Efficacy and safety of dapagliflozin by baseline glycemic status: a pre-specified analysis from the DAPA-CKD trial

Frederik Persson MD[1], Peter Rossing MD[1,2], Priya Vart PhD[3], Glenn M. Chertow MD[4], Fan Fan Hou MD[5], Niels Jongs MSc[3], John J.V. McMurray MD[6], Ricardo Correa-Rotter MD[7], Harpreet S. Bajaj MD[8], Bergur V. Stefansson MD[9], Robert D. Toto MD[10], Anna Maria Langkilde MD[9], David C. Wheeler MD[11,12], Hiddo J.L. Heerspink PhD[3,12], for the DAPA-CKD Trial Committees and Investigators

Affiliations:

1. Steno Diabetes Center Copenhagen, Gentofte, Denmark
2. Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
3. Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
4. Departments of Medicine and Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA
5. Division of Nephrology, Nanfang Hospital, Southern Medical University, National Clinical Research Center for Kidney Disease, Guangzhou, China
6. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
7. National Medical Science and Nutrition Institute Salvador Zubirán, Mexico City, Mexico
8. LMC Diabetes and Endocrinology, Brampton, Ontario, Canada

9. Late-stage Development, Cardiovascular, Renal and Metabolism, Biopharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden
10. Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA
11. Department of Renal Medicine, University College London, London, UK
12. The George Institute for Global Health, Sydney, Australia

Corresponding author: Frederik Persson (frederik.persson@regionh.dk)

Steno Diabetes Center Copenhagen,

Gentofte,

Denmark

Phone: +45 27 51 26 22

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Objective

DAPA-CKD 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) 25-75ml/min/1.73m^2 and urinary albumin-to-creatinine ratio 200-5000mg/g. The primary composite endpoint was sustained eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death.

Results

Of 4304 participants, 738 had normoglycemia, 660 pre-diabetes, and 2906 type 2 diabetes. The effect of dapagliflozin on the primary outcome was consistent (p-interaction=0.19) in normoglycemia (HR 0.62; 0.39-1.01), pre-diabetes (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 pre-diabetes.

Conclusions

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

In the DAPA-CKD trial of participants with 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 pre-specified analysis, we report the efficacy and safety of dapagliflozin in participants with normal glucose status, pre-diabetes, and type 2 diabetes.

Research Design and Methods

DAPA-CKD was a multicenter, double-blind, placebo-controlled, randomized trial. Participants had CKD defined as eGFR of 25-75 mL/min/1.73m^2, and urinary albumin-to-creatinine ratio (UACR) of 200-5000 mg/g. We randomized participants in a 1:1 ratio to dapagliflozin 10 mg/day or placebo, and followed participants for a median 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} less than 5.7% (39 mmol/mol), pre-diabetes as HbA_{1c} of at least 5.7% (39 mmol/mol) and less than 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 endpoint was the composite of time to the first occurrence of a sustained decline in eGFR ≥50%, onset of end-stage kidney disease, or death from kidney or cardiovascular causes. Secondary endpoints were the time to: a kidney-specific composite outcome, which included the same components as the primary outcome except cardiovascular death; a composite cardiovascular endpoint

(hospitalization for heart failure or cardiovascular death); and death from any cause (all-cause mortality).

A Cox proportional hazards regression model, stratified by baseline glycemic status, with UACR as stratification factor and adjusted for baseline eGFR, was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) 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 4304 participants enrolled, 738 had normoglycemia, 660 had pre-diabetes, and 2906 had type 2 diabetes at baseline (**Supplemental 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 normoglycemic and pre-diabetes participants 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% (–0.2, 0.0; p=0.0378; –1.1 mmol/mol [95%CI –2.1, 0.0]).

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

We observed consistent effects for the secondary kidney-composite endpoint of ≥50% eGFR decline, end-stage kidney disease, or death from kidney causes (p-interaction 0.42; **Supplemental Figure 1**), and the pre-specified exploratory outcome of maintenance dialysis, kidney transplantation or death from kidney causes (p-interaction 0.88**; Supplemental Figure 1**).

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-interaction 0.43; **Supplemental Figure 1**). The 31% relative risk reduction for all-cause mortality was also consistent (p-interaction 0.25; **Supplemental Figure 1**).

The proportion of participants experiencing a serious adverse event was similar between dapagliflozin and placebo, within each glycemic subgroup (p-interaction 0.18; **Supplemental Table 2**). Regarding adverse events of special interest, there was no case of diabetic ketoacidosis in the dapagliflozin group, while two cases in the placebo group occurred in participants with type 2 diabetes at baseline (**Supplemental Table 2**). No dapagliflozin-treated participants with

normoglycemia or pre-diabetes 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 to placebo, 14 versus 28 cases (**Supplemental Table 2**). There were no between-treatment or glycemia subgroup differences in the number of fractures, amputations or kidney-related events, and no interaction in between glycemic subgroups regarding events of volume depletion.

Conclusions

In this pre-specified 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 pre-diabetes providing reassurance that dapagliflozin can be safely used in these individuals.

Our findings from a dedicated kidney outcome trial, substantiate the findings from CREDENCE (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 pre-diabetes and normoglycemia at baseline. The findings reflect those of the DAPA-HF and EMPEROR-Reduced trials, where dapagliflozin and empagliflozin reduced the risk of worsening heart failure or cardiovascular death in participants with heart failure with reduced ejection fraction (HFrEF) irrespective of diabetes status (3; 4).

Few studies have investigated SGLT2 inhibition in pre-diabetes. During a 13-week randomized comparison between dapagliflozin, metformin, exercise or controls, 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 pre-diabetes, dapagliflozin reduced the risk of kidney outcomes without improving glycemic control. These data are in keeping with an analysis of the CANVAS trial (6), where markers of glycemia did not explain 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 HIF1α/HIF2α 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 endpoints. Our findings may not be generalizable to lower levels of albuminuria or eGFR <25 mL/min/1.73m^2.

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

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Author contributions

FP, PR and HJLH researched the data and wrote the first draft manuscript. All authors provided input to a revised draft manuscript. All authors approved the final version of the submitted manuscript. HJLH acts as a guarantor for this manuscript and takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Previous Publication

An abstract of the data presented here has been submitted to the American Diabetes Association 81st Scientific Sessions, June 25th-29th 2021.

Conflict of interests

FP reports having received research grants from Astra Zeneca and lecture fees from AstraZeneca, MSD, Janssen, Eli Lilly, Boehringer Ingelheim, Novo Nordisk A/S, and Novartis, as well as being a consultant/advisory board member for AstraZeneca, Bayer, Amgen, and MSD.

PR has served as a consultant for AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Gilead, Merck, Mundipharma, Vifor, Sanofi, and Novo Nordisk A/S (all honoraria to his institution) and received research grants from AstraZeneca and Novo Nordisk A/S.

PV and NJ have no conflicts of interest to declare.

GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee, research grants from NIDDK, and Amgen; he is on the board of directors for Satellite Healthcare, has received fees for advisory boards for Ardelyx, Baxter, CloudCath, Cricket, DiaMedica, Durect, DxNow, Outset, and Reata; and holds stock options for Ardelyx, CloudCath, Durect, DxNow, and Outset; has received fees from Akebia, Gilead, Sanifit and Vertex for trial steering committees; and has received fees for DSMB service from Angion, Bayer and ReCor.

FFH has received honoraria AstraZeneca as a member of the executive member of the DAPA-CKD study; received honoraria from AbbVie for participation in a steering committee.

JJVM has received support to his institution, Glasgow University, for work on clinical trials, consulting and other activities: Abbvie, Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, Cyclerion, Cytokinetics, DalCor, GSK, Kidney Research UK, Merck, Novartis, Pfizer, Servier, Theracos. Vifor-Fresenius. He has received personal lecture fees: Abbott, Hickman, Sun Pharmaceuticals and Servier.

RC-R has received fees from AstraZeneca for the DAPA-CKD trial steering committee; speaker fees from Boehringer Ingelheim, Amgen, and Janssen; research support from GlaxoSmithKline and Novo Nordisk; honoraria for advisory boards from Boehringer Ingelheim, Novo Nordisk and Medtronic.

HSB has received speaking honoraria from Eli Lilly and Novo Nordisk, and research funding paid to LMC Healthcare from Amgen, AstraZeneca, Boehringer Ingelheim, Ceapro, Eli Lilly, Gilead, Janssen, Kowa Pharmaceuticals Co. Ltd, Madrigal Pharmaceuticals, Merck, Pfizer, Novo Nordisk, Sanofi, and Tricida.

BVS, and AML are employees and stockholders of AstraZeneca.

RDT has received support from AstraZeneca as a member of the executive committee for DAPA-CKD; is a consultant for Boehringer-Ingelheim; has participated on advisory boards for Bayer, and Relypsa; served on data monitoring committees for Akebia and Reata Pharmaceuticals; executive committee for Amgen; and as a faculty associate for Quest Diagnostics.

DCW provides ongoing consultancy services to AstraZeneca and has received honoraria and/or consultancy fees from Amgen, Astellas, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen, Napp, Mundipharma, Merck Sharp and Dohme, Reata, Tricida, and Vifor Fresenius.

HJLH has received support from AstraZeneca to his institution for the DAPA-CKD trial; fees to his institution for his participation in advisory boards for Merck, Mitsubishi Tanabe, Janssen, and Mundipharma; as a consultant for AbbVie, Retrophin, Boehringer Ingelheim, and Novo Nordisk; for participation in steering committees for Janssen, Gilead, Bayer, Chinook, and CSL Pharma; and research support from AbbVie, AstraZeneca, Boehringer Ingelheim and Janssen.

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Figure Legend

Figure 1. (A) Forest plot of the primary composite outcome of ≥50% eGFR decline, end-stage kidney disease, cardiovascular or kidney death with dapagliflozin compared to placebo by glycemic status at baseline. (B) The treatment effect of dapagliflozin compared to placebo as a function of baseline HbA1c (continuous) for the primary outcome. The solid black line represents the hazard ratio of the treatment effect. The grey shaded area represents the 95% confidence interval around the treatment effects. The dotted horizontal line represents a hazard ratio of 1 (i. e. no difference between randomized groups)