Effects of dapagliflozin in patients without diabetes and with microalbuminuria~~: an exploratory analysis from the DAPA-CKD trial~~

Authors: Hiddo JL Heerspink PhD[1,2], Glenn M Chertow MD[3], Niels Jongs PhD[1], Ricardo Correa-Rotter MD[4], Peter Rossing MD[5,6], C David Sjöström MD[7], Anna Maria Langkilde MD[7], David C Wheeler MD[8] – for the DAPA-CKD Trial Committee and Investigators

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands; [2]The George Institute for Global Health, Sydney, Australia; [3]Department of Medicine and Epidemiology and Population Health, Stanford University School of Medicine, Stanford, USA; [4]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [5]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [6]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [7]Late-Stage Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [8]Department of Renal Medicine, University College London, London, UK

Corresponding author:

Prof. H.J.L. Heerspink

Department of Clinical Pharmacy and Pharmacology

University Medical Center Groningen

Haneplein 1

Tel: 050-3614071

E-mail: h.j.lambers.heerspink@umcg.nl

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Sodium glucose co-transporter 2 (SGLT2) inhibitors slow progressive loss of kidney function in patients with type 2 diabetes across a wide range of estimated glomerular filtration rate (eGFR) and albuminuria. In the DApagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial, dapagliflozin reduced the risk of kidney failure by approximately 40% in participants with chronic kidney disease (CKD), with consistent effects in those with and without type 2 diabetes.[1] The majority of participants in the DAPA-CKD trial had severely increased (KDIGO stage A3) albuminuria at baseline, with a median of 949 mg/g. Whether the kidney protective benefits of dapagliflozin, as demonstrated in the DAPA-CKD trial, extend to participants without type 2 diabetes and with lower levels of albuminuria, is unknown.

The DAPA-CKD trial was a double-blind, randomized trial of dapagliflozin 10 mg versus placebo, and recruited 4304 adult participants with CKD. As previously reported, participants were eligible if they had an eGFR of 25 to 75 mL/min/1.73m^2 of body-surface area and urinary albumin:creatinine ratio (UACR) between 200 to 5000 mg/g at the screening visit.[2] In 1398 participants without type 2 diabetes, dapagliflozin reduced the risk of the composite kidney outcome (sustained ≥50% eGFR decline, ~~end-stage kidney disease [ESKD]~~kidney failure, kidney ~~or cardiovascular death~~) by 50%, attenuated eGFR decline during chronic treatment by 1.29 (95%CI 0.73, 1.85) mL/min/1.73m^2 per year, and reduced UACR by 14.8% (95%CI 5.9, 22.9) relative to placebo.[3, 4] In this post-hoc analysis, we assessed the annual rate of eGFR decline and UACR changes in participants without type 2 diabetes by baseline UACR, and report results without adjustment for multiplicity.

Of all participants without type 2 diabetes, at baseline 136 had KDIGO stage A2 albuminuria (microalbuminuria;UACR 30 - < 300 mg/g, of whom 24 had UACR 30 - <200 mg/g at baseline) and 1262 had KDIGO stage A3 albuminuria (macroalbuminuria; UACR ≥300 mg/g). Baseline characteristics of participants with stage A2 and A3 albuminuria showed a mean (SD) age of 61.0 (14.8) and 56.0 (14.5) years; 49/136 (36.0%) and 411/1262 (32.6%) participants were female; mean (SD) eGFR 42.0 (11.2) and 41.7 (11.8) mL/min/1.73 m^2 and median UACR

245 [25th–75th percentile 207–266] and 955 [25th–75th percentile 557–1639] mg/g, respectively (**Supplementary Table 1**).

Dapagliflozin compared to placebo changed eGFR from baseline to week 2 with similar effects in participants without diabetes with UACR <300 mg/g (-2.4 mL/min/1.73m^2 [95%CI -4.5, -0.4]) or ≥300 mg/g (-2.0 mL/min/1.73m^2 [95%CI -2.7, -1.3]; p for interaction 0.46). Thereafter, dapagliflozin compared to placebo led to a slower decline in the chronic eGFR slope in participants without diabetes with UACR <300 mg/g (between-group difference 1.8 mL/min/1.73m^2 per year [95%CI 0.4, 3.1]; **Figure 1A**) and in participants without diabetes with UACR ≥300 mg/g (between-group difference 1.2 mL/min/1.73m^2 per year [95%CI 0.6, 1.8]; **Figure 1B**; p for interaction 0.62). Corresponding percent reductions in UACR were 16.0% [95%CI -21.2, 41.8] and 14.6% [95%CI 5.3, 22.9]; **Figure 1C**; p for interaction 0.36). Across the two UACR subgroups there were no differences in the risk of adverse events leading to drug discontinuation (UACR <300 mg/g: dapagliflozin 2/72 and placebo 1/64; UACR ≥300 mg/g dapagliflozin 34/624 and placebo 28/635) or serious adverse events (UACR <300 mg/g: dapagliflozin 18/72 and placebo 14/64; UACR ≥300 mg/g dapagliflozin 132/624 and placebo 153/635). Incidence of the kidney composite end point among participants without type 2 diabetes and with UACR <300 mg/g, defined as sustained ≥50% eGFR decline, ~~end-stage kidney disease~~kidney failure, or death due to kidney failure, were infrequent during follow-up (one in the dapagliflozin group and three in the placebo group; **Supplementary table 2**). To assess the robustness of our findings we repeated the analysis and stratified the participants without type 2 diabetes by baseline UACR <500 mg/g or ≥500 mg/g. In th~~is~~e subgroup of …..participants with baseline UACR <500 mg/g dapagliflozin compared to placebo led to a slower decline in the chronic eGFR slope (between-group difference … mL/min/1.73m^2 per yea [95%CI …, ….] and in participants without diabetes with UACR ≥500 mg/g (between-group difference ….mL/min/1.73m^2 per year [95%CI …, ….]; p for interaction …..).

Dapagliflozin attenuated the decline in kidney function (week 2 to end of study) in participants without diabetes whether there was stage A2 or stage A3 albuminuria at baseline. These data suggest that the kidney protective effects of dapagliflozin may extend to patients with CKD without type 2 diabetes and lower levels of albuminuria, as has reported in patients with CKD with type 2 diabetes. Further data on the efficacy and safety of SGLT2 inhibition in patients without diabetes with stages A1 and A2 albuminuria will be provided by the EMPA-Kidney trial which finished in 2022, and has enrolled 3570 participants without diabetes, of whom 1604 had UACR <300 mg/g.[5]

While the number of patients without diabetes and with stage A2 albuminuria enrolled in DAPA-CKD was relatively small, these data suggest that benefits of dapagliflozin are extended to patients with CKD with and without diabetes and with lower levels of albuminuria. The safety and efficacy of dapagliflozin in patients with CKD due to conditions excluded from the DAPA-CKD trial (autosomal dominant polycystic kidney disease, type 1 diabetes, ANCA-associated vasculitis, and lupus nephritis) remain to be established.

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Disclosures

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study), Abbvie, Travere Pharmaceuticals, Janssen, Gilead, Bayer, Chinook, Merck, CSL Pharma, consulting fees from Boehringer Ingelheim and Novo Nordisk, honoraria for lectures from AstraZeneca and participated in advisory boards for Mitsubishi Tanabe and Mundipharma. GMC has received fees from AstraZeneca for service on the DAPA-CKD trial steering committee. He serves on the Board of Directors for Satellite Healthcare. He has served on other trial steering committees for Akebia, AstraZeneca, Gilead, Sanifit, and Vertex, and on data safety monitoring boards for Angion, Bayer, Mineralys, and ReCor. He has served as an advisor and received fees and/or stock options from Ardelyx, CloudCath, Cricket, DiaMedica, Durect, DxNow, Miromatrix, Outset, Physiowave, and Unicycive. He has received research grants from NIDDK, NHLBI, and NIAID.

NJ has nothing to disclose.

RC-R has received honoraria from AbbVie, AstraZeneca, GlaxoSmithKline, Medtronic, and Boehringer Ingelheim, and has lectured for Amgen, Janssen, Takeda, AstraZeneca, and Boehringer Ingelheim and has received research support from GlaxoSmithKline, Novo Nordisk and AstraZeneca.

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CDS and AML are employees and stockholders of AstraZeneca.

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Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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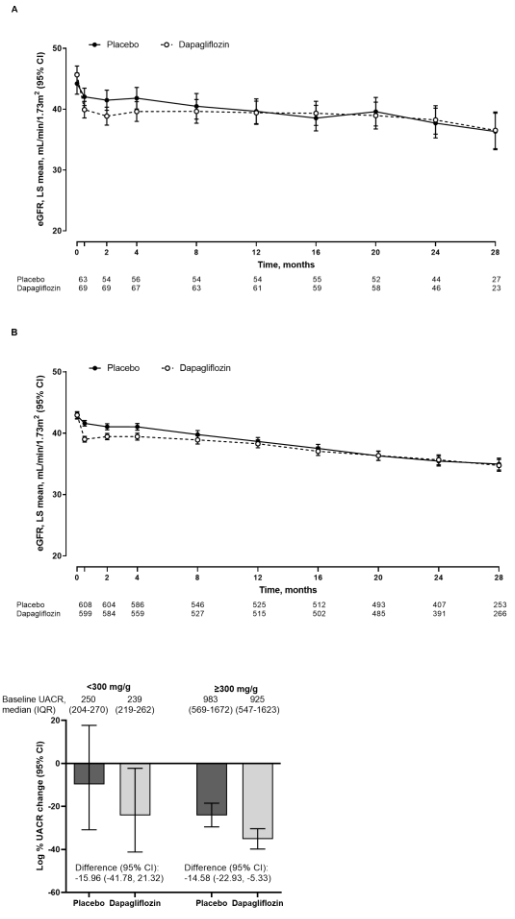
Figure 1: Effects of dapagliflozin compared to placebo on the rate of change in eGFR and albuminuria in patients without type 2 diabetes and with stage A2 albuminuria. Panel A shows the effects of dapagliflozin in reducing eGFR decline in patients without type 2 diabetes with stage A2 albuminuria. Panel B shows the effects of dapagliflozin in reducing eGFR decline in patients without type 2 diabetes with stage A3 albuminuria. Panel C shows the effects on albuminuria.



Supplement Table

Table 1: Baseline characteristics

	UACR <300 mg/g		UACR ≥300 mg/g	
Characteristic	Dapagliflozin (n=xxx)	Placebo (n=xxx)	Dapagliflozin (n=xxx)	Placebo
Age (years), mean (SD)				
Female sex, n (%)				
Race, n (%)				
Asian				
Black				
White				
Other				
CKD etiology, n (%)				
Diabetic Nephropathy				
Glomerulonephrites				
Ischemic or Hypertensive CKD				
Other/Unknown				
Weight (kg), mean (SD)				
Blood pressure (mmHg), mean (SD)				
Systolic				
Diastolic				
HbA1c (%), mean (SD)				
eGFR (mL/min/1.73m^2), mean (SD)				
Urinary albumin-to-creatinine ratio, median (Q1–Q3)				

History of heart failure, n (%)	
Baseline medication, n (%)	
ACE inhibitor	
ARB	
Diuretic	
Statin	

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate

Supplementary Table 2: Number of primary and secondary endpoints among participants without diabetes and with microalbuminuria

	Dapagliflozin	Placebo
Primary composite endpoint, n (%)		
Secondary endpoint, n (%)		
Composite kidney endpoint		
Composite cardiovascular endpoint		
All-cause mortality		

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