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Dapagliflozin in Patients With Heart Failure and Deterioration in Renal Function

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ABSTRACT

BACKGROUND Sodium-glucose cotransporter-2 (SGLT2) inhibitors are guideline recommended in the management of heart failure (HF). Although these therapies can be initiated even in patients with comorbid chronic kidney disease, some patients may face deterioration of kidney function over time.

OBJECTIVES In this study, the authors sought to examine the safety and efficacy of continuing SGLT2 inhibitors in HF when the estimated glomerular filtration rate (eGFR) falls below thresholds for initiation.

METHODS Associations between a deterioration of eGFR to <25 mL/min/1.73 m^2, efficacy, and safety outcomes and treatment with dapagliflozin were evaluated in time-updated Cox proportional hazard models in a participant-level pooled analysis of the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trials.

RESULTS Among 11,007 patients, 347 (3.2%) experienced a deterioration of eGFR to <25 mL/min/1.73 m^2 at least once in follow-up. These patients had a higher risk of the primary composite outcome (HR: 1.87; 95% CI: 1.48-2.35; $P < 0.001$). The risk of the primary outcome was lower with dapagliflozin compared with placebo among patients who did (HR: 0.53; 95% CI: 0.33-0.83) as well as did not (HR: 0.78; 95% CI: 0.72-0.86) experience deterioration of eGFR to <25 mL/min/1.73 m^2 ($P_{interaction} = 0.17$). The risk of safety outcomes, including drug discontinuation, was higher among patients with deterioration of eGFR to <25 mL/min/1.73 m^2; however, rates remained similar between treatment groups including among those who remained on study drug.

CONCLUSIONS Patients with deterioration of eGFR to <25 mL/min/1.73 m^2 had elevated risks of cardiovascular outcomes yet appeared to benefit from continuation of dapagliflozin with no excess in safety outcomes between treatment groups. The benefit-to-risk ratio may favor continuation of dapagliflozin treatment in patients with HF experiencing deterioration of kidney function. Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF]; NCT03036124; and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) (J Am Coll Cardiol 2023;82:1854–1863) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Heart failure (HF) and chronic kidney disease (CKD) have shared epidemiology and frequently coexist in clinical practice. This comorbid intersection is associated with higher risks of clinical events than conferred by either individual condition alone.[1] Many patients with HF may experience dynamic kidney function or progressive deterioration of kidney function over time, underscoring the necessity to optimize therapy in this high-risk group of patients. Yet declines in renal function are often associated with treatment interruption or discontinuation, in part related to uncertainties about the safety and efficacy of established guideline-directed medical therapies in the management of HF when patients experience a deterioration of kidney function.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are now considered to be foundational in the management of patients with HF across the spectrum of

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left ventricular ejection fraction (LVEF).[2,3] Previous studies have shown that the small initial decline (dip) in estimated glomerular filtration rate (eGFR) with SGLT2 inhibitor initiation is not adversely prognostic.[4] In addition, secondary analyses of pivotal trials have demonstrated consistent efficacy and safety of dapagliflozin across a wide range of kidney function down to eGFR as low as 30 mL/min/1.73 m^2 in DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) and 25 mL/min/1.73 m^2 in DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure).[5,6] Accordingly, current U.S. Food and Drug Administration labeling[7] does not recommend initiation of dapagliflozin in patients with eGFR <25 mL/min/1.73 m^2. The clinical benefits of SGLT2 inhibitors have been previously reported in the subgroup of patients with stage IV CKD (eGFR <30 mL/min/1.73 m^2) at baseline, but those studies were not conducted in populations of HF.[8,9] There are limited data examining the safety and efficacy of continuing SGLT2 inhibitors in HF when eGFR falls below those thresholds allowed for drug initiation.

In this participant-level pooled analysis of the DAPA-HF and DELIVER trials, we assessed the frequency and prognostic implications of a deterioration of kidney function below eGFR of 25 mL/min/1.73 m^2 as well as the association between such declines in kidney function, treatment with dapagliflozin, and clinical outcomes.

ABREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HF = heart failure

LVEF = left ventricular ejection fraction

SGLT2 = sodium-glucose cotransporter-2

METHODS

STUDY DESIGN. This analysis was carried out using a participant-level pooled dataset of the DAPA-HF and DELIVER trials that was prespecified in a dedicated statistical analysis plan. Participant-level data were available for both trials, which facilitated harmonization of key variables and outcomes definitions. The trial designs and primary results of both the DAPA-HF and the DELIVER trials have been previously reported.[2,3] Both DAPA-HF and DELIVER were double-blind placebo-controlled randomized trials that compared dapagliflozin vs placebo. DAPA-HF included patients aged ≥18 years with symptomatic HF, LVEF ≤40%, and elevated natriuretic peptides. DELIVER included patients aged ≥40 years with symptomatic HF, LVEF >40%, elevated natriuretic peptide levels, evidence of structural heart disease, and at least intermittent diuretic use. Institutional review boards at each study center approved the study protocol for each trial.

CLINICAL ENDPOINTS. In both trials, the primary endpoint was the composite of time to first worsening HF event (hospitalization for HF or urgent HF visit requiring intravenous HF therapies) or cardiovascular death. We also examined cardiovascular (CV) death, HF hospitalization, all-cause death, and study drug discontinuation. Potential primary endpoints and all deaths were centrally adjudicated by a designated clinical endpoints committee. Safety outcomes included any serious adverse event (AE), AEs leading

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics According to Deterioration of eGFR to <25 mL/min/1.73 m²

	No Deterioration (n = 10,660)	Deterioration (n = 347)	*P* Value
Age, y	69 ± 11	73 ± 10	<0.001
Male	6,978 (65.5)	173 (49.9)	<0.001
Race			0.99
White	7,529 (70.6)	243 (70.0)	
Asian	2,313 (21.7)	77 (22.2)	
Black or African American	373 (3.5)	12 (3.5)	
Indian or Alaska Native	188 (1.8)	5 (1.4)	
Native Hawaiian/Pacific Islander	2 (0.0)	0 (0.0)	
Other	255 (2.4)	10 (2.9)	
Region			<0.001
Europe and Saudi Arabia	5,028 (47.2)	131 (37.8)	
North America	1,457 (13.7)	71 (20.5)	
South America	1,924 (18.0)	74 (21.3)	
Asia/Pacific	2,251 (21.1)	71 (20.5)	
NYHA functional class			0.67
II	7,675 (72.0)	241 (69.5)	
III	2,926 (27.4)	103 (29.7)	
IV	58 (0.5)	3 (0.9)	
Baseline LVEF, %	44 ± 14	50 ± 13	<0.001
LVEF >40%	5,991 (56.2)	269 (77.5)	<0.001
LVEF ≤40%	4,669 (43.8)	78 (22.5)	<0.001
Body mass index, kg/m²	29 ± 6	30 ± 7	<0.001
Systolic blood pressure, mm Hg	125 ± 16	131 ± 18	<0.001
Heart rate, beats/min	72 ± 12	72 ± 13	0.24
Previous HF hospitalization	4,612 (43.3)	178 (51.3)	0.003
Atrial fibrillation/flutter	3,670 (34.4)	102 (29.4)	0.05
Type 2 diabetes	4,568 (42.9)	221 (63.7)	<0.001
Hypertension	8,756 (82.1)	20 (92.2)	<0.001
eGFR, mL/min/1.73 m²	63.9 ± 19.0	36.2 ± 10.8	<0.001
Serum creatinine, μmol/L	101.7 ± 29.1	153.5 ± 37.7	<0.001
Glycated hemoglobin, %	6.5 ± 1.4	7.1 ± 1.7	<0.001
NT-proBNP, pg/mL	1,167 (701-2,090)	1,690 (763-3,240)	<0.001
ACEI/ARB/ARNI	9,004 (84.5)	270 (77.8)	<0.001
MRA	5,895 (55.3)	142 (40.9)	<0.001
Beta-blocker	9,444 (88.6)	291 (83.9)	0.007
Loop diuretic	10,217 (95.8)	339 (97.7)	0.09

Values are mean ± SD, n (%), or median (IQR).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

to study drug discontinuation or study drug interruption, renal AEs, and AEs suggestive of volume depletion.

STATISTICAL ANALYSIS. The protocols of both trials did not mandate study drug discontinuation if the eGFR fell below the trial threshold for patient inclusion (<30 mL/min/1.73 m² in DAPA-HF and <25 mL/min/1.73 m² in DELIVER) in follow-up. However, it was suggested that investigators first evaluate for potentially reversible causes of kidney injury. All patients who experienced a deterioration of eGFR to <25 mL/min/1.73 m² at least once in follow-up were identified. We included measurements of kidney function that were similarly obtained between the 2 trials: at baseline and at 1, 4, 12, and 24 months. eGFR was calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration equation. Serial changes in eGFR were analyzed among patients who did and did not experience deterioration of eGFR to <25 mL/min/1.73 m².

Baseline characteristics were compared between those who did and did not experience deterioration of eGFR to <25 mL/min/1.73 m² in follow-up and by treatment assignment within these 2 groups. Data are reported as mean ± SD, median (IQR) for skewed distributions, and n (%) for categoric variables. Student's *t*-tests and chi-square tests were used where appropriate.

We assessed the association between deterioration of kidney function to eGFR <25 mL/min/1.73 m² and the development of subsequent CV outcomes and safety outcomes with the use of time-updated Cox proportional hazard models. Patients were initially considered in a window of risk during the period before eGFR <25 mL/min/1.73 m²; if eGFR subsequently fell below this threshold, then the patient was reclassified at that point in time. We then assessed for potential modification of the effect of treatment on clinical outcomes before or after eGFR <25 mL/min/1.73 m² with the use of the same time-updated models. This was carried out based on an intention-to-treat approach such that patients were considered to be under their assigned treatment regardless of whether or not they remained on the study drug. We repeated these analyses in the individual DAPA-HF and DELIVER cohorts (using all available eGFR time points in each trial) to evaluate consistency in patterns of outcomes. Because eGFR may fluctuate, we conducted a sensitivity analysis examining persistent deterioration of kidney function among patients who experienced decline in eGFR to <25 mL/min/1.73 m² on 2 consecutive measurements of kidney function. An additional sensitivity analysis was conducted to assess efficacy and safety outcomes among patients who experienced a deterioration of eGFR to <25 mL/min/1.73 m² and who remained on the study drug (defined as those patients not experiencing permanent premature study drug discontinuation).

All analyses were performed with the use of STATA version 17 (Statacorp). A *P* value of <0.05 was considered to be statistically significant.

RESULTS

Of the total 11,007 randomized patients, 347 (78 in DAPA-HF and 269 in DELIVER; or 3.2% total)

experienced a deterioration of kidney function to eGFR <25 mL/min/1.73 m^2 at least once during trial follow-up. Among the 347 patients with deterioration of kidney function to eGFR <25 mL/min/1.73 m^2, 20% of such deteriorations occurred within 1 month after randomization and 80% occurred after 1 month of trial follow-up. The median time to deterioration of kidney function to eGFR <25 mL/min/1.73 m^2 was 121 days (IQR: 35-361 days) in the overall population and was similar between treatment groups: dapagliflozin 120 days (IQR: 30-358 days) vs placebo 121 days (IQR: 35-361 days) (Supplemental Figure 1). Serial changes in eGFR over time according to patients who do and do not experience eGFR deterioration to <25 mL/min/1.73 m^2 are shown in Supplemental Figure 2. In a landmark analysis with survival analysis time beginning at 30 days to account for the early expected eGFR "dip" with dapagliflozin initiation, the risk of eGFR deterioration to <25 mL/min/1.73 m^2 was similar between treatment groups: HR: 1.12; 95% CI: 0.85-1.47; $P = 0.39$. The majority of patients experiencing a deterioration of eGFR to <25 mL/min/1.73 m^2, regardless of treatment arm (74.4% in the dapagliflozin arm and 73.5% in the placebo arm) remained on the assigned study drug for the duration of the study.

BASELINE CHARACTERISTICS. Patients experiencing deterioration of kidney function to eGFR <25 mL/min/1.73 m^2 at least once during trial follow-up were older, more often women with worse baseline kidney function, had higher natriuretic peptide levels, higher baseline LVEF, generally higher burden of comorbidities, and were less frequently treated with background HF medical therapies (**Table 1**). When baseline characteristics of patients who experienced a deterioration of eGFR to <25 mL/min/1.73 m^2 within 1 month after randomization and after 1 month were compared, no clinically meaningful differences were identified (Supplemental Table 1). In addition, when stratified according to treatment assignment, baseline characteristics between arms were similar among patients who did and did not experience deterioration of eGFR to <25 mL/min/1.73 m^2 (Supplemental Table 2).

ASSOCIATION BETWEEN DETERIORATION OF KIDNEY FUNCTION TO eGFR <25 mL/min/1.73 m^2 AND SUBSEQUENT CV OUTCOMES. During trial follow-up, the primary composite outcome occurred in 2,010 patients. The incidence of the primary composite outcome was nearly double in patients experiencing deterioration of eGFR to <25 mL/min/1.73 m^2 (incidence rate per 100 patient-years: 18.6; 95% CI: 14.9-23.5) compared with patients without such deterioration of kidney function (incidence rate per 100 patient-years: 10.2; 95% CI: 9.7-10.6; HR: 1.87; 95% CI: 1.48-2.35; $P < 0.001$). A similar pattern was observed for all other outcomes assessed, including CV death, HF hospitalization, and all-cause death (**Table 2**, **Figure 1**).

TABLE 2 Associations Between Deterioration of eGFR to <25 mL/min/1.73 m^2 and Subsequent Outcomes

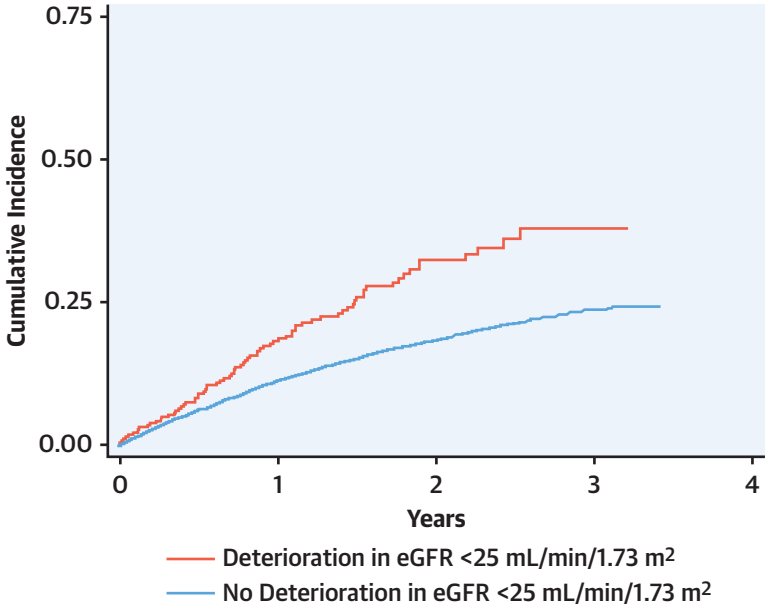
	No Deterioration	Deterioration	HR (95% CI)	*P* Value
Primary composite			1.87 (1.48-2.35)	<0.001
Events, n	1,934	76		
Event rate, per 100 PY	10.2 (9.7-10.6)	18.6 (14.9-23.5)		
Cardiovascular death			1.50 (1.07-2.08)	0.02
Events, n	955	37		
Event rate, per 100 PY	4.7 (4.4-5.0)	7.3 (5.3-10.4)		
Hospitalization for heart failure			2.16 (1.65-2.83)	<0.001
Events, n	1,240	56		
Event rate, per 100 PY	6.5 (6.1-6.8)	13.5 (10.4-17.7)		
All-cause death			1.92 (1.53-2.40)	<0.001
Events, n	1,547	81		
Event rate, per 100 PY	7.6 (7.2-8.0)	16.0 (12.9-20.1)		

Time-to-first events analyses were performed with the use of Cox proportional hazard models.
CV = cardiovascular; eGFR = estimated glomerular filtration rate; PY = person-years.

ASSOCIATIONS BETWEEN DETERIORATION OF KIDNEY FUNCTION TO eGFR <25 mL/min/1.73 m^2, TREATMENT WITH DAPAGLIFLOZIN, AND CLINICAL OUTCOMES. The incidence of the primary composite outcome was lower among patients treated with dapagliflozin compared with placebo regardless of whether patients experienced (HR: 0.53; 95% CI: 0.33-0.83) or did not experience (HR: 0.78; 95% CI: 0.72-0.86) deterioration of eGFR to <25 mL/min/1.73 m^2 ($P_{\text{Interaction}} = 0.17$) (**Figure 2**, Supplemental Table 3A). Results were nearly identical in adjusted models (Supplemental Table 3B). In light of higher risk for clinical events in those with deterioration of kidney function to eGFR <25 mL/min/1.73 m^2 in follow-up, absolute risk reduction with dapagliflozin was higher among patients experiencing such deterioration of renal function (placebo: 25.2 per 100 person-years; dapagliflozin: 14.5 per 100 person-years; estimated absolute risk reduction: 10.7 per 100 person-years) compared with those who did not experience deterioration (placebo: 11.4 per 100 person-years; dapagliflozin: 9.0 per 100 person-years; estimated absolute risk reduction: 2.4 per 100 person-years). In addition, when analyzed according to trial, results remained qualitatively similar regardless of HF phenotype (reduced vs mildly reduced or preserved ejection fraction) (Supplemental Table 4).

Sensitivity analyses examined patients with sustained eGFR <25 mL/min/1.73 m^2 on 2 consecutive

FIGURE 1 Primary Composite Among Patients With and Without Deterioration of eGFR to <25 mL/min/1.73 m²



Time to first event analyses were performed using Cox proportional hazard models landmarked at time of estimated glomerular filtration rate (eGFR) decline to <25 mL/min/1.73 m² for those experiencing deterioration of eGFR and time of randomization for those not experiencing deterioration of eGFR.

kidney function assessments (n = 80), and overall findings were qualitatively similar (Supplemental Table 5). Regarding the primary composite outcome, there appeared to be a nominal treatment difference favoring dapagliflozin among patients experiencing sustained eGFR deterioration ($P_{\text{Interaction}}$ = 0.043). Additional sensitivity analysis examining those patients who remained on treatment produced qualitatively similar findings (Supplemental Table 6).

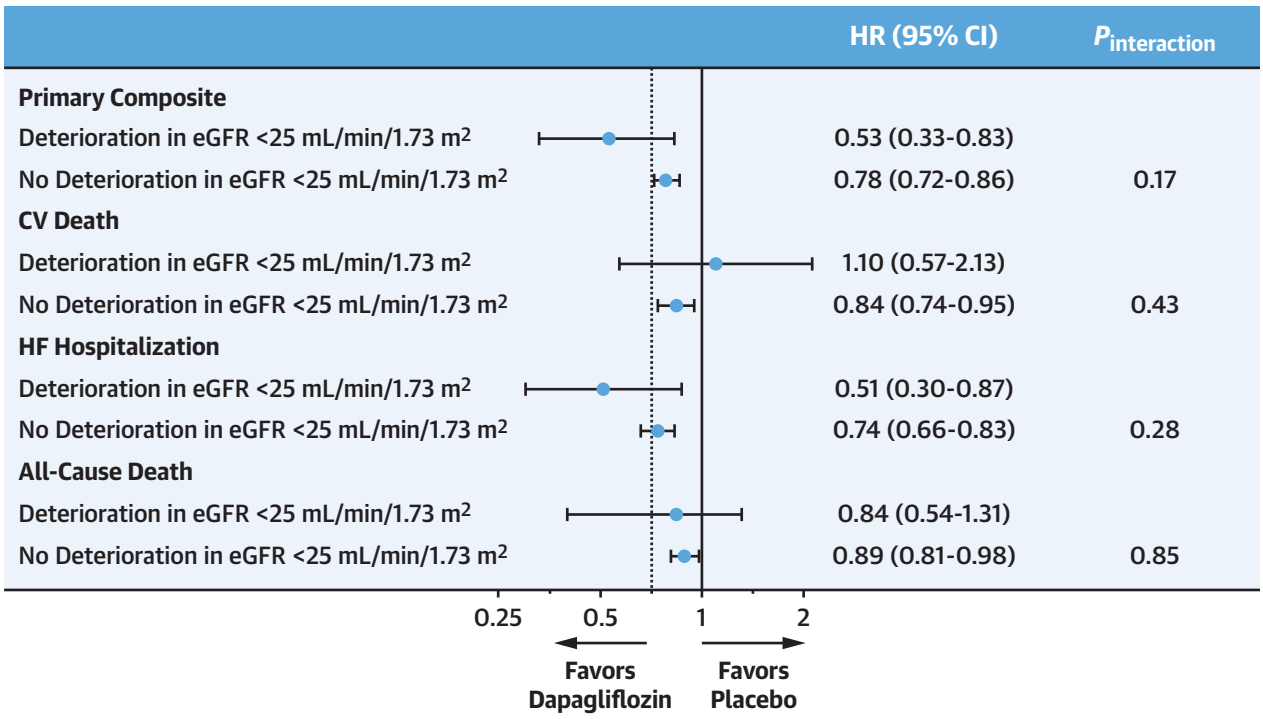
ASSOCIATIONS BETWEEN DETERIORATION OF KIDNEY FUNCTION TO eGFR <25 mL/min/1.73 m², TREATMENT WITH DAPAGLIFLOZIN, AND SAFETY OUTCOMES. The rates of any serious AEs and AEs of interest (Table 3) were higher among patients experiencing deterioration of eGFR to <25 mL/min/1.73 m² compared with those who did not experience deterioration. However, the rates of all safety outcomes including study drug discontinuation remained similar between treatment groups regardless of a deterioration of eGFR to <25 mL/min/1.73 m² (Table 3). A sensitivity analysis examining patients who experienced a deterioration of eGFR to <25 mL/min/1.73 m² and who continued on the study drug produced qualitatively similar results (Supplemental Table 7).

DISCUSSION

In this participant-level pooled analysis of the DAPA-HF and DELIVER trials, we found that deterioration of kidney function to eGFR <25 mL/min/1.73 m² at least once during trial follow-up occurred in approximately 3% of patients. Patients with HF experiencing a decline in renal function to eGFR <25 mL/min/1.73 m² during the trial were at heightened risk for development of subsequent CV outcomes. Compared with placebo, treatment with dapagliflozin was associated with lower rates of the primary composite outcome regardless of deterioration of eGFR to <25 mL/min/1.73 m², with a higher absolute risk reduction. The rates of safety outcomes remained similar between treatment groups regardless of whether or not patients experienced a deterioration of eGFR to <25 mL/min/1.73 m², including among those who remained on the study drug. Overall, these data suggest that the benefit-to-risk ratio may favor continued treatment with dapagliflozin in patients with HF and deterioration of kidney function to eGFR <25 mL/min/1.73 m² (Central Illustration).

Although both DAPA-HF and DELIVER used strict eligibility criteria for study entry based on baseline

FIGURE 2 Associations Between Deterioration of eGFR to <25 mL/min/1.73 m^2, Treatment, and Subsequent Outcomes



Time to first event analyses were performed using time-updated Cox proportional hazard models. Patients were considered in a window of risk during the period before estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2; if eGFR subsequently fell below this threshold, then the patient was reclassified at that point in time. CV = cardiovascular; HF = heart failure.

kidney function, the study protocols did not mandate drug discontinuation or interruption if eGFR fell below the thresholds allowed for initial trial eligibility. Final clinical decision making was left to the discretion of the treating clinician. In DAPA-HF and DELIVER, most patients did in fact remain on the study drug providing a unique opportunity to examine the clinical course of those continued on dapagliflozin even when eGFR had fallen below the thresholds allowed for drug initiation. Although the rates of study drug discontinuation were higher among patients experiencing deterioration of kidney function to eGFR <25 mL/min/1.73 m^2, the rates of discontinuation were similar between treatment groups regardless of deterioration of eGFR to <25 mL/min/1.73 m^2.

Consistent with previous observations of a "risk-treatment paradox," these analyses from DAPA-HF and DELIVER found that patients who experienced a decline in renal function faced higher risks of CV outcomes but were less likely to receive background HF medical therapies. In our primary analyses, we examined individuals experiencing eGFR <25 mL/min/1.73 m^2 at least once. Although this might be transient in some, nonetheless, patients experiencing deterioration of eGFR at least once in trial follow-up had markedly elevated subsequent CV outcomes. Results remained consistent in a sensitivity analysis evaluating the subset of patients experiencing a sustained deterioration of eGFR to <25 mL/min/1.73 m^2 for at least 2 consecutive assessments.

Although SGLT2 inhibitors are known to be associated with an "early eGFR dip" in the days to weeks after treatment initiation, deterioration of kidney function over time to eGFR <25 mL/min/1.73 m^2 in these trials much more frequently occurred outside that early window. Indeed, the median time frame for eGFR to fall below 25 mL/min/1.73 m^2 was around 4 months after randomization. These data highlight that kidney function may be dynamic in the longitudinal care of patients with HF, and clinicians may face decisions about whether to continue or interrupt medical therapies well beyond initial treatment commencement.

TABLE 3 Associations Between Safety Outcomes, Treatment, and Deterioration of eGFR to <25 mL/min/1.73 m²

	No Deterioration		Deterioration		
	Placebo	Dapagliflozin	Placebo	Dapagliflozin	$P_{interaction}$
Any SAE					
Events, n	2,319	2,134	55	73	
Event rate, per 100 PY	29.5 (28.3-30.8)	26.2 (25.2-27.4)	47.6 (35.6-63.9)	40.1 (31.6-51.2)	
HR (95% CI)	0.89 (0.84-0.95)		0.83 (0.58-1.17)		0.76
AE leading to study drug discontinuation					
Events, n	288	276	17	17	
Event rate, per 100 PY	2.8 (2.5-3.2)	2.8 (2.5-3.2)	9.1 (5.7-15.4)	7.1 (4.5-11.9)	
HR (95% CI)	0.99 (0.84-1.17)		0.79 (0.40-1.56)		0.43
AE leading to study drug interruption					
Events, n	812	686	31	34	
Event rate, per 100 PY	8.8 (8.2-9.4)	7.3 (6.8-7.9)	18.9 (13.2-27.7)	14.6 (10.4-20.9)	
HR (95% CI)	0.84 (0.76-0.93)		0.71 (0.4-1.17)		0.73
AE suggestive of volume depletion					
Events, n	188	213	6	7	
Event rate, per 100 PY	1.9 (1.6-2.2)	2.2 (1.9-2.5)	2.9 (1.3-7.7)	2.7 (1.3-6.4)	
HR (95% CI)	1.14 (0.94-1.39)		0.82 (0.27-2.45)		0.62
Renal AE					
Events, n	228	204	21	22	
Event rate, per 100 PY	2.3 (2.0-2.6)	2.1 (1.8-2.4)	11.5 (7.6-18.2)	9.2 (6.0-14.6)	
HR (95% CI)	0.90 (0.74-1.08)		0.79 (0.43-1.44)		0.71

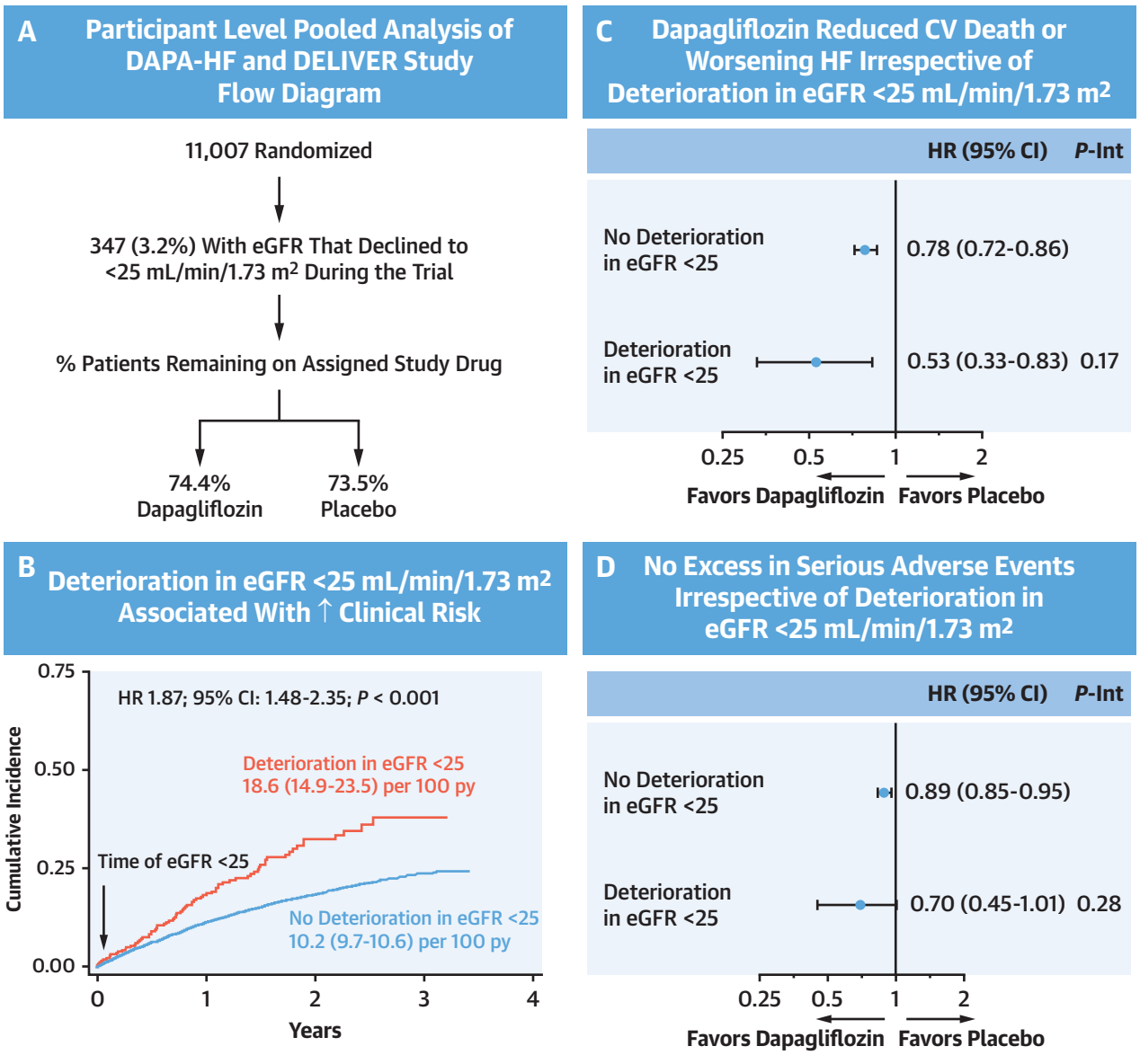
Time to first events analyses were performed with the use of Cox proportional hazards models.
AE = adverse event; eGFR = estimated glomerular filtration rate; SAE = serious adverse event.

Previous subgroup analyses have demonstrated consistent safety and efficacy of dapagliflozin to eGFR as low as 30 mL/min/1.73 m² in DAPA-HF and 25 mL/min/1.73 m² in DELIVER.[5,6] Similarly, the beneficial effects of the SGLT2 inhibitor empagliflozin were consistent across the spectrum of kidney function including among patients with eGFR as low as 20 mL/min/1.73 m² in both EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction).[10,11] Our results extend these findings, suggesting potentially preserved clinical benefits of dapagliflozin in patients with HF who experience deterioration of kidney function to below the threshold for initiation (based on the regulatory labeling).

Importantly, these data might inform only continuation of SGLT2 inhibitors and not new initiation of these therapies in patients with advanced CKD. Although there is a growing evidence base for the use of SGLT2 inhibitors in stage IV CKD, data in stage V CKD are considerably more limited. The RENAL LIFECYCLE trial (RCT to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients With Severe CKD; NCT05374291) is underway to examine dapagliflozin in patients with advanced CKD (eGFR <25 mL/min/1.73 m²), patients on chronic dialysis, and patients after kidney transplantation.

STUDY LIMITATIONS. The results of this analysis should be considered in the context of certain limitations. First, this is a post hoc analysis and must be considered as hypothesis generating only. Second, comparisons between patients who did and did not experience a deterioration of eGFR to <25 mL/min/1.73 m² were made after randomization; however, baseline characteristics according to treatment remained well balanced. Third, deterioration of eGFR below the threshold of inclusion may reflect natural variation in kidney function at the time of assessment rather than true progression of disease. However, it is reassuring that results remained qualitatively similar in a sensitivity analysis assessing persistent deterioration of eGFR to <25 mL/min/1.73 m² on 2 consecutive assessments of kidney function. The number of patients whose eGFR fell below 25 mL/min/1.73 m² was small. Finally, data on other markers of kidney dysfunction, including albuminuria, as well as the etiology of eGFR deterioration (eg, exposure to nephrotoxins such as contrast dye or nonsteroidal antiinflammatory drugs) were not available; however, investigators were encouraged to assess for potentially reversible causes of kidney dysfunction.

CENTRAL ILLUSTRATION **Benefit-to-Risk Ratio Favors Dapagliflozin Continuation in Heart Failure Patients With eGFR <25 mL/min/1.73 m^2**



Chatur S, et al. J Am Coll Cardiol. 2023;82(19):1854–1863.

Time-to-first events analyses were performed using time-updated Cox proportional hazards models. (A) Approximately 3.2% of patients experienced deterioration in estimated glomerular filtration rate (eGFR) to <25 ml/min/1.73 m^2 in trial follow-up. (B) Such patients experienced elevated risk for clinical events. (C) Treatment with dapagliflozin consistently reduced the primary composite outcome, (D) without excess in serious adverse events, irrespective of deterioration in eGFR <25 mL/min/1.73 m^2. CV = cardiovascular; HF = heart failure; Int = interaction.

CONCLUSIONS

Deterioration of kidney function to an eGFR threshold below that allowed for trial inclusion (eGFR <25 mL/min/1.73 m^2) was infrequent but was associated with heightened risk of the development of subsequent CV outcomes. The beneficial effects of dapagliflozin relative to placebo on CV outcomes appeared to be preserved, regardless of a decline in renal function to an eGFR <25 mL/min/1.73 m^2, with

no excess in safety outcomes between treatment groups. Taken together, these data suggest that the benefit-to-risk ratio may favor continuation of dapagliflozin in patients with HF experiencing a deterioration of kidney function to eGFR <25 mL/min/1.73 m^2 and highlight the need for randomized evidence in advanced CKD.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with HF, continuing dapagliflozin may be beneficial even when kidney function falls to eGFR <25 mL/min/1.73 m^2.

TRANSLATIONAL OUTLOOK: Additional research is warranted to better characterize the role for SGLT2 inhibitors in patients with HF and advanced CKD.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.

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