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The effects of dapagliflozin on cardio-renal risk factors in patients with type 2 diabetes with or without renin-angiotensin system inhibitor treatment: a post hoc analysis

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Abstract

Aims: Renin-angiotensin system inhibitors (RASi) are the most effective treatments for diabetic kidney disease but significant residual renal risk remains, possibly because of other mechanisms of kidney disease progression unrelated to RAS that may be present. Sodium-glucose co-transporter-2 inhibitors reduce albuminuria and may complement RASi by offering additional renal protection. This post hoc analysis investigated the effects of dapagliflozin on cardio-renal risk factors in patients with type 2 diabetes (T2D) with increased albuminuria treated with or without RASi at baseline.

Materials and methods: We evaluated the effects of dapagliflozin 10 mg/day over 12–24 weeks across 13 placebo-controlled studies in patients with T2D with a urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g at baseline. Patients were divided into two subgroups based on treatment with or without RASi at baseline.

Results: Compared with patients with RASi at baseline (n = 957), patients without RASi (n = 302) were younger, had a shorter duration of diabetes (7 vs. 12 years), higher estimated glomerular filtration rate (eGFR) and lower UACR, serum uric acid (sUA), body weight and systolic blood pressure. Placebo-adjusted treatment effects of dapagliflozin on UACR, eGFR, glycated haemoglobin and haematocrit over 24 weeks were similar across groups. Mean reductions in body weight and sUA were more distinct in patients without RASi treatment at baseline.

Conclusions: Treatment with dapagliflozin over 24 weeks provides similar clinically relevant improvements in metabolic and haemodynamic parameters, and similar reductions in UACR, in patients with T2D with elevated albuminuria treated with or without RASi at baseline.

KEYWORDS
cardiac and renal risk factors, dapagliflozin, RASi, SGLT-2 inhibitors, type 2 diabetes

1 | INTRODUCTION

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, such as dapagliflozin, lower blood glucose levels by blocking glucose reuptake in the proximal tubule, resulting in urinary glucose excretion.[1] Beyond their glucose-lowering effect, evidence from recent cardiovascular (CV) outcomes trials (CVOTs)[2-4] indicates that whereas the effects of SGLT-2 inhibitors on major adverse CV events might be limited to patients with established CV disease, the beneficial effects on heart failure and renal function might be applicable to a broad population of patients with type 2 diabetes (T2D).[5-7] In particular, in these trials, SGLT-2 inhibitors delayed the progression of nephropathy.[2,3,8] Given the large burden of both CV disease and diabetic kidney disease in patients with T2D—despite optimal treatment of CV and renal risk factors using a multifactorial intervention[9]—these SGLT-2 inhibitor-induced cardiac and renal effects are highly salutary.

However, currently, it is unclear how the use of background medication may potentially alter the effects of SGLT-2 inhibition on cardiac and renal risk factors, such as urinary albumin-to-creatinine ratio (UACR), blood pressure (BP) or serum uric acid (sUA), as they have only reported the effect of background medication on outcomes. Most important in this regard are the renin-angiotensin system inhibitors (RASi): angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers. These drugs are known to affect systemic haemodynamics, reverse cardiac remodelling after injury and modulate renal haemodynamics by dilating the renal efferent arteriole. It is important to ascertain whether the beneficial effects of dapagliflozin on cardiac and renal risk factors are modified by concomitant RAS inhibition and, equally important, whether RAS inhibition could alter the safety and tolerability of SGLT-2 inhibitors.

Therefore, in the current post hoc analysis of previously reported dapagliflozin studies, we investigated the effect of dapagliflozin on multiple important markers of cardiac and kidney function as well as on safety aspects in patients with T2D treated with or without RASi.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a post hoc analysis of data pooled from 13 previously reported phase II and III, randomized, placebo- or active-controlled, 12- or 24-week studies conducted during 2005–2012 (Table S1; see Supporting Information).[10-22] The studies included patients with T2D aged ≥18 years, with body mass index ≤40–45 kg/m^2 and glycated haemoglobin (HbA1c) ≥6.5%–12% (47.5–107.7 mmol/mol). The protocols of the original studies used for this post hoc analysis did not require RASi use as an entry criterion. In this analysis, patients with T2D with a UACR ≥30 mg/g at baseline were divided into two groups: patients who received RASi at baseline (with RASi treatment) and patients who did not receive RASi at baseline (without RASi treatment). Single spot urine samples were collected at each study visit.

The pooled patient population was randomized to receive dapagliflozin 10 mg/day or placebo for up to 24 weeks.

2.2 | Outcome measures

Baseline demographics and disease characteristics were assessed. Changes in the following parameters were assessed from baseline over the 24-week treatment period with dapagliflozin versus placebo: UACR, estimated glomerular filtration rate (eGFR), HbA1c, haematocrit, body weight, sUA, systolic BP (SBP) and diastolic BP (DBP). We analysed the impact of change in UACR on the overall population adjusting for UACR, age, sex, race, body weight, SBP, eGFR and RASi treatment at baseline. The overall safety profile, including adverse events (AEs) and serious AEs (SAEs), was also assessed.

2.3 | Statistical analyses

Descriptive statistics were used for presenting baseline characteristics and safety data. For efficacy parameters, the mean change from baseline values and 95% confidence intervals (CIs) were derived using a longitudinal repeated-measures mixed model with fixed terms for study, treatment, week, subgroup, week-by-treatment interaction, treatment-by-subgroup interaction and treatment-by-week-by-subgroup interaction, as well as the fixed covariates of baseline, baseline-by-study and baseline-by-week interactions. In addition, for the percentage change in UACR, a longitudinal repeated-measures mixed model pooling subgroups was performed, with fixed terms for study, treatment, week and week-by-treatment interaction, as well as the fixed covariates of baseline, baseline-by-study, baseline-by-week interactions and baseline age, sex, race, weight, SBP, eGFR and treatment with RASi at baseline. UACR values were log transformed (using the natural logarithm) and then exponentiated back to the original scale. Group differences comparing the renin-angiotensin system inhibitors (RASi) blockade groups for continuous data were tested using ANOVA with group and study in the model. All statistical analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Disposition and baseline characteristics

Demographic and baseline characteristics are shown in Table 1. Of the 1259 patients analysed, at baseline most (n = 957) participants among these studies were prescribed RASi treatment as compared with the group without RASi treatment (n = 302). Patients without RASi treatment compared with those with RASi treatment at baseline were younger (by approximately 5 years), had a shorter duration of diabetes (approximately 7 vs. 12 years), had higher eGFR and had lower UACR, sUA, body weight and SBP at baseline (Table 1). In both

TABLE 1 Baseline characteristics

Characteristic	With RASi (N = 957)			Without RASi (N = 302)			P-value[a]
	PBO n = 481	DAPA 10 mg n = 476	Total N = 957	PBO n = 146	DAPA 10 mg n = 156	Total N = 302	
Age, years, mean (SD)	61.6 (8.4)	61.1 (9.2)	61.4 (8.8)	56.8 (11.2)	55.4 (10.8)	56.1 (11.0)	0.0095
Women, n (%)	170 (35.3)	168 (35.3)	338 (35.3)	58 (39.7)	64 (41.0)	122 (40.4)	0.0554
Race, n (%)							
White	414 (86.1)	406 (85.3)	820 (85.7)	104 (71.2)	110 (70.5)	214 (70.9)	
Black or African American	11 (2.3)	24 (5.0)	35 (3.7)	3 (2.1)	6 (3.8)	9 (3.0)	<0.0001
Asian	34 (7.1)	37 (7.8)	71 (7.4)	31 (21.2)	32 (20.5)	63 (20.9)	
Other[a]	22 (4.6)	9 (1.9)	31 (3.2)	8 (5.5)	8 (5.1)	16 (5.3)	
Duration of T2D, years, mean (SD)	11.6 (8.8)	11.6 (8.4)	11.6 (8.6)	6.9 (7.7)	7.6 (9.3)	7.2 (8.6)	0.9592
UACR, mg/g, median (Q1, Q3)	80.0 (45.0, 195.0)	81.5 (47.0, 192.5)	81.0 (46.0, 193.0)	60.0 (41.0, 150.0)	64.1 (40.0, 132.0)	61.5 (41.0, 138.0)	0.3279
(min, max)	(30.0, 2584.0)	30.0, 3544.0	(30.0, 3544.0)	30.0, 2089.0	30.0, 1888.0	(30.0, 2089.0)	
Body weight, kg, mean (SD)	92.4 (19.0)	94.0 (20.9)	93.2 (20.0)	85.9 (22.2)	86.2 (20.8)	86.1 (21.4)	0.1000
HbA1c, %, mean (SD)	8.3 (0.9)	8.3 (0.9)	8.3 (0.9)	8.5 (1.1)	8.4 (0.9)	8.4 (1.0)	0.8603
sUA, mg/dL, mean (SD)	5.9 1.7	5.9 1.6	5.9 1.6	5.3 1.6	5.3 1.6	5.3 1.6	0.0612
UGCR, g/g, mean (SD)	3.1 (14.4[b])	3.0 (9.8[c])	3.0 (12.3)	9.1 (18.8[d])	7.5 (18.7[e])	8.3 (18.7)	0.0501
SBP, mmHg, mean (SD)	137.0 (14.6[f])	139.3 (14.5[g])	138.2 (14.6)	130.8 (14.3[h])	129.1 (14.0[i])	129.9 (14.1)	<0.0001
DBP, mmHg, mean (SD)	79.3 (9.4[f])	79.3 (9.6[g])	79.3 (9.5)	78.7 (8.2[h])	78.2 (9.5[i])	78.4 (8.9)	0.0006
eGFR, mL/min/1.73 m^2, mean (SD)	78.8 (21.9)	78.3 (21.0)	78.5 (21.5)	89.7 (24.0)	89.4 (24.4)	89.6 (24.2)	0.0379
<30, n (%)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
≥30 to <45, n (%)	15 (3.1)	22 (4.6)	37 (3.9)	2 (1.4)	1 (0.6)	3 (1.0)	
≥45 to <60, n (%)	70 (14.6)	66 (13.9)	136 (14.2)	12 (8.2)	14 (9.0)	26 (8.6)	<0.0001
≥60 to <90, n (%)	258 (53.6)	258 (54.2)	516 (53.9)	66 (45.2)	69 (44.2)	135 (44.7)	
≥90, n (%)	137 (28.5)	130 (27.3)	267 (27.9)	66 (45.2)	72 (46.2)	138 (45.7)	
Diuretic use, n (%)	217 (45.1)	211 (44.3)	428 (44.7)	16 (11.0)	11 (7.1)	27 (8.9)	<0.0001
Loop diuretic, n (%)	95 (19.8)	84 (17.6)	179 (18.7)	10 (6.8)	6 (3.8)	16 (5.3)	<0.0001
Thiazide diuretic, n (%)	147 (30.6)	140 (29.4)	287 (30.0)	6 (4.1)	6 (3.8)	12 (4.0)	<0.0001

Abbreviations: DAPA, dapagliflozin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; PBO, placebo; RASi, renin-angiotensin system inhibitors, SBP, systolic blood pressure; SD, standard deviation; sUA, serum uric acid; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio; UGCR, urinary glucose-to-creatinine ratio.

[a]RASi versus without RASi groups; [a]includes patients with a reported race of American Indian/Alaska Native, Native Hawaiian/other Pacific Islander or other; [b]n = 462; [c]n = 455; [d]n = 143; [e]n = 151; [f]n = 473; [g]n = 471; [h]n = 139; [i]n = 151.

groups, most patients were white and there were more men than women.

3.2 | Effect of dapagliflozin on urinary albumin-to-creatinine ratio, estimated glomerular filtration rate, glycated haemoglobin and haematocrit

The observed changes in the placebo-adjusted treatment effects of dapagliflozin at week 24 in UACR (Figure 1A), eGFR (Figure 1B) and HbA1c (Figure 1C) were of similar magnitudes in patients without RASi treatment compared with those with RASi treatment at baseline.

The effect of dapagliflozin on haematocrit was similar in patients without RASi treatment compared with those with RASi treatment at baseline (Figure 1D). Table S2 (see Supporting Information) shows more detailed data for these parameters.

3.3 | Effect of dapagliflozin on body weight, serum uric acid, and systolic and diastolic blood pressure

The placebo-adjusted mean reductions (95% CI at week 24) in body weight and sUA were more pronounced in patients without RASi treatment compared with those treated with RASi at baseline at week
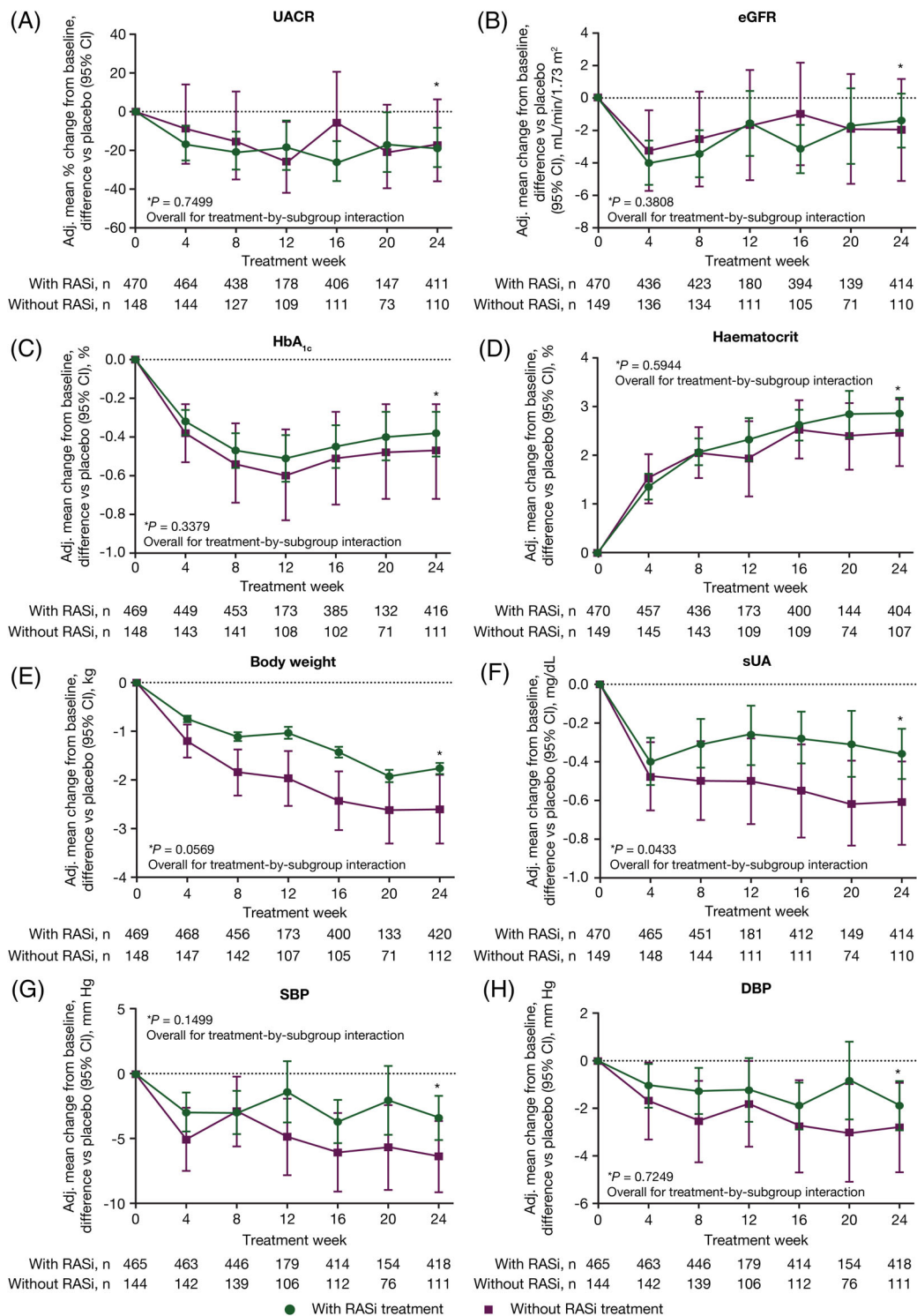
FIGURE 1 A, UACR. B, eGFR. C, HbA1c. D, Haematocrit. E, Body weight. F, sUA. G, SBP. H, DBP. Placebo-adjusted changes in CV and renal risk factors in patients receiving dapagliflozin 10 mg/day with or without RASi treatment at baseline. Abbreviations: Adj., adjusted; CI, confidence interval; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; RASi, renin-angiotensin system inhibitors; SBP, systolic blood pressure; sUA, serum uric acid; UACR, urinary albumin-to-creatinine ratio

24; that is, −2.60 kg (−3.31, −1.90) versus −1.76 kg (−2.19, −1.34) (P = 0.0569 treatment by RASi subgroup interaction; Figure 1E) and −0.61 (−0.83, −0.40) mg/dL versus −0.36 (−0.49, −0.23) mg/dL (P = 0.0433 treatment by RASi subgroup interaction; Figure 1F), respectively. Although a decrease was observed in both groups, the

placebo-adjusted mean reductions in SBP and DBP at week 24 were numerically greater in patients without RASi treatment compared with those with RASi treatment at baseline (Figure 1G and 1H). Similarly, placebo-adjusted mean reduction in SBP and DBP at week 24 was numerically greater in patients who were not on diuretics than in those

on diuretics [−4.40 (−6.03, −2.77) vs. −3.17 (−5.91, −0.43); −2.05 (−3.12, −0.98) vs. −2.01 (−3.60, −0.42)].

3.4 | Effect of covariates on placebo-adjusted change in urinary albumin-to-creatinine ratio in all patients receiving dapagliflozin

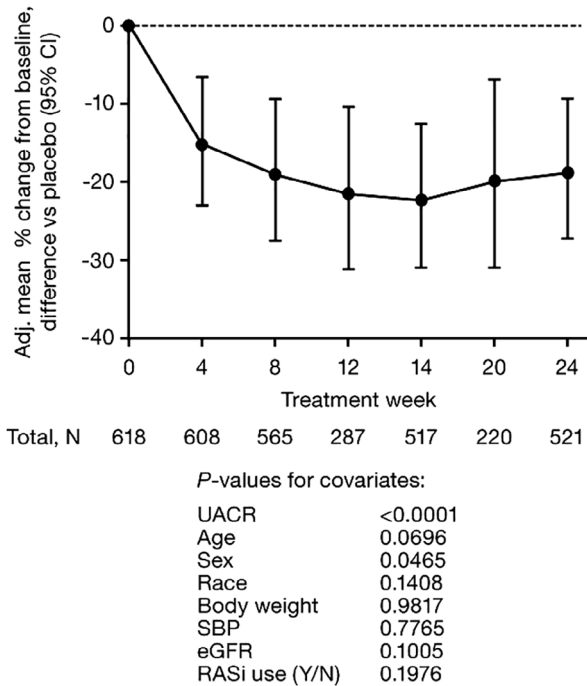The placebo-adjusted effect of dapagliflozin treatment on UACR was not affected by treatment with RASi at baseline and was largely independent of other covariates such as age, race, body weight, SBP and eGFR (Figure 2).

3.5 | Safety

Overall, AEs were more common in patients treated with RASi (who were also older and had a longer duration of T2D) compared with patients without RASi treatment. However, among patients with RASi treatment, the AE profile was similar in the placebo and dapagliflozin treatment groups (Table 2). Among the group without RASi treatment, the proportion of patients with at least one AE was greater in the dapagliflozin-treated patients than in the placebo-treated patients (Table 2).

4 | DISCUSSION

We show here, using a pooled analysis of 13 phase II and III studies in patients with T2D and increased albuminuria, that treatment with the SGLT-2 inhibitor dapagliflozin over 24 weeks provides similar clinically relevant improvements in CV and renal risk parameters, irrespective of treatment with RASi at baseline.

The cardio-renal protective effects of SGLT-2 inhibitors have been recently established by three large CVOTs.[2-4] However, it is unclear whether the use of co-medication, specifically RASi, could modulate the beneficial effects on cardiac and renal outcomes and the safety profiles of SGLT-2 inhibitors. Thus, in this post hoc analysis we investigated the effect of dapagliflozin on multiple markers of cardio-renal function, as well as on safety aspects in patients with T2D treated with or without RASi before dapagliflozin initiation.

Regarding CV disease markers, an important observation was that regardless of RAS inhibition at baseline, haematocrit levels were increased, which could indicate either volume contraction[23,24] or increase in erythropoiesis.[25] Volume contraction corresponds to one of the main hypotheses for the CV benefits observed in the SGLT-2 inhibitor CVOTs: an increase in haematocrit, resulting in beneficial

| Total, N | 618 | 608 | 565 | 287 | 517 | 220 | 521 |

P-values for covariates:

UACR	<0.0001
Age	0.0696
Sex	0.0465
Race	0.1408
Body weight	0.9817
SBP	0.7765
eGFR	0.1005
RASi use (Y/N)	0.1976

FIGURE 2 Placebo-adjusted percentage change in UACR for all patients receiving dapagliflozin 10 mg/day. Abbreviations: Adj., adjusted; CI, confidence interval; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitors; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio

TABLE 2 Summary of adverse events

| Description | With RASi (N = 957) | | Without RASi (N = 302) | |
	PBO n = 481	DAPA 10 mg n = 476	PBO n = 146	DAPA 10 mg n = 156
At least one AE	294 (61.1)	313 (65.8)	75 (51.4)	100 (64.1)
AEs leading to study drug discontinuation	29 (6.0)	24 (5.0)	4 (2.7)	5 (3.2)
At least one hypoglycaemic event	85 (17.7)	90 (18.9)	11 (7.5)	13 (8.3)
At least one SAE	51 (10.6)	41 (8.6)	2 (1.4)	6 (3.8)
SAEs leading to study drug discontinuation	10 (2.1)	0 (0.0)	1 (0.7)	1 (0.6)
Deaths	4 (0.8)	3 (0.6)	0 (0.0)	1 (0.6)

Abbreviations: AE, adverse event; DAPA, dapagliflozin; PBO, placebo; RASi, renin-angiotensin system inhibitors; SAE, serious adverse event. Data are represented as n (%). Data shown include non-serious/serious AEs with onset on or after the first date of treatment and on or before the last day of treatment plus 4 days/30 days or up to and including the start date of the long-term period or up to the follow-up visit if earlier. Only hypoglycaemia reported as an SAE is included in the AE, related AE, SAE, related SAE and AE leading to discontinuation summaries.

cardiac haemodynamics.[23] For example, Inzucchi et al showed in a mediation analysis of the EMPA-REG OUTCOME trial that the change in haematocrit from baseline mediated 51.8% of the effect of empagliflozin versus placebo in the reduction of the risk of CV death.[23] Conversely, although an increase in erythropoiesis could be a complementary mechanism for the increased levels of haematocrit, the extent to which this mechanism contributes to the CV benefits observed with empagliflozin is not clear.[25]

As expected,[3] a decrease in body weight was observed in patients treated with dapagliflozin. However, in combination with RASi the reduction in body weight was not as pronounced as without RASi. Previous studies have shown that the glucose-lowering efficacy of SGLT-2 inhibitors depends on renal function.[26] In parallel, attenuation of weight loss would be expected with declining renal function. However, surprisingly, the reduction in body weight is found to be independent of eGFR[27] and the underlying mechanism is still not understood. Given the post hoc nature of the analysis, any proffered mechanism for this weight loss pattern would probably be speculative.

In the present analysis, a decrease in sUA levels was observed in patients treated with or without RASi. To the extent that this may have CV benefit this is a salutary effect. Fractional excretion of UA has been shown to be related to urinary glucose excretion.[28] Keeping in mind that in the present analysis the majority of the patients without RASi had normal kidney function, the glucose-mediated excretion of UA could possibly be larger compared with that in patients with RAS inhibition.

The most cited explanation for the renoprotective properties of SGLT-2 inhibitors is their ability to activate tubuloglomerular feedback,[29-32] thereby reducing intraglomerular pressure.[33] Clinically, this is reflected in a decline in eGFR upon initiation of SGLT-2 inhibition and a rapid and sustained reduction in albuminuria,[34] followed by stabilization and preservation of kidney function. The same was observed in the current analysis and has been demonstrated in other studies of other SGLT-2 inhibitors.[2,4] The beneficial effects of SGLT-2 inhibition on renal outcomes, such as eGFR, have been shown in the EMPA-REG OUTCOME trial, CREDENCE, CANVAS Program and DECLARE-TIMI 58 trial.[2,4,7,36] However, none of these studies reported whether SGLT-2 inhibitors according to baseline RASi use modulated the effect on UACR.

Our analysis also showed that the magnitude of UACR reduction was similar in patients treated with and without RASi at baseline. This is in contrast to previous literature in which it has been proposed that SGLT-2 inhibition with concomitant RASi may synergistically boost the alternative RAS axis, leading to upregulation of angiotensin (1–7).[37] In our analysis, we did not find modulation by RASi or any indication of a possible synergistic effect, thus the effect of RASi is probably smaller. This would also explain why the magnitude of UACR reduction in our analysis was comparable in patients with and without RASi at baseline.

Interestingly, the placebo-adjusted treatment effect of dapagliflozin-induced UACR reduction was mostly independent of haemodynamic, metabolic, biochemical or physical factors. Nevertheless, these data suggest possible differences between sexes.[38,39]

This largely independent UACR reduction is in line with previous findings with dapagliflozin, empagliflozin and canagliflozin.[34,40,41] The albuminuria- and UACR-lowering effect of dapagliflozin is known to show large interindividual variations, and may only be partly explained by haemodynamic factors such as eGFR and SBP.[40,42] Apparently, other effects of dapagliflozin, such as reduction in intraglomerular hypertension, account for the albuminuria-lowering properties, although we cannot eliminate confounding caused by measurement variability.

With respect to safety, concomitant use of RASi and dapagliflozin appears to show a safety profile similar to the known profile of dapagliflozin (i.e. no increase in drug discontinuation because of AEs or SAEs).

The present analysis has some limitations. First, patients with RASi had a longer duration of T2D and higher UACR and SBP, as well as lower eGFR, compared with those without RASi use at baseline. Thus, in general, patients with RASi had more severe chronic kidney disease and had more comorbid conditions at baseline. Further, this was a post hoc analysis of 13 randomized controlled studies, and the original studies were not designed to assess the interaction of dapagliflozin with concurrent RASi use. Hence, patients were not randomized according to treatment with or without RAS inhibition. Consequently, baseline characteristics differed between the dapagliflozin and placebo groups and this limited the analysis. Therefore, this analysis can only be interpreted as hypothesis generating. Another limitation was the heterogeneity across the pooled clinical studies, possibly caused by differences in study design, duration and baseline characteristics, which may cause variability in the treatment effects estimated across studies.

5 | CONCLUSIONS

In this post hoc analysis, the placebo-adjusted treatment effects of dapagliflozin on UACR, eGFR, HbA1c and haematocrit over 24 weeks were similar between patients with and without RAS inhibition at baseline. There were no additional safety findings for the dapagliflozin/RASi combination compared with RAS inhibition alone. Therefore, our data suggest that the use of RASi in combination with SGLT-2 inhibitors does not impact the biomarkers associated with CV and kidney function.

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SUPPORTING INFORMATION

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