blood pressure (mmHg)	74.1 ± 10.7	73.0 ± 9.9	<0.001
Pulse (bpm)	72.5 ± 12.0	69.5 ± 10.9	<0.001
AFF (ECG), *n* (%)	3036 (41.7)	736 (19.7)	<0.001
Time from diagnosis of HF to baseline, *n* (%)			<0.001
0–3 months	466 (10.1)	102 (6.2)	
>3–6 months	421 (9.1)	171 (10.4)	
>6–12 months	638 (13.8)	204 (12.5)	
>1–2 years	754 (16.3)	241 (14.7)	
>2–5 years	1157 (25.0)	412 (25.2)	
>5 years	1185 (25.6)	507 (31.0)	
NYHA class, *n* (%)			0.05
I	1 (0.0)	0 (0.0)	
II	5277 (72.5)	2639 (70.7)	
III	1952 (26.8)	1077 (28.9)	
IV	46 (0.6)	15 (0.4)	

Table 1 (Continued)

Characteristic	No previous myocardial infarction ($n = 7276$)	Previous myocardial infarction ($n = 3731$)	*p*-value
KCCQ-TSS	71.4 ± 22.2	71.9 ± 21.7	0.28
KCCQ-OSS	67.4 ± 20.6	67.2 ± 20.2	0.56
KCCQ-CSS	69.5 ± 20.9	69.7 ± 20.6	0.62
LVEF (%)	46.4 ± 14.3	40.0 ± 12.1	<0.001
LVEF category, *n* (%)			<0.001
≤40%	2654 (36.5)	2093 (56.1)	
41–49%	1280 (17.6)	833 (22.3)	
≥50%	3342 (45.9)	805 (21.6)	
NT-proBNP in AFF (ECG)	1509 [1009–2438]	1728 [1137–2765]	<0.001
NT-proBNP when no AFF (ECG)	926 [547–1772]	1015 [602–1898]	<0.001
Creatinine (μmol/L)	101.8 ± 30.7	106.2 ± 30.7	<0.001
Baseline eGFR (ml/min/1.73 m^2)	63.2 ± 19.7	62.9 ± 18.8	0.45
HbA1c (%)	6.5 ± 1.3	6.7 ± 1.5	<0.001
Smoking status, *n* (%)			<0.001
Current	674 (9.3)	503 (13.5)	
Former	2543 (35.0)	1810 (48.5)	
Never	4059 (55.8)	1418 (38.0)	
Treatment, *n* (%)			
Loop diuretic	5747 (79.0)	2889 (77.4)	0.06
ACEi	3020 (41.5)	1936 (51.9)	<0.001
ARB	2487 (34.2)	1092 (29.3)	<0.001
ARNI	502 (6.9)	307 (8.2)	0.011
Beta-blocker	6308 (86.7)	3427 (91.9)	<0.001
MRA	3761 (51.7)	2276 (61.0)	<0.001
Nitrates	730 (10.0)	754 (20.2)	<0.001
Anticoagulants	3983 (54.7)	1368 (36.7)	<0.001
Calcium channel blocker	1777 (24.4)	646 (17.3)	<0.001
Antiplatelet drug	2414 (33.2)	2808 (75.3)	<0.001
Statin	3955 (54.4)	3260 (87.4)	<0.001
Non-statin lipid-lowering drug	409 (5.6)	366 (9.8)	<0.001
Device therapy, *n* (%)			
ICD or CRT-D	690 (9.5)	720 (19.3)	<0.001
Pacemaker	911 (12.5)	415 (11.1)	0.033

Values are mean ± standard deviation, *n* (%), or median [interquartile range].
P-values are reported for differences between participants with and without history of myocardial infarction.
ACEi, angiotensin-converting enzyme inhibitor; AFF, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT-D, cardiac resynchronization therapy with defibrillator; CSS, clinical summary score; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSS, overall summary score; TSS, total symptom score.

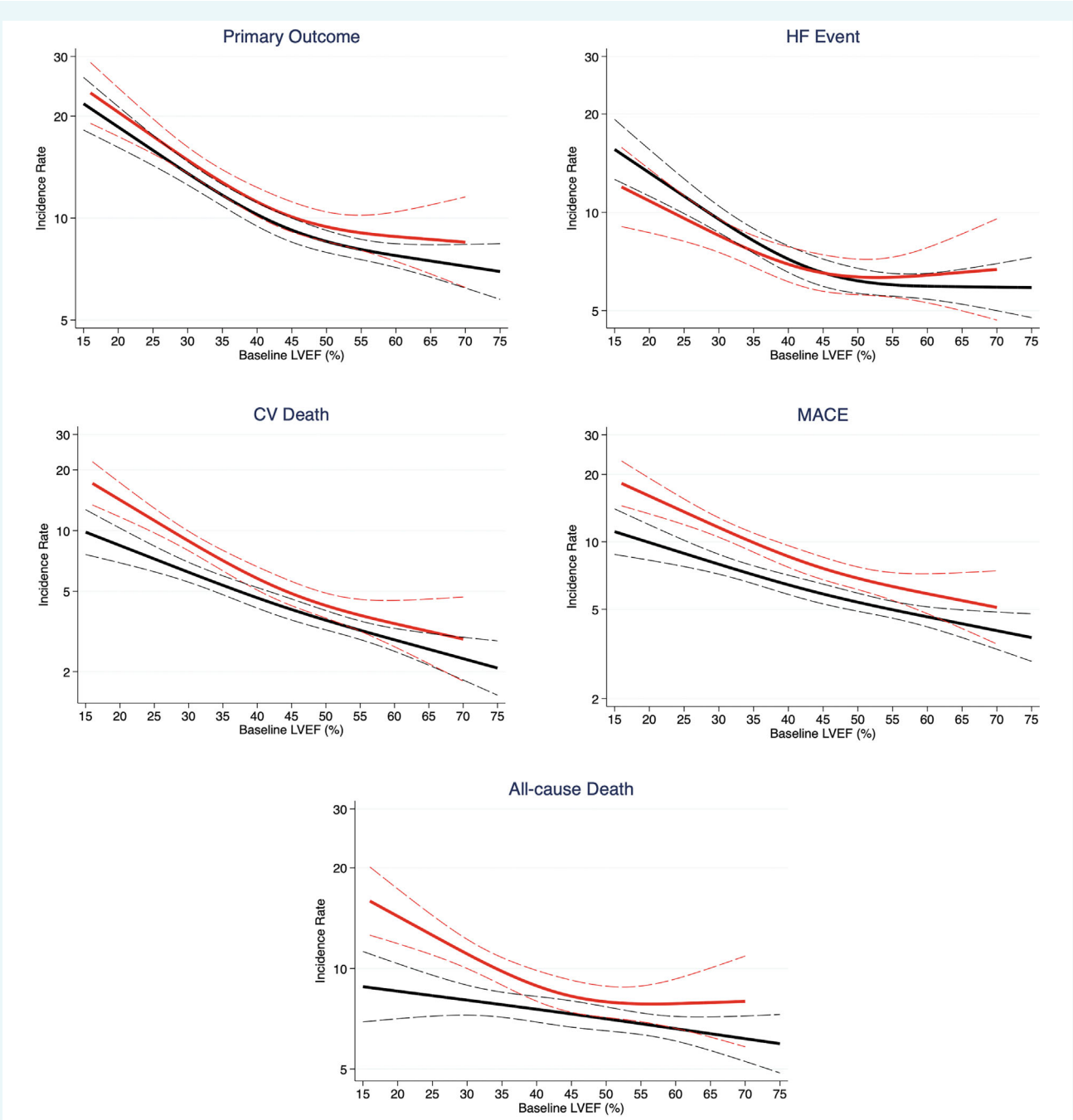


Figure 1 Incidence rates of key outcomes across the spectrum of left ventricular ejection fraction (LVEF) by history of myocardial infarction. Incidence rates of the primary composite outcome (first occurrence of cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent HF visit), CV death, worsening HF events (HF hospitalization and urgent HF visit), the composite of myocardial infarction, stroke, or CV death (major adverse CV events [MACE]), and all-cause death across the spectrum of LVEF according to history of myocardial infarction. Incidence rates for patients with and without previous myocardial infarction are shown in red and black, respectively.

[CI] 1.03–1.24), which remained consistent after adjustment for baseline demographics and prognostic variables (HR 1.12, 95% CI 1.02–1.24) (*Table 2*, *Figure 1*, *Graphical Abstract*). Similarly, a previous MI was associated with a higher risk for cardiovascular death, total HF events and cardiovascular death, the composite of myocardial infarction, stroke, or cardiovascular death (MACE), and all-cause mortality in models with and without covariate adjustment (*Table 2*). HF hospitalizations did not differ between those with and without previous MI in crude, and covariate-adjusted models (*Table 2*).

Table 2 Primary composite outcome and secondary outcomes by history of myocardial infarction

	No previous myocardial infarction ($n = 7276$)	Previous myocardial infarction ($n = 3731$)	*p*-value
Primary composite			
Events, *n* (%)	1270 (17.5)	740 (19.8)	0.010
Rate (per 100 pt-yrs)	9.7	11.9	
HR (95% CI)	Ref.	1.13 (1.03–1.24)	
Adjusted HR (95% CI)	Ref.	1.12 (1.02–1.24)	0.017
HF event			
Events, *n* (%)	928 (12.8)	458 (12.3)	0.74
Rate (per 100 pt-yrs)	7.1	7.3	
HR (95% CI)	Ref.	0.98 (0.88–1.10)	
Adjusted HR (95% CI)	Ref.	1.00 (0.89–1.13)	0.95
CV death			
Events, *n* (%)	570 (7.8)	422 (11.3)	<0.001
Rate (per 100 pt-yrs)	4.1	6.3	
HR (95% CI)	Ref.	1.37 (1.21–1.56)	
Adjusted HR (95% CI)	Ref.	1.29 (1.13–1.48)	<0.001
Total HF events and CV death			
Events, *n*	2009	1147	0.030
Rate (per 100 pt-yrs)	14.4	17.3	
RR (95% CI)	Ref.	1.13 (1.01–1.26)	
Adjusted RR (95% CI)	Ref.	1.12 (1.00–1.25)	0.042
Composite of myocardial infarction, stroke, or CV death (MACE)			
Events, *n* (%)	800 (11.0)	578 (15.5)	<0.001
Rate (per 100 pt-yrs)	5.8	8.9	
HR (95% CI)	Ref.	1.42 (1.27–1.58)	
Adjusted HR (95% CI)	Ref.	1.34 (1.19–1.50)	<0.001
All-cause death			
Events, *n* (%)	1004 (13.8)	624 (16.7)	<0.001
Rate (per 100 pt-yrs)	7.1	9.4	
HR (95% CI)	Ref.	1.28 (1.15–1.42)	
Adjusted HR (95% CI)	Ref.	1.20 (1.08–1.34)	<0.001

P-values are reported for differences between participants with and without history of myocardial infarction.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; pt-yrs, patient-years; RR, rate ratio.
Multivariable models were additionally adjusted for randomized treatment, age, sex, geographic region, baseline systolic blood pressure, baseline heart rate, baseline body mass index, duration of HF, previous HF hospitalizations, New York Heart Association functional class, baseline left ventricular ejection fraction, atrial fibrillation/flutter, hypertension, stroke, chronic obstructive pulmonary disease, baseline estimated glomerular filtration rate, and baseline log-transformed N-terminal pro-B-type natriuretic peptide levels.

Efficacy of dapagliflozin on clinical outcomes according to history of myocardial infarction

Dapagliflozin similarly reduced the risk of the primary composite in patients with (HR 0.83, 95% CI 0.72–0.96) and without previous MI (HR 0.76, 95% CI 0.68–0.85; $p_{interaction} = 0.36$) (*Table 3*, *Figure 2*, *Graphical Abstract*). Likewise, the effect of dapagliflozin on worsening HF events, cardiovascular death, total HF events and cardiovascular death, MACE, and all-cause mortality was consistent by history of MI ($p_{interaction} \geq 0.15$ for all outcomes) (*Table 3*, *Figure 2*, *Graphical Abstract*). Improvements in KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS were greater with dapagliflozin, compared with placebo, in patients with and without previous MI, with smaller proportions treated with dapagliflozin experiencing clinically meaningful deteriorations ≥5 points in KCCQ-CSS among those with previous MI (*Table 3*). The treatment effects on clinical outcomes according to history of MI were not modified by LVEF as a continuous measure ($p_{interaction} \geq 0.24$ for all outcomes) (*Figure 3*).

Safety outcomes

Treatment discontinuation for any reason or due to an AE did not differ between both treatment groups in patients with and without a history of MI, with similar rates of serious AEs, diabetic

Table 3 Treatment effect according to history of myocardial infarction

Outcome	No previous myocardial infarction		Previous myocardial infarction		$p_{interaction}$*
	Dapagliflozin (*n* = 3674)	Placebo (*n* = 3602)	Dapagliflozin (*n* = 1830)	Placebo (*n* = 1901)	
Primary composite					
Events, *n* (%)	566 (15.4)	704 (19.5)	332 (18.1)	408 (21.5)	0.36
Rate (per 100 pt-yrs)	8.4	11.0	10.7	13.0	
HR (95% CI)	0.76 (0.68–0.85)		0.83 (0.72–0.96)		
HF event					
Events, *n* (%)	400 (10.9)	528 (14.7)	205 (11.2)	253 (13.3)	0.23
Rate (per 100 pt-yrs)	5.9	8.3	6.6	8.1	
HR (95% CI)	0.72 (0.63–0.82)		0.83 (0.69–1.00)		
CV death					
Events, *n* (%)	265 (7.2)	305 (8.5)	193 (10.5)	229 (12.0)	0.75
Rate (per 100 pt-yrs)	3.7	4.4	5.9	6.8	
HR (95% CI)	0.84 (0.71–0.99)		0.88 (0.72–1.06)		
Total HF events and CV death					
Events, *n*	859	1150	514	633	0.15
Rate (per 100 pt-yrs)	12.1	16.6	15.8	18.8	
RR (95% CI)	0.72 (0.64–0.82)		0.85 (0.72–1.00)		
Composite of myocardial infarction, stroke, or CV death (MACE)					
Events, *n* (%)	389 (10.6)	411 (11.4)	267 (14.6)	311 (16.4)	0.74
Rate (per 100 pt-yrs)	5.6	6.0	8.4	9.5	
HR (95% CI)	0.92 (0.80–1.06)		0.89 (0.76–1.05)		
All-cause death					
Events, *n* (%)	481 (13.1)	523 (14.5)	292 (16.0)	332 (17.5)	0.83
Rate (per 100 pt-yrs)	6.8	7.5	8.9	9.8	
HR (95% CI)	0.90 (0.79–1.01)		0.92 (0.78–1.07)		
KCCQ-TSS					
Mean change at 8 months	7.1 ± 19.6	4.9 ± 20.6	7.1 ± 18.6	3.8 ± 19.2	
Proportion with increase ≥5 in score at 8 months, *n* (%)	1373 (49.9)	1223 (45.8)	695 (48.8)	624 (42.7)	0.37
OR (95% CI)	1.18 (1.06–1.31)		1.28 (1.11–1.48)		
Proportion with decrease ≥5 in score at 8 months, *n* (%)	606 (22.0)	721 (27.0)	282 (19.8)	415 (28.4)	0.06
OR (95% CI)	0.76 (0.67–0.86)		0.62 (0.52–0.74)		
KCCQ-CSS					
Mean change at 8 months	6.3 ± 17.8	4.3 ± 18.4	6.4 ± 16.7	3.1 ± 17.1	
Proportion with increase ≥5 in score at 8 months, *n* (%)	1352 (49.2)	1187 (44.5)	696 (48.9)	600 (41.0)	0.16
OR (95% CI)	1.21 (1.09–1.34)		1.38 (1.19–1.59)		
Proportion with decrease ≥5 in score at 8 months, *n* (%)	612 (22.3)	691 (25.9)	268 (18.8)	399 (27.3)	0.010
OR (95% CI)	0.82 (0.72–0.93)		0.62 (0.52–0.74)		
KCCQ-OSS					
Mean change at 8 months	6.8 ± 17.7	4.7 ± 17.8	6.7 ± 16.5	4.0 ± 16.3	
Proportion with increase ≥5 in score at 8 months, *n* (%)	1425 (51.8)	1269 (47.6)	709 (49.8)	677 (46.3)	0.75
OR (95% CI)	1.19 (1.07–1.32)		1.15 (0.99–1.33)		
Proportion with decrease ≥5 in score at 8 months, *n* (%)	583 (21.2)	691 (25.9)	275 (19.3)	363 (24.8)	0.59
OR (95% CI)	0.77 (0.68–0.87)		0.73 (0.61–0.87)		

CI, confidence interval; CV, cardiovascular; CSS, clinical summary score; HF, heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire, MACE, major adverse cardiovascular event; OR, odds ratio; OSS, overall summary score; pt-yrs, patient-years; RR, rate ratio; TSS, total symptom score.

*$P_{interaction}$ values are reported for interaction between treatment effect and history of myocardial infraction.

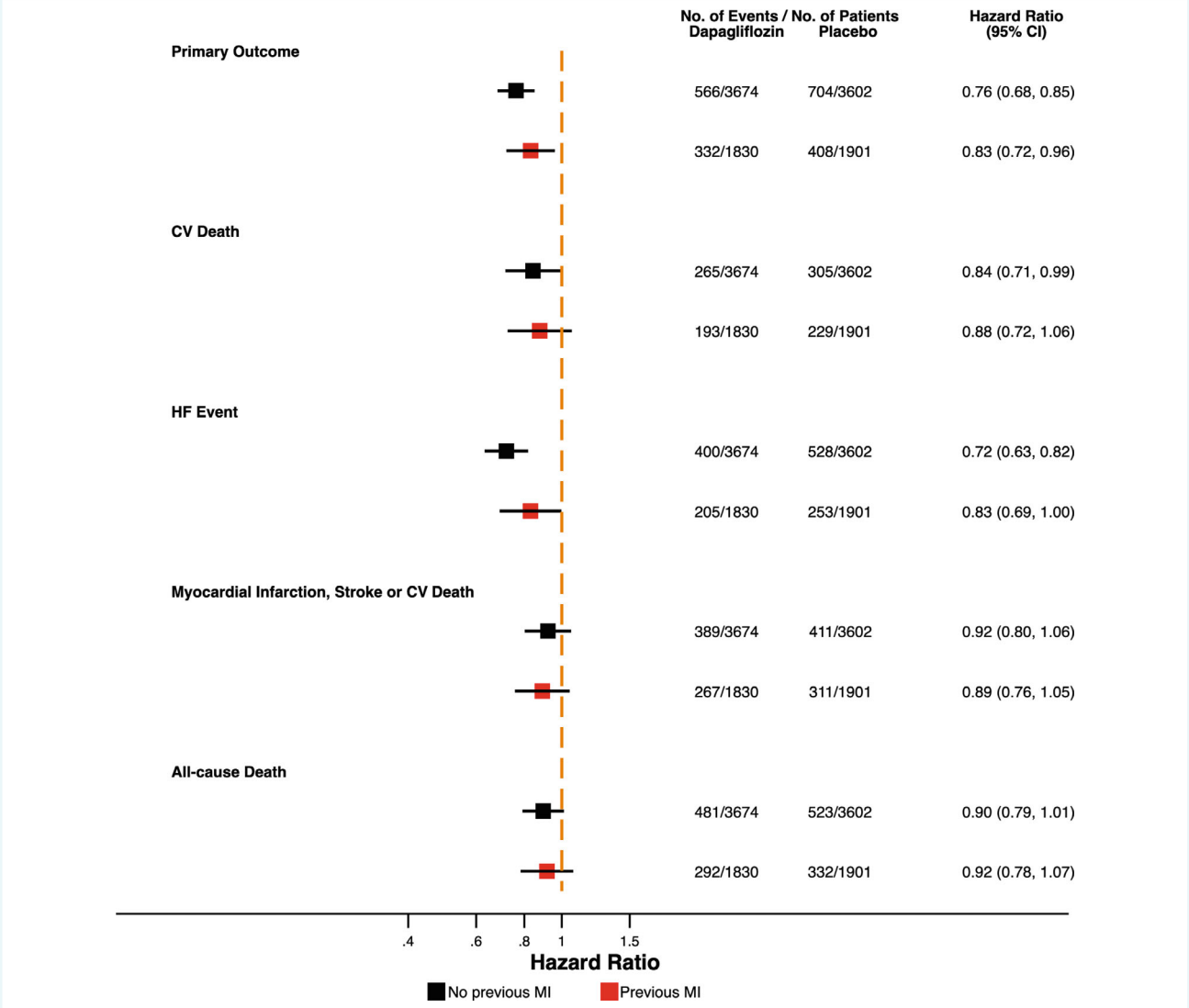


Figure 2 Effect of dapagliflozin according to history of myocardial infarction (MI). Forest plot of treatment effect of dapagliflozin, compared with placebo, on the primary composite outcome (first occurrence of cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent HF visit), CV death, worsening HF events (HF hospitalization and urgent HF visit), the composite of MI, stroke, or CV death (major adverse CV events), and all-cause death according to history of MI, obtained from Cox proportional hazards models. CI, confidence interval.

ketoacidosis, hypoglycaemic events, and serious renal and volume depletion AEs and DAEs (online supplementary *Table Appendix S1*).

Discussion

In this pooled participant-level analysis of 11 007 patients with HF enrolled in the DAPA-HF and DELIVER trials, one-third of the participants had a history of MI, conferring an increased risk of adverse cardiovascular outcomes across the full spectrum of LVEF. The benefits of dapagliflozin on symptoms and clinical events were consistent in patients with or without a history of MI, with no differences in safety outcomes in both groups.

The higher prevalence of previous MI of 44% in patients with LVEF ≤40% compared with 26% in those with LVEF >40% was consistent with patient populations of contemporary randomized trials of HF with reduced and mildly reduced/preserved ejection fraction,[18–22] with similar patterns observed in observational studies.[23,24] Adding to previous studies, in DAPA-HF and DELIVER, a history of MI was associated with a higher risk of clinical events across the spectrum of LVEF.[25,26] Whereas incidence rates for all outcomes increased with declining LVEF, patients with prior MI appeared to be at particularly heightened risk of cardiovascular and all-cause mortality and MACE, modestly elevated risk for the primary composite, with no significant difference in risk for HF hospitalizations between patients with and without previous MI. Indeed, whereas many studies reported a substantially increased risk of HF and death during the early phase post-MI, the long-term risk of HF events among survivors who developed HF following

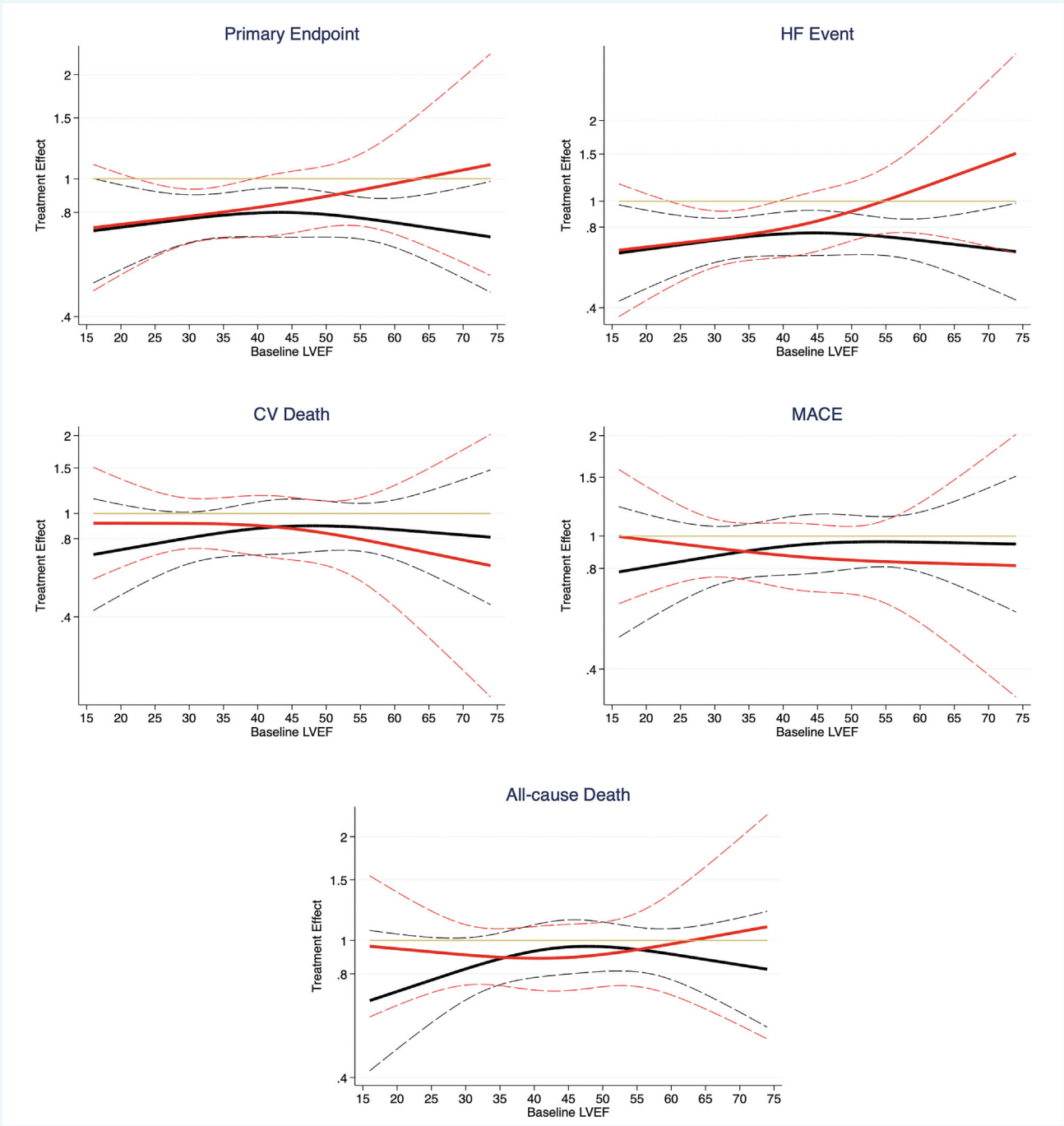


Figure 3 Effect of dapagliflozin according to history of myocardial infarction across the spectrum of left ventricular ejection fraction (LVEF). Treatment effect of dapagliflozin for according to history of myocardial infarction across the spectrum of LVEF for the primary composite outcome (first occurrence of cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent HF visit), CV death, worsening HF events (HF hospitalization and urgent HF visit), the composite of myocardial infarction, stroke, or CV death, and all-cause death. Treatment effects for patients with and without previous myocardial infarction are shown in red and black, respectively.

MI may stabilize following the initial myocardial remodelling period and the use of evidence-based HF therapies.[27–29] While the higher burden of cardiovascular comorbidities and more severe disease surrogates of HF may have contributed to the higher concomitant risk in patients with previous MI, the increased risk for clinical events persisted despite comprehensive covariate adjustment and the observed higher prevalence of use of guideline-directed medical therapies for secondary prevention.

In the present analysis, dapagliflozin consistently reduced worsening HF events or cardiovascular death across the spectrum

of LVEF in patients with and without previous MI, with similar treatment effects on key secondary outcomes. Comparable benefits in reducing the risk of MACE were observed with dapagliflozin in patients with type 2 diabetes and previous MI in the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial.[30] While patients with HF and a history of MI experience substantial limitations in symptoms, function and quality of life, treatment with dapagliflozin improved KCCQ scores in patients with and without previous MI.[31,32] Similarly, DAEs and AEs did not differ between patients receiving dapagliflozin and placebo in those with and without a previous MI. These results add to the previously reported substantial benefits and the favourable safety profile of dapagliflozin across the spectrum of LVEF and support its use in high-risk populations with HF and a history of MI.

While some evidence-based HF therapies, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or mineralocorticoid receptor antagonists, have been shown to equally improve adverse cardiac remodelling and reduce the risk for adverse outcomes in the early stage after acute MI, patients with an MI within 3 months before randomization were not eligible for enrolment in DAPA-HF and DELIVER.[9] SGLT2 inhibitors have been shown to improve surrogate markers such as NT-proBNP levels and LVEF early after acute MI, but their effects on clinical outcomes remain incompletely understood.[33] Although the observed event rates for HF hospitalizations and cardiovascular death in the recent DAPA-MI trial of patients with acute MI without diabetes or established HF were similar in patients randomized to dapagliflozin and placebo, their low incidence in the enrolled population precluded further conclusions regarding these endpoints.[11] Nevertheless, these data from the combined DAPA-HF and DELIVER trials suggest that patients with HF and previous MI clearly benefit from SGLT2 inhibition. Whether SGLT2 inhibitors would prevent the development of HF in patients who remain at risk for HF following MI remains unknown. Importantly, the DAPA-MI trial extended previous evidence for the safety of dapagliflozin, providing reassurance for its use in patients hospitalized for acute MI.[11] The ongoing EMPACT-MI (EMPAgliflozin on Hospitalization for Heart Failure and Mortality in Patients With aCuTe Myocardial Infarction) trial is actively investigating the early initiation of empagliflozin following an acute MI in a population at higher residual risk compared with DAPA-MI, adding to the totality of evidence on the efficacy and safety of SGLT2 inhibitors in patients with acute MI.[34]

Limitations

Several limitations should be noted. Although this study was a prespecified secondary analysis, the DAPA-HF and DELIVER trials were not powered to evaluate efficacy and safety in patients with and without previous MI, limiting the results to an exploratory nature. Data regarding the timing of MI, types of MI, coronary anatomy, Killip class, revascularization therapy during the acute event, residual presence of ischaemia or viability were not specifically collected, preventing consideration in this analysis.

Conclusion

In this pooled participant-level analysis of the DAPA-HF and DELIVER trials, a history of MI was associated with an increased risk of adverse cardiovascular outcomes in patients with HF across the LVEF spectrum, even among those with preserved ejection fraction. Dapagliflozin consistently and safely reduced the risk of clinical events in patients with and without previous MI. These results further support the use of dapagliflozin in patients with HF and a history of MI.

Supplementary Information

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

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