Effects of dapagliflozin in patients with chronic kidney disease, with and without heart failure

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Background

- Studies have shown that sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of heart failure (HF) hospitalisation in patients with type 2 diabetes, including in those with chronic kidney disease (CKD).[1-4]
- This reduced risk was also in patients with HF[5] or CKD[6] with or without type 2 diabetes.
- Here we examine outcomes in patients with CKD with and without type 2 diabetes by history of HF at baseline in the DAPA-CKD study.

Methods

Study Design

- DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter trial.[5]
- The study enrolled adults with or without type 2 diabetes, with an estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g, and who were receiving a stable dose of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 4 weeks unless contraindicated.
- Patients were randomized 1:1 to dapagliflozin 10 mg once daily or placebo.
- This pre-specified analysis assessed outcomes by baseline HF history as reported by the Investigator.

Outcomes

- The primary composite outcome from DAPA-CKD was the time to the first occurrence of any of the following:
  - ≥50% decline in eGFR
  - End-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney transplantation, or eGFR <15 mL/min/1.73m^2 confirmed by a second measurement after at least 28 days)
  - Death from a kidney or cardiovascular cause
- Pre-specified secondary outcomes were, in hierarchal order:
  - A kidney composite outcome the same as the primary endpoint, but excluding death from cardiovascular causes
  - A cardiovascular composite outcome of hospitalisation for HF or death from cardiovascular causes
  - Death from any cause

Results

Baseline characteristics according to history of heart failure

- Of 4304 patients, 468 (10.9%) had a diagnosis of HF at baseline and 3836 (89.1%) did not have HF at baseline

Table 1. Characteristics of the patients at baseline according to history of HF.

Characteristics	With HF (N=468)	Without HF (N=3836)
Age (years), mean (SD)	65.3 (12.1)	61.4 (12.3)
Sex, female, n (%)	299 (63.9)	2580 (67.3)
Race, n (%)		
White	375 (80.1)	1915 (49.9)
Black	28 (6.0)	163 (4.2)
Asian	48 (10.3)	1419 (37.0)
Other	17 (3.6)	339 (8.8)
Heart rate, beats/min, mean (SD)	71.3 (9.7)	73.1 (11.7)
Systolic Blood Pressure, mmHg, mean (SD)	138.9 (15.9)	136.9 (17.6)
HbA1c, %, mean (SD)	7.4 (1.7)	7.0 (1.7)
BMI, kg/m^2, mean (SD)	31.7 (6.8)	29.2 (6.0)
eGFR, mL/min/1.73 m^2, mean (SD)	43.2 (12.4)	43.1 (12.3)
UACR, mg/g, median (IQR)	940 (456–1847)	950 (480–1890)
Cardiovascular and renal medication, n (%)		
Beta-blocker	325 (69.4)	1355 (35.3)
Diuretic	303 (64.7)	1579 (41.2)
Loop diuretic	221 (47.2)	835 (21.8)
Thiazide diuretic	102 (21.8)	804 (21.0)
Mineralocorticoid receptor antagonist	81 (17.3)	148 (3.9)
ACE inhibitor, ARB or other RAS blocker	458 (97.9)	3716 (96.9)
Digitalis glycoside	15 (3.2)	14 (0.4)
Hydralazine	24 (5.1)	78 (2.0)
Calcium channel blocker	240 (51.3)	1943 (50.7)
Antiplatelet	307 (65.6)	1573 (41.0)
Statin	334 (71.4)	2460 (64.1)
Other lipid lowering therapy	47 (10.0)	598 (15.6)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HF, heart failure; RAS, renin-angiotensin system; UACR, urinary albumin-to-creatinine ratio

- Patients with HF at baseline were older, more often white, had a higher BMI, and were more likely to have type 2 diabetes than those without a history of HF.
  - Mean eGFR and UACR were similar in patients with and without HF at baseline.

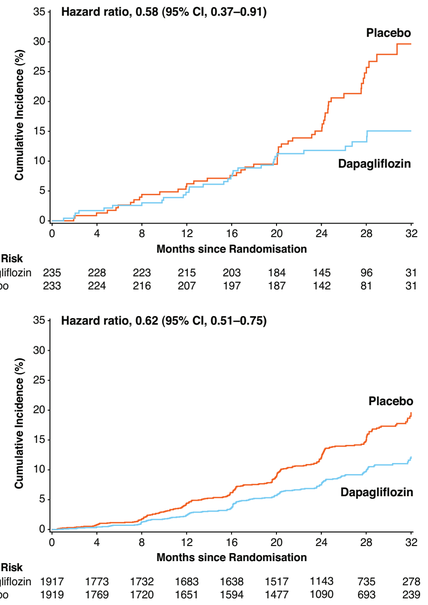
Outcomes according to baseline history of heart failure

- In all patients with a history of HF, the primary composite outcome occurred at a rate of 8.7 per 100 person-years (95% CI 6.9, 10.8), and at a rate of 5.7 per 100 person-years (95% CI 5.1, 6.2) in all patients without a history of HF, regardless of treatment assignment (HR 1.48; 95% CI 1.17, 1.88).
- The occurrence of the kidney-specific secondary outcome was similar in those with and without HF at baseline (HR 0.90; 95% CI 0.65, 1.25).
- The secondary composite outcome of hospitalisation for HF or cardiovascular death occurred at >4-fold higher rate in patients with a history of HF compared to those without (HR 4.31; 95% CI 3.30, 5.63).
- All-cause death also occurred more frequently in patients with HF (HR 2.70; 95% CI 2.03, 3.60).

Effect of dapagliflozin on outcomes according to baseline history of HF

- Among patients with HF, the primary composite outcome occurred in 31 (13.2%) participants in the dapagliflozin group, and 51 (21.9%) in the placebo group. In patients without HF, the primary composite outcome occurred in 166 (8.7%) participants in the dapagliflozin group, and 261 (13.6%) in the placebo group **(Figure 1)**.

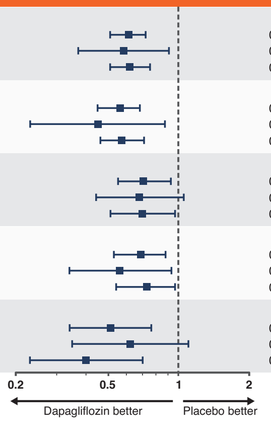
Figure 1. Cumulative incidence of the primary composite outcome in patients with (A) and without (B) HF at baseline



- The kidney-specific secondary outcome, hospitalisation for HF or cardiovascular death and all-cause death outcomes occurred less frequently in the dapagliflozin treatment group than with placebo, regardless of HF history at baseline **(Figure 2)**.

Figure 2. Pre-specified outcomes according to history of HF at baseline

	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Events/100 patient-years	Placebo Events/100 patient-years	Hazard Ratio (95% CI)	P Value for interaction
Primary outcome: eGFR decline ≥50%, ESKD, or kidney or CV death						
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	
HF at baseline	31/235	51/233	6.5	11.0	0.58 (0.37, 0.91)	0.59
No HF at baseline	166/1917	261/1919	4.4	7.0	0.62 (0.51, 0.75)	
Secondary outcome: eGFR decline ≥50%, ESKD, or kidney death						
Overall	142/2152	243/2152	3.3	5.8	0.56 (0.45, 0.68)	
HF at baseline	13/235	27/233	2.7	5.8	0.45 (0.23, 0.87)	0.36
No HF at baseline	129/1917	216/1919	3.4	5.8	0.57 (0.46, 0.71)	
Secondary outcome: CV death or HF hospitalisation						
Overall	100/2152	138/2152	2.2	3.0	0.71 (0.55, 0.92)	
HF at baseline	36/235	48/233	7.1	10.1	0.68 (0.44, 1.05)	0.90
No HF at baseline	64/1917	90/1919	1.6	2.2	0.70 (0.51, 0.97)	
Secondary outcome: All-cause death						
Overall	101/2152	146/2152	2.2	3.1	0.69 (0.53, 0.88)	
HF at baseline	24/235	40/233	4.6	7.9	0.56 (0.34, 0.93)	0.39
No HF at baseline	77/1917	106/1919	1.9	2.6	0.73 (0.54, 0.97)	
Exploratory outcome: HF hospitalisation						
Overall	37/2152	71/2152	0.8	1.6	0.51 (0.34, 0.76)	
HF at baseline	20/235	29/233	3.9	6.1	0.62 (0.35, 1.10)	0.28
No HF at baseline	17/1917	42/1919	0.4	1.0	0.40 (0.23, 0.70)	



eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; CV cardiovascular

Safety

- The rates of all pre-specified adverse events of interest were low, and similar in those with HF and without HF history at baseline **(Table 2)**.

Table 2. Safety Outcomes

		Dapagliflozin n/N (%)	Placebo n/N (%)
Any serious AE*	Without HF	503/1914 (26.3)	607/1916 (31.7)
	With HF	130/235 (55.3)	122/233 (52.4)
AE leading to study drug discontinuation	Without HF	106/1914 (5.5)	113/1916 (5.9)
	With HF	12/235 (5.1)	10/233 (4.3)
Adverse events of interest			
Amputation	Without HF	30/1914 (1.6)	34/1916 (1.8)
	With HF	5/235 (2.1)	5/233 (2.1)
Fracture	Without HF	75/1914 (3.9)	64/1916 (3.3)
	With HF	10/235 (4.3)	5/233 (2.1)
Renal adverse event	Without HF	133/1914 (6.9)	157/1916 (8.2)
	With HF	22/235 (9.4)	31/233 (13.3)
Major hypoglycaemia†	Without HF	12/1914 (0.6)	22/1916 (1.1)
	With HF	2/235 (0.9)	6/233 (2.6)
Volume depletion	Without HF	106/1914 (5.5)	78/1916 (4.1)
	With HF	21/235 (8.9)	12/233 (5.2)

**Including death; †symptoms of severe impairment in consciousness or behaviour, need of external assistance, intervention to treat hypoglycaemia, and prompt recovery from acute symptoms after the intervention.*
HF, heart failure

Conclusions

Dapagliflozin reduced the risk of adverse kidney outcomes, hospitalisation for HF or cardiovascular death, and prolonged survival in people with CKD, with or without type 2 diabetes, independent of history of HF.

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DAPACKD

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