Patient characteristics, outcomes, and effects of dapagliflozin according to the duration of heart failure: A prespecified analysis of the DELIVER trial

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Introduction

Physicians may think that a patient who has longer-standing heart failure (HF) represents a "stable" survivor where adding a new treatment is unnecessary.

On the other hand, patients with long-standing HF may have more advanced disease, and they may no longer respond to or tolerate the addition of new therapies, particularly because of hypotension, kidney dysfunction and electrolyte abnormality.

Few studies have addressed this clinical question in patients with heart failure and mildly reduced and preserved ejection fraction (HFmrEF/HFpEF).

Purpose

To compare patient demographics, HF characteristics, comorbidities, and background therapy according to the duration of HF, as well as the key trial outcomes related to time from diagnosis of HF

To analyze the efficacy and safety of dapagliflozin, compared with a placebo, according to the duration of HF

Methods

DELIVER trial (NCT03619213)

Randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening HF in patients with HFmrEF/HFpEF.

Dapagliflozin 10mg once daily — N=3131

Placebo — N=3132

Key inclusion criteria

Age ≥ 40 years
LVEF >40%
HF diagnosis ≥6 weeks with at least intermittent use of diuretics
NYHA II-IV, evidence of structural heart disease
Elevation of N-terminal pro-B-type natriuretic (NT-proBNP) level ≥300 pg/mL (≥600 pg/mL if atrial fibrillation/flutter on the electrocardiogram at enrollment)

Trial outcome

Primary outcome:
Worsening HF (HF hospitalization/urgent HF visit) event or cardiovascular (CV) death
Secondary outcomes:
Worsening HF event; cardiovascular death; all-cause death;
Total (first and repeat) worsening HF events and CV deaths

Duration of HF (time from diagnosis)

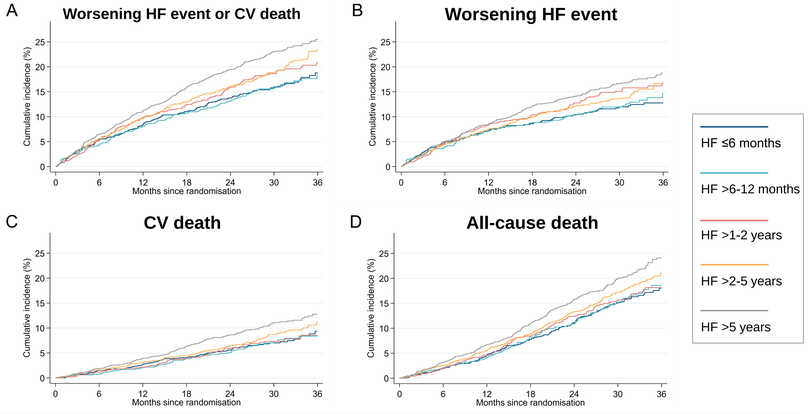
≤6 months, >6-12 months, >1-2 years, >2-5 years and >5 years
(Five patients whose information on time from diagnosis of HF was missing were excluded from the analysis)

Results

Patient characteristics according to duration of HF

	HF ≤6 months N=1,160	HF >6-12 months N=842	HF >1-2 years N=995	HF >2-5 years N=1,569	HF >5 years N=1,692
Age (years)	71	71	71	72	73
Female sex	43%	43%	46%	46%	42%
Body mass index (kg/m^2)	29	29	30	30	30
Pulse (beats/min)	72	71	71	71	72
SBP (mmHg)	128	129	128	128	128
eGFR (mL/min/1.73m^2)	62	62	62	60	60
NT-proBNP (ng/L)	1005	1030	980	1032	1012
Previous LVEF ≤40%	11%	14%	15%	22%	24%
Prior HF hospitalization	41%	37%	37%	42%	43%
NYHA class III or IV	21%	22%	25%	27%	27%
Baseline LVEF (%)	55%	54%	55%	54%	53%
Type 2 diabetes	43%	41%	45%	45%	48%
Atrial fibrillation	52%	51%	54%	57%	59%
Myocardial infarction	24%	24%	24%	26%	30%
COPD	9%	9%	10%	12%	13%
Beta blocker	80%	83%	83%	84%	83%
ACEi, ARB or ARNI	74%	79%	77%	80%	77%
MRA	40%	48%	42%	42%	43%
Loop diuretics	75%	72%	77%	78%	80%

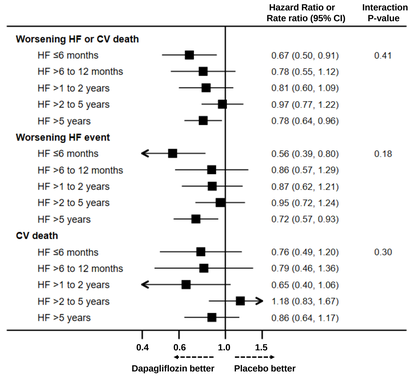
Outcomes according to HF duration

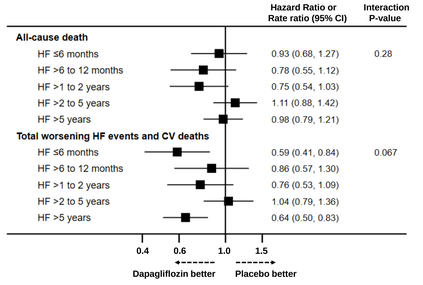


	HF ≤6 months	HF >6-12 months	HF >1-2 years	HF >2-5 years	HF >5 years
Worsening HF or CV death					
No (%)	175 (15.1)	123 (14.6)	172 (17.3)	290 (18.5)	362 (21.4)
Rate (95%CI)	7.3 (6.3-8.4)	7.1 (6.0-8.5)	8.4 (7.2-9.7)	8.9 (7.9-9.9)	10.6 (9.5-11.7)
Unadjusted (95% CI) *	REF	0.98 (0.78-1.23)	1.16 (0.94-1.43)	1.22 (1.01-1.47)	1.46 (1.22-1.74)
Additional adjustment (95% CI) †	REF	1.04 (0.82-1.31)	1.21 (0.98-1.49)	1.20 (0.99-1.45)	1.38 (1.15-1.67)

*baseline model adjusted for randomized treatment
†adjusted for randomized treatment, age, sex, race, region, heart rate, systolic blood pressure, creatinine, previous LVEF ≤40%, history of heart failure hospitalization, NYHA class, LV ejection fraction, type 2 diabetes, atrial fibrillation, hypertension, MI, CABG, stroke, NT-proBNP (log-transformed)

Effect of dapagliflozin





Adverse events

	HF ≤6 months		HF >6-12 months		HF >1-2 years		HF >2-5 years		HF >5 years		P for interaction
	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	
Any AE that led to discontinuation of randomized treatment	7.7%	7.0%	5.6%	5.3%	3.9%	5.3%	5.3%	5.1%	6.2%	6.4%	0.84
Any AE that led to the interruption of randomized treatment	14.3%	12.0%	12.4%	12.8%	17.4%	13.6%	16.8%	14.2%	16.6%	15.8%	0.73
Any SAE or DAE related to volume depletion	0.3%	1.9%	0.7%	1.4%	1.2%	2.0%	1.9%	0.8%	1.3%	1.9%	0.042
Any renal SAE or DAE	2.9%	3.3%	1.9%	1.9%	3.7%	3.6%	2.8%	1.6%	3.2%	3.1%	0.66

AE, adverse event; SAE, serious adverse event; DAE, adverse event leading to discontinuation of randomized treatment

Discussion

Longer-duration HF patients were older, had more comorbidity and symptoms and had higher rates of worsening HF and death, which were broadly consistent with previous results from HFrEF trials.

The benefit of dapagliflozin were consistent regardless of the duration of HF.
With a consistent relative benefit of dapagliflozin across the range of HF duration, patients with HF >5 years have a larger absolute risk reduction than those with ≤6 months duration i.e., number needed to treat (NNT) 24 vs 32.

Adverse events were not more common in patients randomized to receive dapagliflozin irrespective of the duration of HF.

Conclusion

Even patients with long-standing HF and generally mild symptoms are not "stable" and it is not too late for such patients to benefit from an SGLT2 inhibitor.