Initial Decline in Estimated Glomerular Filtration Rate After Initiation of Dapagliflozin in Patients With Heart Failure and Mildly Reduced or Preserved Reduced Ejection Fraction

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DELIVER

Disclosures

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Does the initial eGFR decline with dapagliflozin have prognostic significance among patients in DELIVER?

- An initial decline in eGFR following initiation of SGLT2i has been observed across populations of patients with diabetes and CKD.
- Among patients with HFrEF in the DAPA-HF trial, an initial decline in eGFR>10% was associated with adverse outcomes in the placebo arm, but not in the dapagliflozin arm.
- We explored the association of an initial eGFR decline with cardiovascular and kidney outcomes among patients with heart failure with mildly reduced or preserved ejection fraction enrolled in DELIVER.

Refs

DELIVER Study Design

Randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening heart failure in patients with heart failure and mildly reduced or preserved ejection fraction

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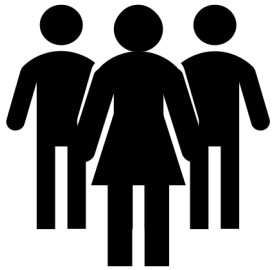
Eligibility Criteria

- Age ≥ 40 years
- NYHA class II-IV
- LVEF > 40% (including prior LVEF ≤ 40%)
- Structural Heart Disease (LVH or LA Enlargement)
- Elevated Natriuretic Peptides (> 300 pg/ml or 600 pg/ml in AFF)
- Either Ambulatory or Hospitalized for Heart Failure

Double-blind Treatment period



Dapagliflozin 10mg once daily

Event Driven (1117 estimated events)

Placebo

eGFR measured at baseline, months 1, 4, 12, 24, & 36

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Analytic approach

Definition of initial eGFR decline 'dip'

Change in eGFR from baseline to month 1 of >10% (vs. ≤10%)

n=5,788 of the original 6,263 participants had available measurements

Primary Cardiovascular Outcome

Cardiovascular death or a worsening heart failure event (hospitalization or urgent visit)

Kidney Outcomes

Composite (post hoc)

- ≥50% decline in eGFR relative to the month 1
- End-stage kidney disease (AE reporting or decline in eGFR to <15 ml/min/1.73m^2)
- Death due to kidney causes

Change in eGFR through month 36 (prespecified exploratory)

Models

Time to event:	Cox regression, landmarked at month 1, stratified by diabetes
eGFR slope:	Mixed effects regression models, starting at month 4
Adjustment:	Age, sex, race, eGFR, BMI, hypertension, LVEF, log-NT-proBNP, SBP, SBP change from baseline to month 1, MRA, ACEi/ARB

Baseline characteristics according to initial eGFR decline

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Characteristic	eGFR Decline <0% (n=2,408)	eGFR Decline 0 to 10% (n=1,499)	eGFR Decline >10% (n=1,881)	P-trend
Age, yrs	71 ±10	71 ±10	72 ±9	0.04
Female, no. (%)	1072 (45)	603 (40)	860 (46)	0.56
Race, no. (%)				0.26
White	1685 (70)	1023 (68)	1360 (72)	
Asian	533 (22)	340 (23)	352 (19)	
Black or African American	51 (2)	41 (3)	50 (3)	
American Indian or Alaska Native	72 (3)	50 (3)	49 (3)	
Other	67 (3)	45 (3)	70 (4)	
Systolic blood pressure, mmHg	128 ±15	128 ±16	129 ±16	0.02
Body-mass index	29.6 ±6.0	29.7 ±6.0	30.2 ±6.3	0.003
Serum creatinine, mg/dL	1.2 ±0.4	1.1 ±0.3	1.1 ±0.3	<0.001
eGFR, mL/min/1.73 m^2	58 ±19	66 ±20	61 ±18	<0.001
Left ventricular ejection fraction, %	54 ±9	54 ±9	55 ±9	0.03
NT-proBNP [Q1, Q3], pg/mL	1007 [627, 1741]	972 [599, 1619]	1022 [637, 1800]	0.54
Diabetes, no. (%)	1028 (43)	637 (42)	933 (50)	<0.001

Baseline medications according to initial eGFR decline

Characteristic	eGFR Decline <0% (n=2,408)	eGFR Decline 0 to 10% (n=1,499)	eGFR Decline >10% (n=1,881)	P-trend
Loop diuretic, n(%)	1870 (78)	1089 (73)	1478 (79)	0.66
ACE inhibitor or ARB, n(%)	1719 (71)	1114 (74)	1393 (74)	0.04
Mineralocorticoid-receptor antagonist, n(%)	1034 (43)	631 (42)	825 (44)	0.58
Beta-blocker, n(%)	1985 (82)	1220 (81)	1578 (84)	0.25
ARNI, n(%)	113 (5)	81 (5)	83 (4)	0.73
Randomized to dapagliflozin, n(%)	977 (41)	771 (51)	1144 (61)	<0.001

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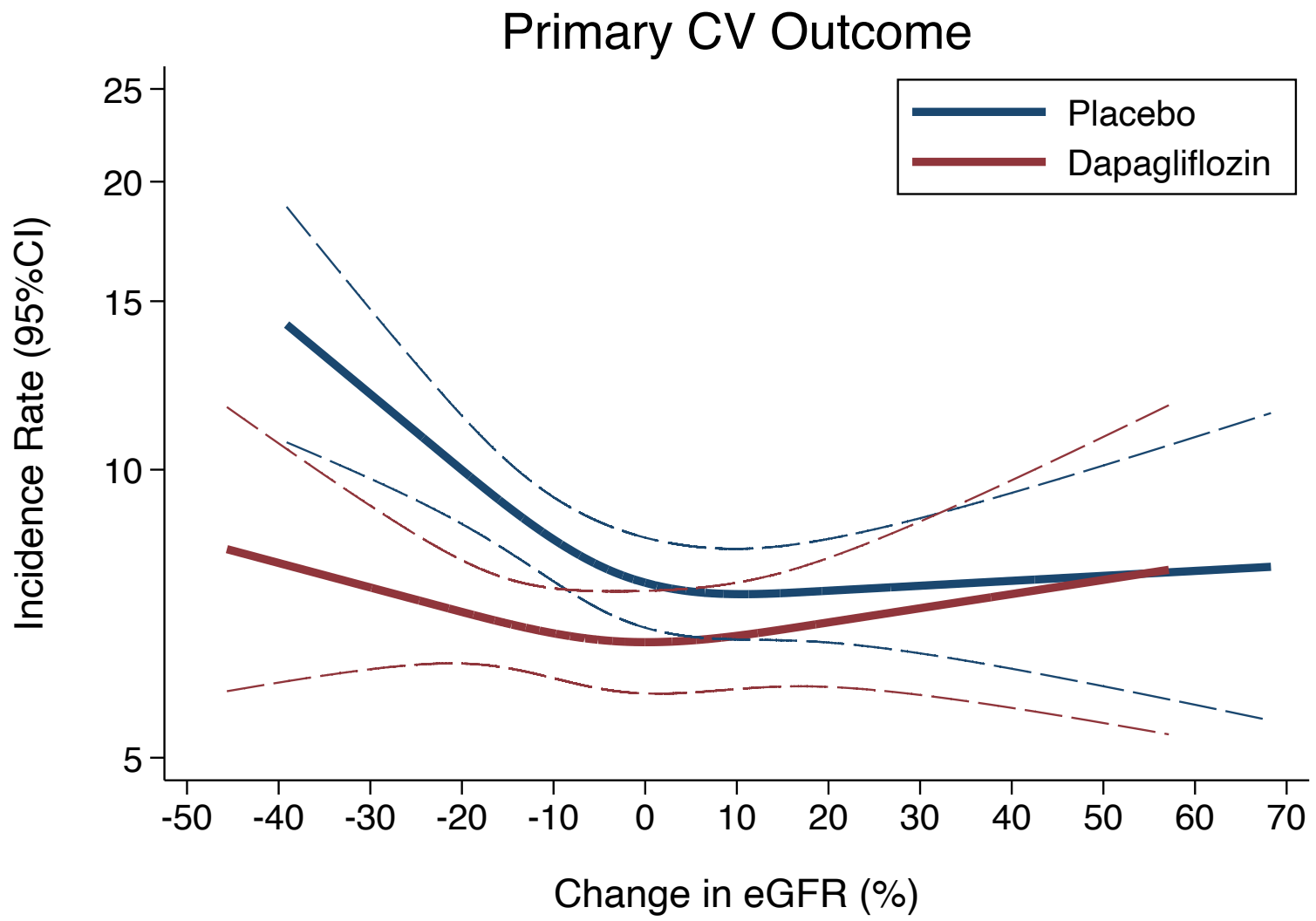
Cardiovascular Composite Outcome

	Placebo No. events/No. patients (%)		Dapagliflozin No. events/No. patients (%)		**Placebo**	**Dapa**	
	No Dip	Dip	No Dip	Dip	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**	P-int
eGFR dip >10%	357/2,140 (17)	156/720 (22)	274/1,739 (16)	175/1,135 (15)	**1.33 (1.10, 1.62)**	**0.90 (0.74, 1.09)**	0.01

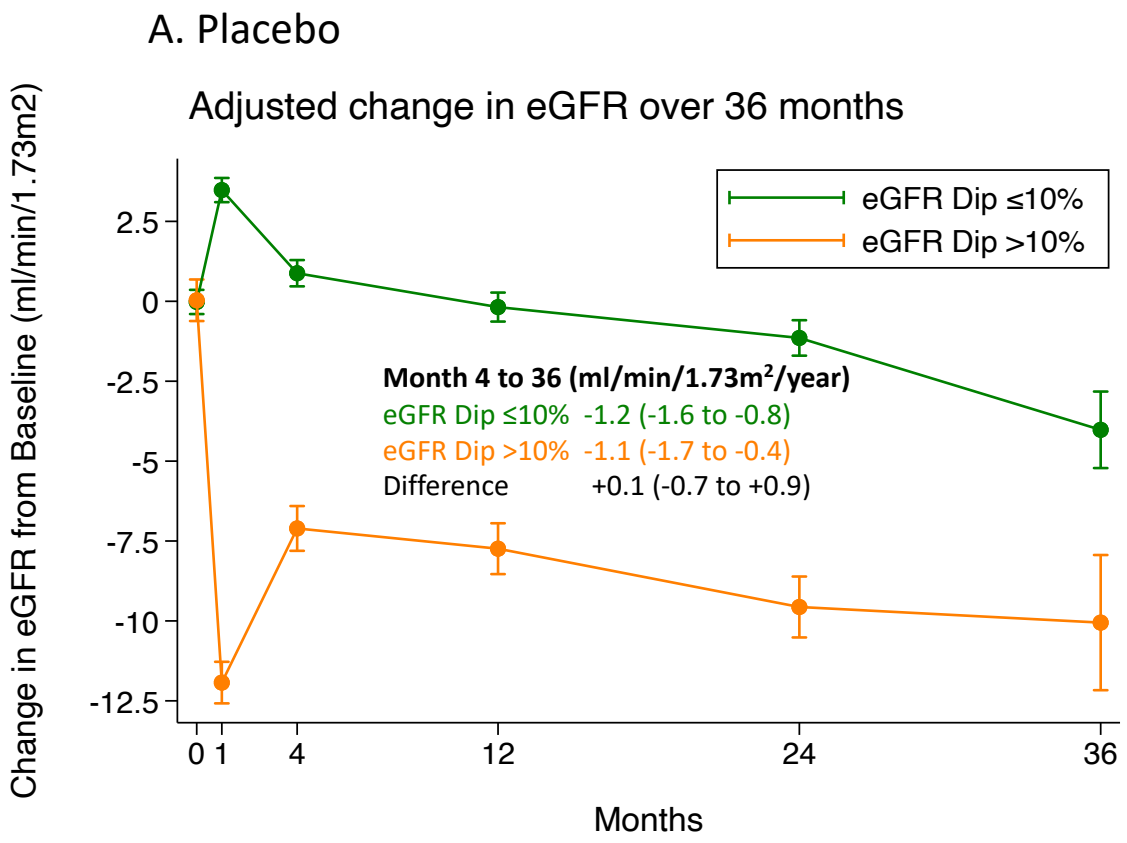
Adjusted incidence rates of the primary outcome according to eGFR decline and treatment assignment

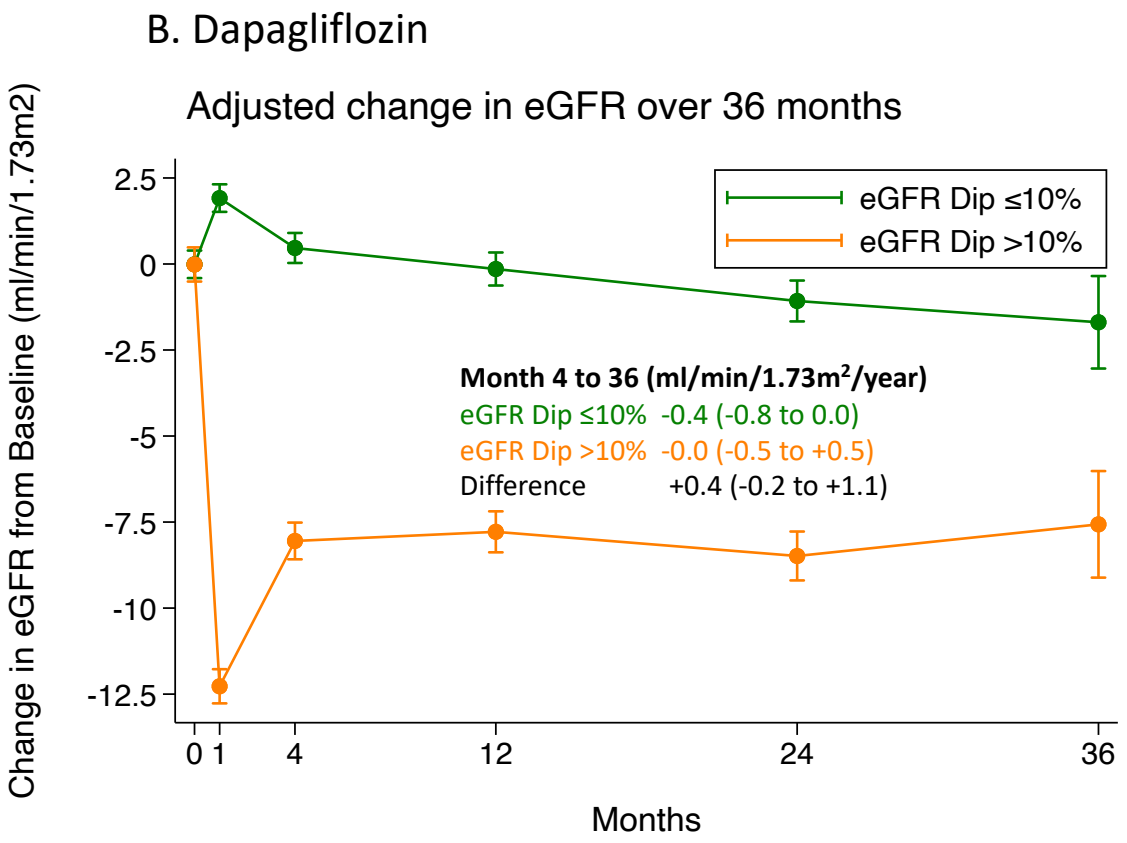


Kidney Composite Outcome

	Placebo No. events/No. patients (%)		Dapagliflozin No. events/No. patients (%)		**Placebo**	**Dapa**	
	No Dip	Dip	No Dip	Dip	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**	P-int
eGFR dip >10%	38/2,150 (1.8)	17/734 (2.3)	23/1,744 (1.3)	15/1,143 (1.3)	**1.62 (0.90, 2.89)**	**0.94 (0.49, 1.82)**	0.35

Change in eGFR over time, according to an initial eGFR decline





Conclusions

- Among patients with heart failure with mildly reduced or impaired ejection fraction treated with dapagliflozin, an initial eGFR decline was relatively frequent, but was not associated with subsequent risk of adverse cardiovascular or kidney events.

- These data reinforce clinical guidance that SGLT2i should not be interrupted or discontinued in response to an initial eGFR decline.

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