Efficacy and Safety of Dapagliflozin by Baseline Glycemic Status: A Prespecified Analysis From the DAPA-CKD Trial

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OBJECTIVE

The Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) study demonstrated risk reduction for kidney and cardiovascular outcomes with dapagliflozin versus placebo in participants with chronic kidney disease (CKD) with and without diabetes. We compared outcomes according to baseline glycemic status.

RESEARCH DESIGN AND METHODS

We enrolled participants with CKD, estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73 m^2, and urinary albumin-to-creatinine ratio 200–5,000 mg/g. The primary composite end point was sustained eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death.

RESULTS

Of 4,304 participants, 738 had normoglycemia, 660 had prediabetes, and 2,906 had type 2 diabetes. The effect of dapagliflozin on the primary outcome was consistent (*P* for interaction = 0.19) in normoglycemia (hazard ratio [HR] 0.62 [95% CI 0.39, 1.01]), prediabetes (HR 0.37 [0.21, 0.66]), and type 2 diabetes (HR 0.64 [0.52, 0.79]). We found no evidence for effect modification on any outcome. Adverse events were similar, with no major hypoglycemia or ketoacidosis in participants with normoglycemia or prediabetes.

CONCLUSIONS

Dapagliflozin safely reduced kidney and cardiovascular events independent of baseline glycemic status.

In the Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial of participants with chronic kidney disease (CKD) with or without type 2 diabetes, the sodium–glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin led to a 39% relative risk reduction in the primary composite outcome of sustained decline in the estimated glomerular filtration rate (eGFR) of ≥50%, end-stage kidney disease, or death from kidney or cardiovascular causes (1). In this prespecified analysis, we report the efficacy and safety of dapagliflozin in participants with normal glucose status, prediabetes, and type 2 diabetes.

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RESEARCH DESIGN AND METHODS

DAPA-CKD was a multicenter, double-blind, placebo-controlled, randomized trial. Participants had CKD defined as an eGFR of 25–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 200–5,000 mg/g. We randomized participants in a 1:1 ratio to dapagliflozin, 10 mg/day, or placebo, and monitored participants for a median of 2.4 years. The trial was stopped early for overwhelming efficacy on recommendation from the Independent Data Monitoring Committee (1).

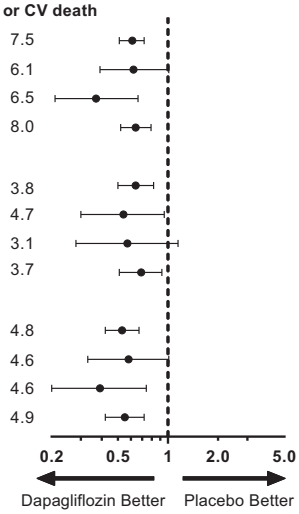
We classified patients by baseline glycemic status: normoglycemia was defined as HbA_{1c} <5.7% (39 mmol/mol), prediabetes as HbA_{1c} of at least 5.7% (39 mmol/mol) and <6.5% (48 mmol/mol), and type 2 diabetes as a history of diabetes or HbA_{1c} of at least 6.5% (48 mmol/mol).

The primary end point was the composite of time to the first occurrence of a sustained decline in the eGFR ≥50%, onset of end-stage kidney disease, or death from kidney or cardiovascular causes. Secondary end points were the time to a kidney-specific composite outcome (which included the same components as the primary outcome except cardiovascular death), a composite cardiovascular end point (hospitalization for heart failure or cardiovascular death), and death from any cause (all-cause mortality).

A Cox proportional hazards regression model stratified by baseline

A

	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Events/100 patient-years	Placebo Events/100 patient-years	Hazard Ratio (95% CI)	P Value for Interaction	Absolute Risk Difference, % (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)		5.3 (3.4, 7.3)	
Normal glucose	28/368	41/370	4.1	6.1	0.62 (0.39, 1.01)	0.19	3.5 (-0.7, 7.7)	0.42
Pre-diabetes	17/329	42/331	2.6	6.5	0.37 (0.21, 0.66)		7.5 (3.2, 11.8)	
Diabetes	152/1455	229/1451	5.2	8.0	0.64 (0.52, 0.79)		5.3 (2.9, 7.8)	
ESKD								
Overall	109/2152	161/2152	2.5	3.8	0.64 (0.50, 0.82)		2.4 (1.0, 3.9)	
Normal glucose	19/368	32/370	2.8	4.7	0.54 (0.30, 0.95)	0.72	3.5 (-0.2, 7.1)	0.81
Pre-diabetes	13/329	20/331	2.0	3.1	0.57 (0.28, 1.15)		2.1 (-1.2, 5.4)	
Diabetes	77/1455	109/1451	2.6	3.7	0.69 (0.51, 0.92)		2.2 (0.4, 4.0)	
eGFR decline 50%								
Overall	112/2152	201/2152	2.6	4.8	0.53 (0.42, 0.67)		4.1 (2.6, 5.7)	
Normal glucose	20/368	31/370	2.9	4.6	0.58 (0.33, 1.01)	0.60	2.9 (-0.7, 6.6)	0.71
Pre-diabetes	13/329	30/331	2.0	4.6	0.39 (0.20, 0.74)		5.1 (1.4, 8.9)	
Diabetes	79/1455	140/1451	2.7	4.9	0.55 (0.42, 0.72)		4.2 (2.3, 6.1)	



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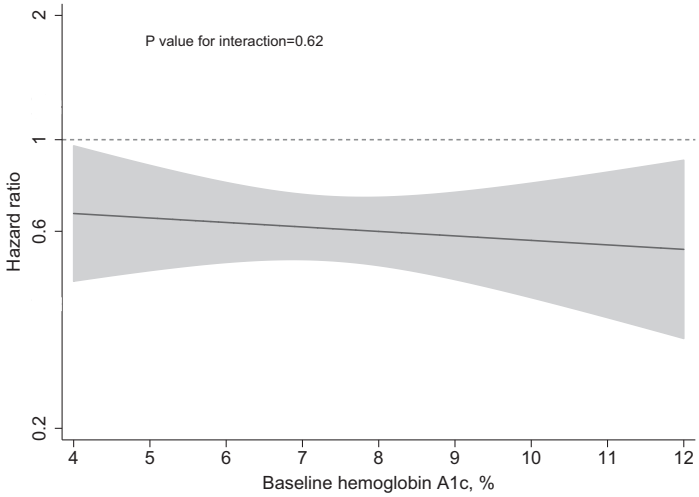

Figure 1—*A*: Forest plot of the primary composite outcome of ≥50% eGFR decline, end-stage kidney disease (ESKD), or death from cardiovascular (CV) or kidney causes with dapagliflozin compared with placebo by glycemic status at baseline. *B*: The treatment effect of dapagliflozin compared with placebo as a function of baseline HbA_{1c} (continuous) for the primary outcome. The solid black line represents the HR of the treatment effect. The gray shaded area represents the 95% CI around the treatment effects. The dotted horizontal line represents a HR of 1 (i.e., no difference between randomized groups).

glycemic status, with UACR as the stratification factor and adjusted for the baseline eGFR, was used to estimate the hazard ratio (HRs) and 95% CIs for dapagliflozin compared with placebo within each glycemic subgroup. We tested for heterogeneity by adding interaction terms between glycemic subgroup and randomized treatment assignment. We calculated annualized incidence rates (events per 100 patient-years). Absolute risk reductions were calculated by subtracting the annualized incidence rate in the dapagliflozin group from the placebo group, and heterogeneity in absolute treatment effects was estimated using fixed-effects meta-analysis.

We examined the effect of treatment according to continuous HbA_{1c} using a linear interaction model.

RESULTS

Of the 4,304 participants enrolled, 738 had normoglycemia, 660 had prediabetes, and 2,906 had type 2 diabetes at baseline (Supplementary Table 1).

The difference in HbA_{1c} between dapagliflozin and placebo during follow-up was –0.1% (95% CI –0.1, 0.0; $P = 0.0018$; –0.9 mmol/mol [95% CI –1.5, 0.3]). The between-group difference in HbA_{1c} during follow-up in participants with normoglycemia and prediabetes was 0.0% (95% CI –0.2, 0.2; $P = 0.8597$; 0.2 mmol/mol [95% CI –1.8, 2.2]) and –0.0% (95% CI –0.2, 0.2; $P = 0.8764$; –0.2 mmol/mol [95%CI –2.3, 1.9]), respectively. In participants with type 2 diabetes, the HbA_{1c} difference was –0.1% (95% CI –0.2, 0.0; $P = 0.0378$; –1.1 mmol/mol [95% CI –2.1, 0.0]) (Supplementary Fig. 1).

Rates of the primary composite end point of a ≥50% eGFR decline, end-stage kidney disease, or death from cardiovascular or kidney causes were higher in participants with type 2 diabetes relative to participants with prediabetes or normoglycemia at baseline (Fig. 1*A*). The relative risk reduction by dapagliflozin for the primary composite outcome (HR 0.61 [95% CI 0.51, 0.72]) was consistent across subgroups by baseline glycemic status (P for interaction = 0.19) (Fig. 1*A*). In continuous analysis, the benefit of dapagliflozin on the primary composite outcome was apparent across a range of HbA_{1c} levels (P for interaction = 0.62) (Fig. 1*B*).

We observed consistent effects for the secondary kidney-specific composite end point of a ≥50% eGFR decline, end-stage kidney disease, or death from kidney causes (P for interaction = 0.42) (Supplementary Fig. 2), and the prespecified exploratory outcome of maintenance dialysis, kidney transplantation, or death from kidney causes (P for interaction = 0.88 (Supplementary Fig. 2). For the composite outcome of heart failure hospitalization or cardiovascular death, the 29% (HR 0.71 [95% CI 0.55, 0.92]) relative risk reduction was consistent across glycemic subgroups (P for interaction = 0.43) (Supplementary Fig. 2). The 31% relative risk reduction for allcause mortality was also consistent (P for interaction = 0.25 (Supplementary Fig. 2). In continuous analysis, the benefit of dapagliflozin on the composite of heart failure hospitalization or cardiovascular death and on all-cause death was apparent across a range of HbA_{1c} levels (Supplementary Fig. 3).

The proportion of participants experiencing a serious adverse event was similar between dapagliflozin and placebo within each glycemic subgroup (P for interaction = 0.18) (Supplementary Table 2). No case of diabetic ketoacidosis occurred in the dapagliflozin group, whereas two cases occurred in the placebo group in participants with type 2 diabetes at baseline (Supplementary Table 2). No dapagliflozin-treated participants with normoglycemia or prediabetes at baseline experienced major hypoglycemia during the study. Notably, in dapagliflozin-treated participants with type 2 diabetes, there was a lower rate of major hypoglycemia compared with placebo (14 vs. 28 participants) (Supplementary Table 2). For other events of special interest (based on predefined lists of preferred terms), there were no between-treatment or glycemia subgroup differences in the number of fractures, amputations, or kidney-related events, and no interaction between glycemic subgroups regarding events of volume depletion.

CONCLUSIONS

In this prespecified analysis of the DAPA-CKD trial, we demonstrate that the effects of dapagliflozin on kidney failure, heart failure, and mortality outcomes were consistent regardless of the glycated hemoglobin subgroups. Major hypoglycemia or ketoacidosis events did not occur in participants with normoglycemia or prediabetes, providing reassurance that dapagliflozin can be safely used in these individuals.

Our findings from a dedicated kidney outcome trial substantiate the findings from the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) study (2), suggesting that the kidney benefits seen with SGLT2 inhibition appear to be independent of their glucose-lowering effects, and extend these results further to those with prediabetes and normoglycemia at baseline. The findings reflect those of the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trials, where dapagliflozin and empagliflozin, respectively, reduced the risk of worsening heart failure or cardiovascular death in participants with heart failure with reduced ejection fraction, irrespective of diabetes status (3,4).

Few studies have investigated SGLT2 inhibition in prediabetes. During a 13-week randomized comparison between dapagliflozin, metformin, exercise, or control intervention, Færch et al. (5) found that dapagliflozin treatment led to improved glycemic variability, with minor reductions in HbA_{1c} (0.1% or 1.3 mmol/mol) and fasting plasma glucose (0.1 mmol/L or 1.8 mg/dL).

In participants with normoglycemia or prediabetes, dapagliflozin reduced the risk of kidney outcomes without improving glycemic control. These data are in keeping with an analysis of the CANagliflozin cardioVascular Assessment Study (CANVAS) trial (6), where markers of glycemia did not explain the effect of canagliflozin on kidney outcomes. Instead, albuminuria, hemoglobin, and hematocrit were identified as important mediators, pointing to a potential reduction in fluid overload. The recognized effect of SGLT2 inhibitors on

hemoglobin and hematocrit may reflect improvement in renal hypoxia and restoration in the hypoxia-inducible factor $1\alpha/2\alpha$ balance, stimulating erythropoiesis and reducing inflammation (7). Glucose-independent effects may include osmotic diuretic and natriuretic effects as observed in individuals with type 2 diabetes and CKD (8).

Because the DAPA-CKD trial was stopped early, this may have limited the statistical power to examine other end points. Our findings may not be generalizable to lower levels of albuminuria or an eGFR <25 mL/min/1.73 m^2.

In conclusion, dapagliflozin prevented the progression of CKD in individuals with normoglycemia, prediabetes, and type 2 diabetes, with similar safety across these subgroups. These data support the favorable benefit-to-risk ratio of dapagliflozin in patients with CKD independent of glycemic status.

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