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Effect of once-weekly exenatide on estimated glomerular filtration rate slope depends on baseline renal risk

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BRIEF REPORT

Renal haemodynamic response to sodium-glucose cotransporter-2 inhibition does not depend on protein intake: An analysis of three randomized controlled trials

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Abstract

High protein intake may increase intraglomerular pressure through dilation of the afferent arteriole. Sodium-glucose cotransporter-2 (SGLT2) inhibitors may reduce intraglomerular pressure through activation of tubuloglomerular feedback. Given these opposing effects, we assessed whether the effect of dapagliflozin on glomerular filtration rate (GFR) and urinary albumin-to-creatinine ratio (UACR) was modified by estimated dietary protein intake using data from three separate randomized controlled trials (DELIGHT, IMPROVE and DIAMOND). The median protein intake was 58.4, 63.6 and 90.0 g/d, respectively. In the DELIGHT trial (n = 233), dapagliflozin compared to placebo caused an acute and reversible dip in GFR of 2.1 and 2.2 mL/min/1.73 m², and reduced UACR by 20.5% and 28.4% in participants with high and low protein intake, respectively. Similarly, in IMPROVE (n = 30) and DIAMOND (n = 53), the effect of dapagliflozin on GFR and UACR was comparable in participants with high and low protein intake (all P for interaction > 0.40). This post hoc, exploratory analysis of three clinical trials suggests that dietary protein intake does not modify the individual response of clinical kidney variables to dapagliflozin.

KEYWORDS

dapagliflozin, SGLT2 inhibitor, type 2 diabetes, diabetic nephropathy

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1 | INTRODUCTION

Sodium glucose cotransporter-2 (SGLT2) inhibitors delay progression of kidney function decline and reduce the risk of kidney failure.¹⁻³ These beneficial effects are attributed to decreased sodium resorption in the proximal tubule and normalization of tubuloglomerular feedback, resulting in reduced intraglomerular pressure. Clinically this is manifested by an acute reversible dip in glomerular filtration rate (GFR).^{4,5} However, although effective at a population level, the albuminuric response to SGLT2 inhibitors varies markedly between individual patients, leaving a proportion of patients at high risk of kidney and cardiovascular outcomes.⁶⁻⁹ As of yet, the cause of this variability in response is unclear.

High-protein diets are a popular strategy to achieve weight loss and glycaemic control in patients with type 2 diabetes. However, high protein intake has been associated with an increase in glomerular pressure and subsequently a higher risk of chronic kidney disease progression.¹⁰ How exactly protein intake influences renal haemodynamics is not fully understood, but inhibition of tubuloglomerular feedback and increased glucagon secretion resulting in kidney production of vasodilatory prostaglandins are thought to be contributing mechanisms via dilation of the afferent arteriole.¹¹

Given the opposite effects of protein load and SGLT2 inhibitors on renal haemodynamics, Mazzucato et al¹² recently hypothesized that high-protein diets may offset the beneficial kidney effects of SGLT2 inhibitors. We tested this hypothesis in three randomized controlled clinical trials comparing dapagliflozin with placebo in patients with chronic kidney disease, with and without type 2 diabetes.^{6,13,14}

2 | METHODS

2.1 | Study design and patient population

We used data from three randomized controlled clinical trials: DELIGHT (NCT02547935), IMPROVE (Netherlands Trial Register [NTR] 4439) and DIAMOND (NCT03190694). The study design, baseline characteristics and primary results of these trials have all been published previously.^{6,13,14} The three trials assessed the effects of the SGLT2 inhibitor dapagliflozin 10 mg/d on albuminuria in patients with chronic kidney disease with type 2 diabetes (DELIGHT and IMPROVE) and without diabetes (DIAMOND). In our analysis, we included all trial participants for whom a baseline 24-hour urinary urea measurement was available. DELIGHT participants assigned to the dapagliflozin plus saxagliptin group of the trial were excluded from the analysis.

2.2 | Measurements

In all trials, 24 urine samples were collected to assess 24-hour urinary urea, albumin and creatinine excretion. In addition, participants in the DELIGHT and IMPROVE trials also collected three consecutive first morning void urine samples at each study visit. Measured GFR (mGFR) was determined from plasma clearance of non-radioactive iohexol at the start and end of each treatment period in the DIAMOND trial. In the two other trials, GFR was estimated using serum creatinine concentration.

Protein intake was estimated at baseline from 24-hour urinary urea excretion using the Maroni formula¹⁵:

$$\text{protein intake (g/d)} = 6.25 * \\ [\text{urinary urea nitrogen (g/d)} + 0.031 * \text{body weight (kg)}],$$

where urinary urea nitrogen = 0.028 * 24-hour urea excretion (mmol/24 h).

2.3 | Endpoints

Study endpoints were change from baseline in estimated or iohexol-measured GFR and change from baseline in UACR at the last on-treatment study visit ($t = 24$ weeks in the DELIGHT study and $t = 6$ weeks in the IMPROVE and DIAMOND study). Since UACR may vary from visit to visit, and to increase statistical power, we assessed the change from baseline in UACR taking all follow-up measurements into account over 24 weeks in the DELIGHT study, as previously recommended.¹⁶ In the IMPROVE and DIAMOND study only one follow-up visit was available at week 6.

2.4 | Statistical analysis

Analyses included patients with non-missing baseline protein intake, and excluded variables which were assessed after permanent treatment discontinuation. For each trial, median protein intake was calculated and two subgroups were defined (high vs. low protein intake). To assess the effect of dapagliflozin compared to placebo on GFR and UACR, longitudinal repeated-measures models of change (UACR on log-scale) were used in the DELIGHT trial. An unstructured model was used for within-subject correlations. Treatment effects (Week 24 for estimated GFR [eGFR], and average over 24 weeks for UACR) were evaluated by Student *t*-tests of differences in least square, and inference was drawn from two-sided *P* values. A mixed linear regression model was also used in the IMPROVE and DIAMOND trial. The repeated-measures models included patients as a random effect and treatment and categorical time periods as fixed-effect covariates. An

TABLE 1 Baseline demographic, clinical and biochemical characteristics

	DELIGHT			IMPROVE			DIAMOND		
	Low protein intake, placebo (n = 56)	Low protein intake, dapagliflozin (n = 61)	High protein intake, placebo (n = 58)	High protein intake, dapagliflozin (n = 58)	Low protein intake (n = 14)	High protein intake (n = 15)	Low protein intake (n = 27)	High protein intake (n = 26)	
Estimated protein intake, g/d	40.6 (35–47)	43.0 (35–48)	76.4 (66–94)	78.0 (68–88)	63.4 (56.8–70.7)	89.5 (79.6–134.9)	60.6 (47.3–80.2)	104.2 (96.6–117.5)	
Age, years	65.0 (8.5)	65.0 (8.6)	64.7 (8.4)	64.2 (8.5)	62.1 (8.4)	62.3 (8.0)	52.4 (12.7)	50.2 (13.9)	
Gender, n (%)									
Male	38 (67.9)	39 (63.9)	45 (77.6)	44 (75.9)	8 (57.1)	14 (93.3)	13 (48.1)	23 (88.5)	
Female	18 (32.1)	22 (36.1)	13 (22.4)	14 (24.1)	6 (42.9)	1 (6.7)	14 (51.9)	3 (11.5)	
Bodyweight, kg	78.7 (17.2)	79.1 (20.5)	87.4 (19.2)	87.6 (17.1)	90.4 (18.5)	100.5 (23.0)	71.2 (14.9)	95.2 (18.0)	
BMI, kg/m ²	28.7 (5.3)	29.3 (5.6)	31.0 (5.5)	31.1 (4.9)	31.2 (6.3)	31.5 (4.6)	26.1 (4.6)	30.0 (4.8)	
Systolic BP, mmHg	137.5 (16.6)	139.0 (18.3)	142.3 (19.4)	138.9 (14.2)	141.8 (19.0)	143.6 (9.2)	126.8 (15.5)	125.2 (14.3)	
Diastolic BP, mmHg	74.1 (9.3)	77.3 (10.5)	77.2 (10.0)	77.5 (8.3)	76.9 (5.8)	77.0 (6.4)	76.0 (9.2)	76.5 (7.3)	
HbA1c, %	8.5 (1.2)	8.2 (1.1)	8.4 (1.2)	8.5 (1.0)	7.3	7.3	5.7 (0.4)	5.5 (0.4)	
Sodium, mmol/L	138.3 (2.2)	138.5 (2.6)	138.3 (3.2)	138.7 (2.7)	139.9 (2.5)	139.7 (3.8)	138.5 (2.8)	139.0 (2.1)	
Urea, mmol/L	8.8 (3.5)	8.1 (3.4)	9.8 (3.9)	9.7 (3.8)	6.5 (2.4)	7.3 (1.8)	9.0 (4.3)	10.2 (4.5)	
eGFR, mL/min/1.73 m ²	48.6 (13.2)	48.8 (13.6)	51.1 (14.7)	51.2 (13.5)	74.3 (22.2)	69.1 (22.2)	59.2 (31.9)	58.9 (22.9)	
mGFR, mL/min/1.73 m ²	-	-	-	-	-	-	56.9 (26.0)	59.8 (19.7)	
UAACr, mg/mmol	36.6 (10.7–114.2)	47.1 (9.0–100.0)	16.1 (6.8–91.0)	26.8 (7.8–77.6)	32.3 (12.9–78.3)	28.8 (15.8–45.8)	85.7 (56.4–121.7)	53.3 (38.9–79.4)	
Urinary sodium excretion, mmol/24 h	138.9 (77.2)	133.8 (58.1)	186.5 (89.7)	197.8 (101.3)	133.6 (38.9)	217.3 (69.3)	123.5 (34.9)	173.5 (54.0)	
Urinary potassium excretion, mmol/24 h	45.9 (23.3)	43.5 (20.3)	72.1 (38.7)	65.9 (30.0)	58.9 (20.9)	89.1 (19.5)	45.3 (25.8)	79.1 (25.5)	
Urinary urea excretion, mmol/24 h	144.6 (54.1)	152.6 (49.9)	389.5 (156.6)	377.0 (113.0)	260.6 (42.8)	488.0 (169.3)	284.2 (88.41)	523.1 (95.6)	
Osmolality, mOsm/kg	NA	NA	NA	NA	586.4 (163.8)	505.4 (142.0)	374.0 (126.1)	510.2 (154.9)	
Medications									
RAAS inhibitors, n (%)	56 (100)	60 (98)	57 (98)	57 (98)	14 (100)	14 (100)	27 (100)	26 (100)	
Diuretic use, n (%)	22 (39)	22 (36)	30 (52)	26 (45)	NA	NA	6 (22)	8 (31)	
Type 2 diabetes	56 (100)	61 (100)	58 (100)	58 (100)	14 (100)	15 (100)	0 (0)	0 (0)	

Abbreviations: BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; NA, not available; RAAS, renin-angiotensin-aldosterone system; UAACr, urine albumin-to-creatinine ratio.

Note: Data are mean (SD) or median [25th to 75th percentile], unless otherwise specified.

Estimated protein intake was calculated using the formula: Protein intake (g/d) = 6.25 * [urinary urea nitrogen (g/d) + 0.031 * body weight (kg)], where urinary urea nitrogen = 0.028 * 24-hour urea excretion (mmol/24 h).

interaction term between treatment and strata of protein intake was added to each model to assess whether the effects of dapagliflozin compared to placebo were modified by baseline protein intake. A *P* value <0.05 was taken to indicate statistical significance. Analyses were performed using SAS software version 9.4.

3 | RESULTS

Baseline characteristics of the participants are described in Table 1. Urea measurements were available for 236 participants (81%) in the DELIGHT trial, 30 participants (91%) in the IMPROVE trial, and 53 participants (100%) in the DIAMOND trial. The median protein intakes were 58.4, 63.6 and 90.0 g/d, respectively.

Participants with protein intake above the median were predominantly male and had, in general, a higher body weight than participants with low protein intake. The mean baseline eGFR/mGFR was comparable in participants with high and low protein intake in all three trials. Patients with high protein intake had higher urinary 24-hour sodium and potassium excretion, as well as higher 24-hour urinary volume.

The effects of dapagliflozin versus placebo over time on UACR in the DELIGHT trial are shown in Figure S1A. After 4 weeks, a reduction in albuminuria was seen in participants with low and high protein intake, with a change in UACR of -32.8% (95% confidence interval [CI] -45.1 to -17.7) and -19.6% (95% CI -34.5 to -1.4), respectively. This effect was maintained in both groups during follow-up. Over 24 weeks, participants assigned to dapagliflozin experienced an

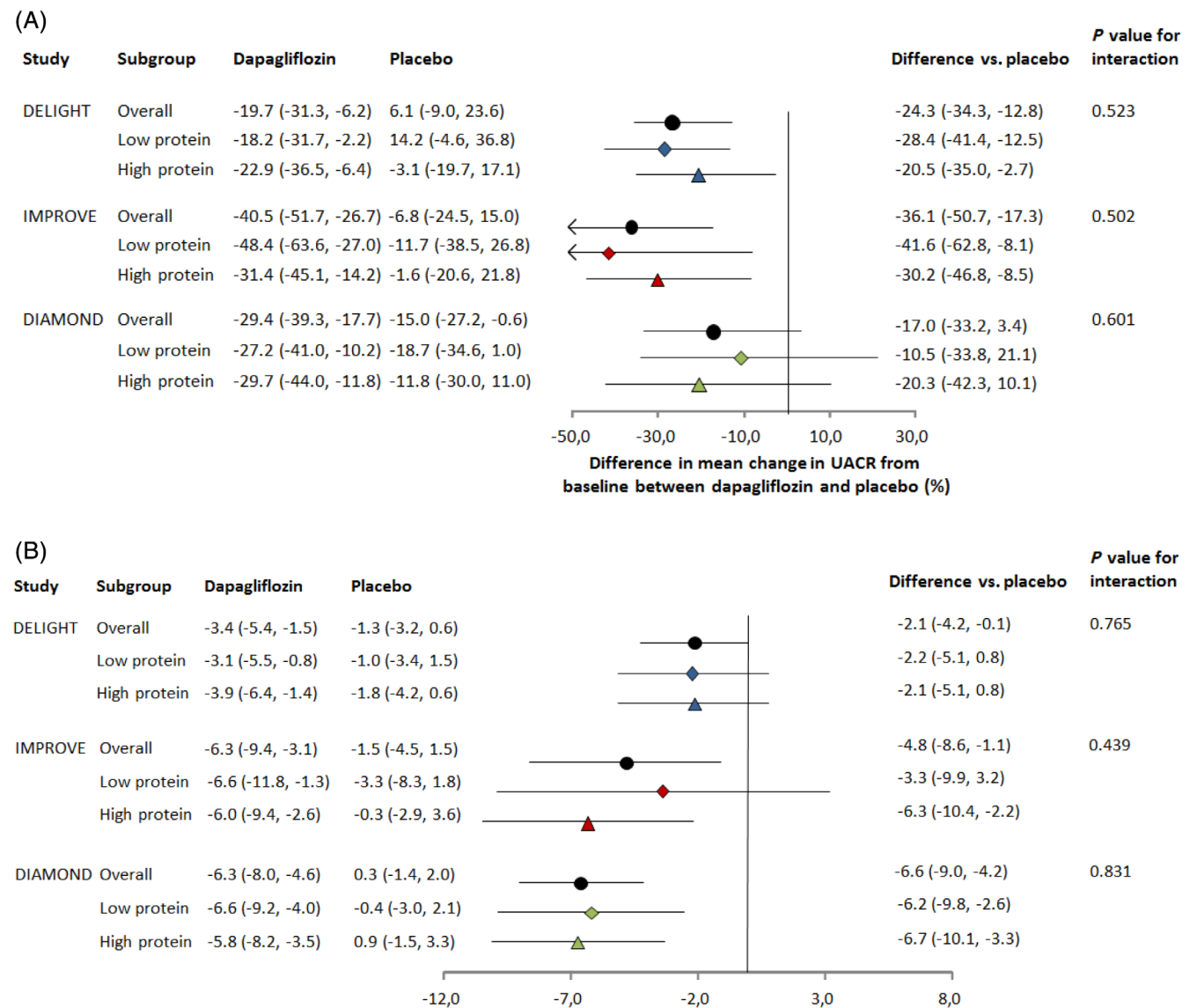


FIGURE 1 Effect of dapagliflozin on urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) according to baseline protein intake. **A**, Effect of dapagliflozin versus placebo on UACR from baseline to week 24 in the DELIGHT trial, and from baseline to week 6 (IMPROVE /DIAMOND). **B**, Effect of dapagliflozin versus placebo on eGFR at week 24 in the DELIGHT trial and at week 6 in the IMPROVE and DIAMOND trials

overall placebo-corrected adjusted mean percent change in UACR from baseline over 24 weeks of -24.3% (95% CI -34.3 to -12.8). This effect was consistent in participants with low protein intake (adjusted mean percent change in UACR from baseline over 24 weeks -28.4% [95% CI -41.4 to -12.5]) and high protein intake (adjusted mean percent change in UACR -20.5% [95% CI -35.0 to -2.7]; P value for interaction = 0.523 [Figure 1A]).

In the DELIGHT trial, an initial dip in eGFR occurred in the dapagliflozin group. At week 1, the difference in mean eGFR change from baseline versus placebo was -4.4 mL/min/1.73 m² (95% CI -6.2 to -2.7). This effect was sustained throughout follow-up, with a difference in mean eGFR change from baseline versus placebo at week 24 of -2.1 mL/min/1.73 m² (95% CI -4.2 to -0.1 ; Figure S1B). The effect of dapagliflozin on eGFR was consistent in participants with low and high protein intake, with corresponding differences in eGFR versus placebo at week 24 of -2.2 mL/min/1.73 m² (95% CI -5.1 to 0.8) and -2.1 mL/min/1.73 m² (95% CI -5.1 to 0.8), respectively (P value for interaction = 0.765; Figure 1B).

The effects of dapagliflozin compared to placebo on urinary albumin excretion in the IMPROVE and DIAMOND trials were consistent with the findings from the DELIGHT trial. Dapagliflozin reduced urinary albumin excretion in the IMPROVE and DIAMOND trials, irrespective of protein intake (P for interaction 0.502 and 0.601, respectively [Figure 1A]). In addition effects on eGFR and mGFR were also similar in participants with protein intake above or below the median (P for interaction 0.439 and 0.831, respectively, Figure 1B).

4 | DISCUSSION

This analysis of three randomized controlled clinical trials, using individual patient-level data from varying populations, evaluated the influence of dietary protein intake on the effects of dapagliflozin on GFR and UACR. In none of the trials were we able to demonstrate a significant difference in the effect of dapagliflozin on change in UACR or GFR between participants with high and low protein intake. These data thus indicate that protein intake does not modify the individual response of kidney variables to SGLT2 inhibitors.

Sodium-glucose cotransporter-2 inhibitors reduce sodium reabsorption in the proximal tubule, resulting in increased sodium delivery to the macula densa and restoration of tubuloglomerular feedback. This leads to a decrease in intraglomerular pressure and an acute reversible dip in eGFR which is associated with long-term preservation of kidney function in large outcome trials.^{2,5,17} Despite the kidney benefits of SGLT2 inhibitors on a population level, there is a large inter-individual variation in response. High dietary intake of protein, usually defined as protein consumption of more than 1.5 g/kg per day, is known to dilate glomerular afferent arterioles and increase intraglomerular pressure, causing glomerular hyperfiltration and albuminuria.¹¹ Although the underlying mechanism has not been fully elucidated, it is proposed that this

protein-induced hyperfiltration is mediated by tubuloglomerular feedback.¹¹ High protein intake increases the filtration of amino acids, which in turn increases amino acid reabsorption in the proximal tubule. Since the reabsorption of most amino acids is sodium-dependent, this is accompanied by an increased reabsorption of sodium.¹⁸ Consequently, the delivery of sodium chloride to the macula densa decreases, thereby reducing tubuloglomerular feedback and increasing glomerular filtration. Mazzucato et al¹² hypothesize that, as a result of the opposite effects of protein intake and SGLT2 inhibition on renal haemodynamics and sodium metabolism, high-protein diets may counteract the beneficial kidney effects of SGLT2 inhibitors. However, the results of the present *post hoc* analysis of the DELIGHT trial, the IMPROVE trial and the DIAMOND trial do not support this hypothesis.

In the present study protein intake was estimated from urine urea concentration. Urea is a waste product that is formed during protein metabolism in the liver. Urea is, in addition to sodium, an important osmolyte in controlling extracellular volume.¹⁹ During high salt intake, renal excretion of excess salt is accompanied by increased catabolic urea production in the liver and skeletal muscle, and increased urea recycling in the kidney. The resulting accumulation of urea in the medulla drives reabsorption of water from the tubule, thereby preserving body water balance. Thus estimated high protein intake from urea may reflect increased sodium intake. Indeed, in the present analysis, urinary sodium excretion at baseline was almost twice that in participants with high protein intake compared to participants with low protein intake. Further study using validated food questionnaires to accurately estimate protein intake are required to confirm or refute our findings.

The strength of the present analysis is that we were able to investigate the influence of protein intake on the renal effects of SGLT2 inhibitors in three trials, with a substantial number of participants, with and without type 2 diabetes. In the DIAMOND trials, we had access to mGFR, providing more accurate information on kidney function than eGFR. The absence of effect of protein intake on GFR and albuminuria in all three trials indicates that protein intake is unlikely to affect the performance of SGLT2 inhibitors. A limitation of the analysis is that it was a *post hoc* analysis in a subgroup of trial participants. Also, two of the three trials had a relatively short follow-up period of 6 weeks, and the effect of dapagliflozin on UACR was not statistically significant in the DIAMOND trial. However, the focus of our analysis was the difference in effect in the high- and low-protein-intake groups rather than the absolute effect of dapagliflozin versus placebo, and the analysis consistently indicates that protein intake does not modify the kidney effects of dapagliflozin.

In conclusion, in this *post hoc*, exploratory analysis of three dapagliflozin trials, we found no evidence that protein intake affects the beneficial kidney effects of SGLT2 inhibitors. Further research is needed to elucidate which factors do contribute to the variation in renal response to SGLT2 inhibitors, and which subgroups benefit the most from SGLT2 inhibitor therapy.

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CONFLICTS OF INTEREST

A.B.v.d.A.-v.d.B. declares no competing interests. D.Z.I.C. has received consulting fees or speaking honoraria or both from Janssen, Bayer, Boehringer Ingelheim-Eli Lilly, AstraZeneca, Merck & Co Inc, Prometic, Novo Nordisk and Sanofi, and has received operating funds from Janssen, Boehringer Ingelheim-Eli Lilly, Novo Nordisk, Sanofi, AstraZeneca and Merck & Co Inc. G.D.L. has received research grants and consulting fees from Sanofi and AstraZeneca, and research grants from Novo Nordisk. B.S., D.R. and P.J.G. are employees of AstraZeneca. D.H.v.R. has consulting relationships with Boehringer Ingelheim, Eli Lilly, Merck and Sanofi, and receives research operating funding from AstraZeneca, Boehringer Ingelheim-Eli Lilly Diabetes Alliance and MSD. K.H. has consulting relationships with Novo Nordisk and Sanofi, and receives research operating funding from Novo Nordisk. Q.L. reports employment with the George Institute for Global Health. G.L.D.T. served as methodological consultant for Amgen Inc. until December 2020. H.L.H. has served as a consultant for AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe, Novo Nordisk and Travere, and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim and Janssen.


PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. <https://doi.org/10.1056/NEJMoa1811744>.
- Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. <https://doi.org/10.1056/NEJMoa2024816>.
- Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol*. 2020;8(1):27-35. [https://doi.org/10.1016/S2213-8587\(19\)30384-5](https://doi.org/10.1016/S2213-8587(19)30384-5).
- Kraus BJ, Weir MR, Bakris GL, et al. Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose co-transporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney Int*. 2020;99:750-762. <https://doi.org/10.1016/j.kint.2020.10.031>.
- Oshima M, Jardine MJ, Agarwal R, et al. Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice. *Kidney Int*. 2020;99(4):999-1009. <https://doi.org/10.1016/j.kint.2020.10.042>.
- Petrykiv S, Laverman G, Zeeuw D, Heerspink H. The albuminuria lowering response to dapagliflozin is variable and reproducible between individual patients: albuminuria lowering effects of dapagliflozin. *Diabetes Obes Metab*. 2017;19:1363-1370. <https://doi.org/10.1111/dom.12936>.
- Heerspink HJL, Sjöström CD, Inzucchi SE, et al. Reduction in albuminuria with dapagliflozin cannot be predicted by baseline clinical characteristics or changes in most other risk markers. *Diabetes Obes Metab*. 2019;21(3):720-725. <https://doi.org/10.1111/dom.13579>.
- Oshima M, Neuen BL, Li J, et al. Early change in albuminuria with Canagliflozin predicts kidney and cardiovascular outcomes: a post hoc analysis from the CREDENCE trial. *J Am Soc Nephrol*. 2020;31(12):2925-2936. <https://doi.org/10.1681/ASN.2020050723>.
- Waijer SW, Di X, Inzucchi Silvio E, et al. Short-term changes in albuminuria and risk of cardiovascular and renal outcomes in type 2 diabetes mellitus: a post hoc analysis of the EMPA-REG OUTCOME trial. *J Am Heart Assoc*. 2020;9(18):e016976. <https://doi.org/10.1161/JAHA.120.016976>.
- Ko G-J, Rhee CM, Kalantar-Zadeh K, Joshi S. The effects of high-protein diets on kidney health and longevity. *J Am Soc Nephrol*. 2020;31(8):1667-1679. <https://doi.org/10.1681/ASN.2020010028>.
- Schwingshackl L, Hoffmann G. Comparison of high vs. normal/low protein diets on renal function in subjects without chronic kidney disease: a systematic review and meta-analysis. *PLoS One*. 2014;9(5):e97656. <https://doi.org/10.1371/journal.pone.0097656>.
- Mazzucato M, Fioretto P, Avogaro A. High-protein diet: a barrier to the nephroprotective effects of sodium-glucose co-transporter-2 inhibitors? *Diabetes Obes Metab*. 2020;22(9):1511-1515. <https://doi.org/10.1111/dom.14071>.
- Pollock C, Stefánsson B, Reyner D, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7(6):429-441. [https://doi.org/10.1016/S2213-8587\(19\)30086-5](https://doi.org/10.1016/S2213-8587(19)30086-5).
- Cherney DZI, Dekkers CCJ, Barbour SJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. *Lancet Diabetes Endocrinol*. 2020;8(7):582-593. [https://doi.org/10.1016/S2213-8587\(20\)30162-5](https://doi.org/10.1016/S2213-8587(20)30162-5).
- Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int*. 1985;27(1):58-65. <https://doi.org/10.1038/ki.1985.10>.
- Kröpelin TF, Zeeuw D, Andress DL, et al. Number and frequency of albuminuria measurements in clinical trials in diabetic nephropathy. *Clin J Am Soc Nephrol*. 2015;10(3):410-416. <https://doi.org/10.2215/CJN.07780814>.
- Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31-39. [https://doi.org/10.1016/S0140-6736\(18\)32590-X](https://doi.org/10.1016/S0140-6736(18)32590-X).
- Gonska T, Hirsch J, Schlatter E. Amino acid transport in the renal proximal tubule. *Amino Acids*. 2000;19:395-407. <https://doi.org/10.1007/s007260070019>.

19. Kitada K, Daub S, Zhang Y, et al. High salt intake reprioritizes osmolyte and energy metabolism for body fluid conservation. *J Clin Invest*. 2017;127(5):1944-1959. <https://doi.org/10.1172/JCI88532>.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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