48. Philipponnet C, Guérin C, Canet E et al. Kidney biopsy in the critically ill patient, results of a multicentre retrospective case series. *Minerva Anestesiol* 2013; 79: 53–61

49. Augusto J-F, Lassalle V, Fillatre P et al. Safety and diagnostic yield of renal biopsy in the intensive care unit. *Intensive Care Med* 2012; 38: 1826–1833

50. Azoulay E, Mokart D, Pène F et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium–a groupe de recherche respiratoire en réanimation onco-hématologique study. *J Clin Oncol* 2013; 31: 2810–2818

Effects of the sodium–glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b–4 chronic kidney disease

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ABSTRACT

Background. The sodium–glucose co-transporter 2 inhibitor dapagliflozin decreases haemoglobin A1c (HbA1c), body weight, blood pressure (BP) and urinary albumin:creatinine ratio (UACR) in patients with type 2 diabetes. The efficacy and safety of this drug have not been properly defined in patients with type 2 diabetes and Stages 3b–4 chronic kidney disease (CKD).

Methods. In a pooled analysis of 11 phase 3 randomized controlled clinical trials, we determined least square mean changes in HbA1c, body weight, BP, estimated glomerular filtration rate (eGFR) and UACR over 102 weeks in patients with type 2 diabetes and an eGFR between 12 to less than 45 mL/min/1.73 m^2 receiving placebo ($n = 69$) or dapagliflozin 5 or 10 mg ($n = 151$). Effects on UACR were determined in a subgroup of patients with baseline UACR $\geq$30 mg/g ($n = 136$).

Results. Placebo-corrected changes in HbA1c with dapagliflozin 5 and 10 mg were 0.03% [95% confidence interval (CI) −0.3–0.3] and 0.03% (95% CI −0.2–0.3) during the overall 102-week period. Dapagliflozin 5 and 10 mg compared with placebo reduced UACR by − 47.1% (95% CI −64.8 to − 20.6) and −38.4% (95% CI −57.6 to − 10.3), respectively. Additionally, dapagliflozin 5 and 10 mg compared with placebo reduced BP and body weight. eGFR increased with placebo during the first 4 weeks but did not change with dapagliflozin. There were no between-group differences in eGFR at the end of follow-up. Adverse events associated with renal function occurred more frequently in the dapagliflozin 10-mg group. These events were mainly asymptomatic increases in serum creatinine.

Conclusions. Dapagliflozin did not decrease HbA1c in patients with type 2 diabetes and Stages 3b–4 CKD, but decreased UACR, BP and body weight to a clinically meaningful extent. These results support a large outcome trial in this population to confirm long-term safety and efficacy in reducing adverse clinical endpoints.

Keywords: dapagliflozin, diabetic nephropathy, kidney, SGLT2 inhibitor, type 2 diabetes

INTRODUCTION

Approximately 30–40% of all patients with diabetes also have chronic kidney disease (CKD) [1]. Both diabetes and CKD account for an increased risk of premature mortality, cardiovascular morbidity and end-stage kidney failure [2]. Few effective therapies are available for such patients and novel therapeutic options aimed at improving clinical outcomes in this high-risk population are therefore highly desirable.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors are anti-diabetes drugs that block the reabsorption of glucose and sodium

in the S1 segment of the proximal tubule, thereby augmenting urinary glucose and sodium excretion [3]. Inhibition of urinary glucose reabsorption results in a reduction in plasma glucose and haemoglobin A1c (HbA1c). Inhibition of sodium reabsorption, on the other hand, leads to increased delivery of sodium to the macula densa, which stimulates tubuloglomerular feedback and afferent arterial vasoconstriction and reduces glomerular hyper-filtration. This is clinically manifested as an acute reduction in glomerular filtration rate (GFR) and albuminuria. The GFR de-cline is completely reversible after drug discontinuation [4, 5].

Only a few clinical studies have explored the efficacy and safety of SGLT2 inhibitors in patients with impaired kidney function [6–8]. These studies have predominantly included patients with Stage 3 CKD [estimated GFR (eGFR) 30–60 mL/min/1.73 m^2], and have demonstrated that the glucose-lowering efficacy of SGLT2 inhibitors in these patients is diminished com-pared with patients with preserved kidney function [6, 8]. This attenuated hypoglycemic action is most likely a result of reduced glucose filtration. Whether SGLT2 inhibitors are effective and safe in patients with more severely impaired kidney function (i.e. Stages 3b and 4 CKD, characterized by an eGFR of 15–45 mL/min/1.73m^2) is not fully known. We therefore performed a pooled analysis of multiple phase 3 clinical trials to characterize the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with type 2 diabetes with Stages 3b and 4 CKD.

MATERIALS AND METHODS

Study designs and patient populations

Eleven phase 3, randomized placebo-controlled clinical trials in patients with type 2 diabetes receiving dapagliflozin were in-cluded in this pooled analysis. Supplementary data, Table S1 shows the characteristics of the study populations included in this analysis. The study designs, populations and primary results of all these studies have been previously reported [7, 9–18].

In short, all studies had a core study period of 24 weeks and the majority had an extension period of up to 102 or 104 weeks (Supplementary data, Figure S1).

The effects of dapagliflozin 5 and 10 mg as monotherapy or in combination with metformin, sulfonylurea derivatives, thia-zolidinediones, dipeptidyl peptidase 4 inhibitors or insulin ver-sus placebo were examined. The studies characterized the effects of dapagliflozin treatment in patients with a range of eGFR levels whose diabetes was inadequately controlled with diet and exercise alone or with the above-mentioned glucose-lowering therapies. Each study protocol was approved by inde-pendent local/central ethics committees and informed consent was obtained from all patients.

Measurements and outcomes

Patients with diabetes and an eGFR between 12 to less than 45 mL/min/1.73 m^2 were included in this pooled analysis. We characterized the effects of dapagliflozin 5 mg/day or dapagliflozin 10 mg/day versus placebo on HbA1c, markers of kidney function [eGFR, urinary albumin:creatinine ratio (UACR), potassium and phosphate] and other cardiovascular parameters [hematocrit, blood pressure (BP), body weight and uric acid] by assessing the

changes from baseline to 4 weeks and/or to 102 weeks follow-up. Additionally, the overall least square means were calculated. Spot urine samples were used to measure UACR.

Statistical analyses

Descriptive statistics were used for presenting baseline char-acteristics and safety data. The mean change from baseline value and 95% confidence interval (CI) were derived using a longitudinal repeated measures mixed model with fixed terms for treatment, study week and study week-by-treatment interac-tion as well as the fixed covariates of baseline, baseline-by-study and baseline-by-week interactions. UACR values were log-transformed (using the natural log) and then exponentiated back to the original scale. The Kenward–Roger method was used. If the model did not converge, the Satterthwaite approxi-mation was used. If this model did not converge, the Kenward–Roger method was used, first with the baseline-by-study and then baseline-by-week terms removed. Finally, if this model still did not converge, analysis of covariance (ANCOVA) was done for each week separately.

Subgroup analyses were performed to assess if the effects of dapagliflozin on UACR at week 24 were consistent across subgroups. The population was stratified by median baseline UACR levels and by micro- and macroalbuminuria stages. An ANCOVA model was used with albuminuria subgroup added as a factor and treatment × albuminuria subgroup as in-teraction term. The week 24 data were chosen since this was the time point used for the primary analysis in the included studies, and data form a large number of patients were available for meaningful analysis.

The influence of other covariates on the effects of dapagliflo-zin on UACR was also explored. Continuous fixed covariates of change from baseline to Week 24 in HbA1c, systolic BP or body weight were added to an ANCOVA model that included treat-ment as a fixed factor. All analyses for both safety and efficacy variables also included data from patients who had received gly-caemic rescue therapy. Patients received open-label rescue ther-apy with an antihyperglycemic agent if predefined rescue criteria were exceeded. Changes in antihypertensive medica-tions were not controlled for in this study. The statistical analy-ses were performed with SAS versions 9.2 and 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 220 diabetic patients with an eGFR between 12 and <45 mL/min/1.73 m^2 at baseline were included in this post hoc analysis. The baseline characteristics of this population are reported in Table 1. The mean baseline eGFR with placebo, dapagliflozin 5 mg and dapagliflozin 10 mg groups was 38.4 (SD 5.7), 37.6 (SD 4.6) and 38.0 (SD 5.0) mL/min/1.73 m^2, respectively. The median UACR was 52.0, 51.0 and 40.0 mg/g in the placebo, dapagliflozin 5 mg and dapagliflozin 10 mg groups, respectively. A total of 136 patients (62%) had a UACR ≥30 mg/g.

Table 1. Baseline characteristics

	Placebo (n = 69)	Dapagliflozin 5 mg (n = 58)	Dapagliflozin 10 mg (n = 93)
Age (years)	66.5 (7.7)	66.0 (9.0)	66.3 (7.4)
Female, n (%)	29 (42.0)	26 (44.8)	44 (47.3)
Race, n (%)			
White	60 (87.0)	46 (79.3)	83 (89.2)
Black	1 (1.4)	5 (8.6)	6 (6.5)
Asian	4 (5.8)	2 (3.4)	1 (1.1)
Other	4 (5.8)	5 (8.6)	3 (3.2)
eGFR (mL/min/1.73 m^2)	38.4 (5.7)	37.6 (4.6)	38.0 (5.0)
<30	5 (7.1)	4 (6.9)	3 (3.2)
≥30–<45	64 (91.4)	54 (93.1)	90 (96.8)
Weight (kg)	97.7 (19.6)	97.1 (21.1)	98.2 (20.4)
BMI (kg/m^2)	34.6 (5.5)	34.7 (5.9)	34.8 (6.3)
Diabetes duration (years)	13.5 (8.3)	17.2 (9.5)	16.7 (10.3)
HbA1c (%)	8.1 (1.0)	8.4 (1.1)	8.2 (0.9)
Systolic BP (mmHg)	129.7 (15.7)	131.3 (18.5)	134.3 (17.0)
Diastolic BP (mmHg)	73.9 (9.7)	74.0 (9.7)	75.0 (8.5)
Pulse pressure (mmHg)	55.8 (13.9)	57.3 (16.4)	59.3 (16.0)
UACR (mg/g)	52.0 (17.0–180.0)	51.0 (18.0–539.0)	40.0 (9.0–285.0)

Data are mean (SD) unless stated otherwise. UACR values represent median (25th–75th percentile). BMI, body mass index.

Effects of dapagliflozin on glycemic parameters

Dapagliflozin compared with placebo did not change HbA1c. The least square mean differences between dapagliflozin and placebo in percent change in HbA1c during the 102-week period were 0.03% (95% CI −0.3–0.3) for the 5-mg group and 0.03% (95% CI −0.2–0.3) for the 10-mg group. The effect of dapagliflozin compared with placebo on HbA1c was similar when all patients receiving rescue therapy were excluded.

Effects of dapagliflozin on parameters of kidney function

From baseline to 4 weeks, the mean eGFR increased in the placebo group, whereas in the dapagliflozin 10-mg treatment group the mean eGFR remained fairly stable (Figure 1A). Compared with placebo, the mean eGFR change from baseline after 4 weeks of dapagliflozin therapy was −3.6 mL/min/1.73 m^2 (95% CI −6.0 to −1.2) for the 5-mg group and −3.8 mL/min/1.73 m^2 (95% CI −5.9 to −1.7) for the dapagliflozin 10-mg group. During the subsequent 72-week follow-up, eGFR remained lower in both dapagliflozin groups than the placebo group (Figure 1A). Thereafter, eGFR levels were similar among the three treatment groups.

In the subgroup of 136 patients with UACR ≥30 mg/g, the difference between dapagliflozin compared with placebo in UACR was −49.7% (95% CI −66.9 to −23.6) and −30.2% (95% CI −52.3–2.2) in the 5- and 10-mg groups, respectively, after 4 weeks. This effect was sustained throughout the remaining follow-up period. The least square mean differences between placebo and dapagliflozin 5 and 10 mg during the overall period were −47.1% (95% CI −64.8 to −20.6) and −38.4% (95% CI −57.6 to −10.3), respectively. The effects of dapagliflozin on UACR 24 weeks post-therapy were consistent in albuminuria subgroups stratified by baseline median albuminuria level (P of interaction = 0.57) and also in subgroups defined by baseline micro- and macroalbuminuria (P of interaction = 0.26).

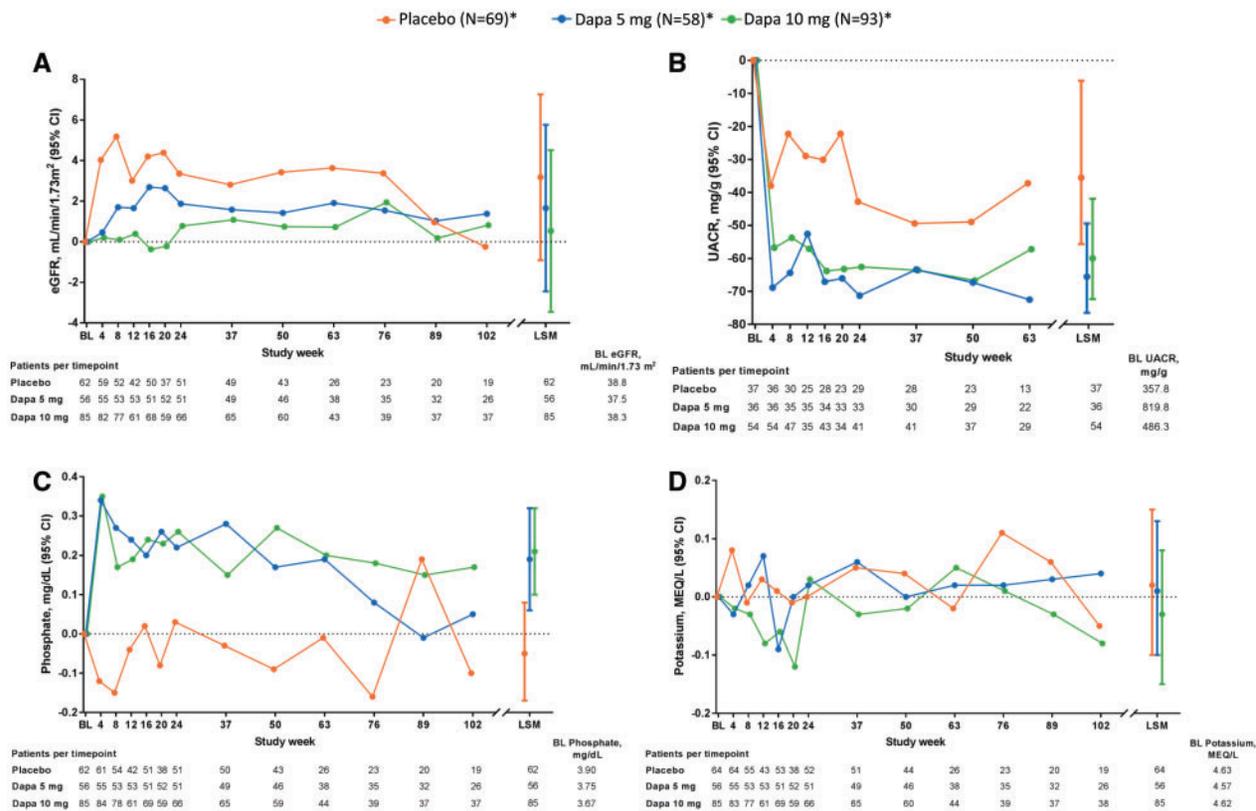Compared with placebo, treatment with dapagliflozin resulted in an elevation of the least square mean serum phosphate level by 0.2 mg/dL (95% CI 0.1–0.4) for the 5-mg group and 0.3 mg/dL (95% CI 0.1–0.4) for the 10-mg group (Figure 1C). No clinically relevant change in potassium was observed for either of the dapagliflozin groups (Figure 1D).

Effects of dapagliflozin on other renal and cardiovascular risk markers

Treatment with both dapagliflozin 5 and 10 mg resulted in an increase in the least square mean hematocrit of 2.5% (95% CI 1.7–3.3) and 2.5% (95% CI 1.7–3.2), respectively, compared with placebo, during the overall 102-week period (Figure 2A). Additionally, dapagliflozin compared with placebo caused a reduction in the least square mean systolic BP of −1.4 mmHg (95% CI −4.8–2.0) and −3.8 mmHg (95% CI −6.9 to −0.7) for the 5- and 10-mg groups, respectively (Figure 2B). Body weight decreased progressively in patients receiving dapagliflozin but increased in the placebo group (Figure 2C). The average reduction in body weight during the whole period was −1.7 kg (95% CI −3.0 to −0.4) for the 5-mg dapagliflozin group and −2.2 kg (95% CI −3.4 to −1.0) for the 10-mg group compared with placebo. The reduction in UACR during dapagliflozin therapy was modestly attenuated after adjustment for HbA1c, systolic BP and body weight (Table 2). Changes in uric acid were similar among the three treatment groups (Figure 2D).

Safety

The average time of follow-up varied due to dropout rates and different studies in the pool including different dose arms. The average follow-up was 384 days in the placebo arm and 527 and 419 days in the dapagliflozin 5- and 10- mg arms, respectively. The overall rate of adverse events was similar in the three treatment groups (Table 3). Serious adverse events occurred in 30.4% of patients in the placebo group and 22.4% and 25.8% in the dapagliflozin 5- and 10-mg groups, respectively. Three patients receiving placebo (4.3%), one patient receiving dapagliflozin 5 mg (1.7%) and two patients receiving dapagliflozin 10 mg (2.2%) died during follow-up.

FIGURE 1: Changes in parameters of kidney function over time during treatment with placebo or dapagliflozin: (**A**) eGFR, (**B**) UACR, (**C**) phosphate, (**D**) potassium. *UACR analysis (UACR ≥30 mg/g): $n = 42$ for placebo, $n = 37$ for dapagliflozin 5 mg and $n = 57$ for dapagliflozin 10 mg. BL, baseline.
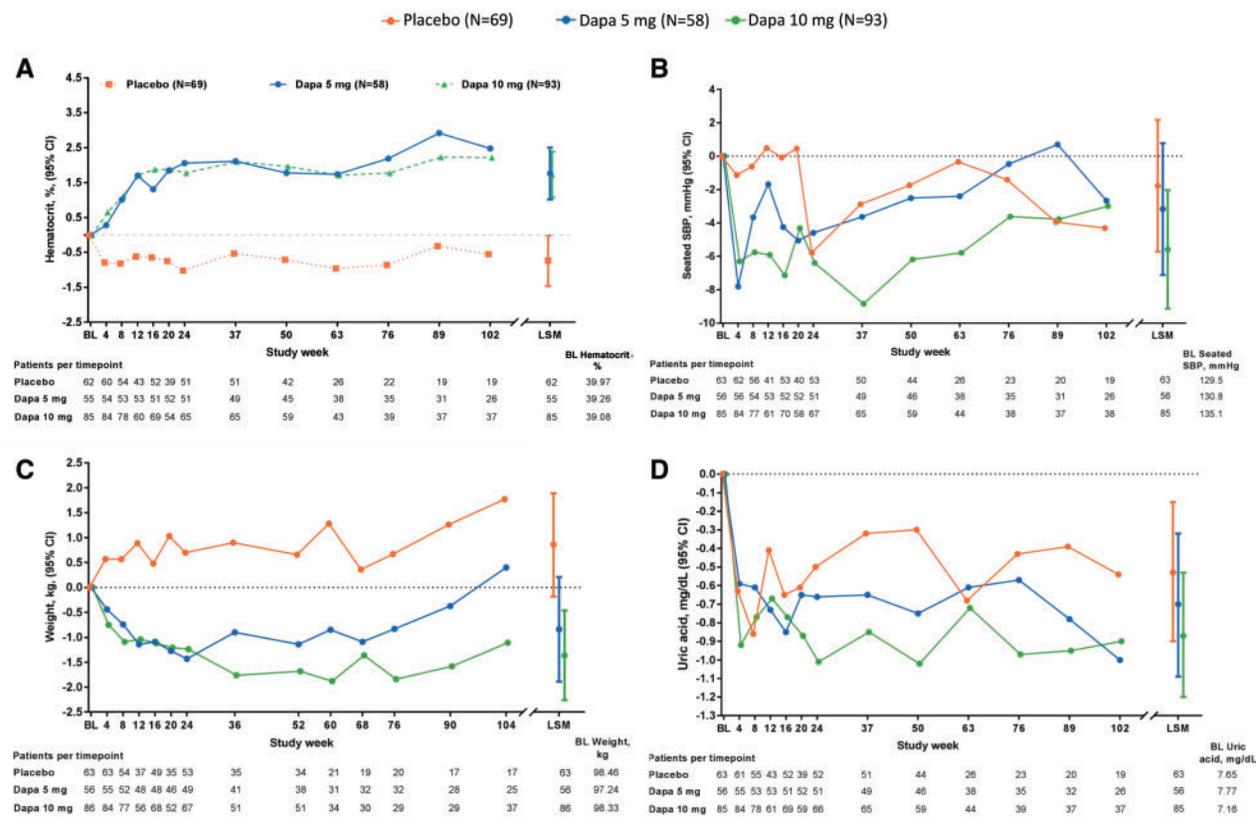
FIGURE 2: Changes in renal or cardiovascular risk markers over time during treatment with placebo or dapagliflozin: (**A**) hematocrit, (**B**) systolic blood pressure (SBP), (**C**) body weight, (**D**) uric acid.

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Overall, the proportion of hypoglycemic events was similar between the three groups. Three patients receiving placebo (4.3%) experienced a major episode of hypoglycemia, whereas none of the patients receiving dapagliflozin had major hypoglycemia. Urinary tract infections occurred more frequently in the placebo group (13%) compared with the dapagliflozin 5- and 10-mg groups (10.3% and 9.7%, respectively), whereas genital infections occurred more frequently in the dapagliflozin groups (5.2% and 4.3%, respectively) compared with the placebo group (1.4%). In the dapagliflozin 10-mg group, more adverse events related to kidney function occurred (25.8%), versus 13% in the placebo group and 6.9% in the 5-mg group. Three serious adverse events of acute renal failure were reported and all three patients received placebo. There were no differences in adverse events related to volume depletion (Table 3).

DISCUSSION

The principal finding of this pooled analysis of a large phase 3 program is that in patients with type 2 diabetes and Stages 3b–4 CKD, dapagliflozin decreases albuminuria, BP and body weight. These beneficial effects were apparent after 4 weeks of treatment with dapagliflozin and generally persisted throughout the 102-week follow-up period. Dapagliflozin did not decrease HbA1c compared with placebo treatment, indicating that the observed effects on albuminuria, BP and body weight are dissociated from hypoglycemic effects and possibly mediated by natriuretic/diuretic mechanisms. eGFR was relatively stable over time, both with dapagliflozin and placebo treatment. Dapagliflozin was generally well tolerated in the study population. The overall proportion of adverse events was similar among dapagliflozin- and placebo-treated patients.

Improving glycemic control has been proven to be important in reducing the risk of microvascular complications of diabetes [19]. In our population of patients with type 2 diabetes and Stages 3b–4 CKD, dapagliflozin did not improve glycemic control. Based on this lack of efficacy, SGLT2 inhibitors are currently not recommended for the treatment of diabetes in patients with impaired renal function [20–23]. Dapagliflozin, however, favorably influenced other cardiovascular risk markers, including BP and albuminuria, in the present study. Similar findings have been observed with two other SGLT2 inhibitors, empagliflozin and canagliflozin [6, 8]. The magnitude of albuminuria reduction was clinically meaningful and, based on large epidemiological studies, might be expected to translate into an ∼40% relative risk reduction for end-stage kidney disease [24]. This finding helps to justify a dedicated clinical outcome trial to investigate the long-term efficacy and safety of SGLT2 inhibitors in patients with type 2 diabetes and Stages 3b–4 CKD.

Table 2. Mean Percentage change (95% CI) from baseline UACR at Week 24: unadjusted for covariates and adjusted for changes from baseline in HbA1c, systolic blood pressure and body weight (BW)

	Placebo (n = 29)	Dapagliflozin 5 mg (n = 33)	Dapagliflozin 10 mg (n = 41)
Change from baseline UACR, unadjusted	−42.8 (−62.2 to −13.5)	−71.3 (−81.1 to − 56.2)	−62.6 (−75.0 to − 44.0)
Change from baseline compared with placebo		−49.7 (−68.5 to − 20.0)	−34.6 (−57.6–0.9)
Change from baseline UACR, adjusted for HbA1c	−33.0 (−58.6–8.5)	−63.6 (−78.2 to − 39.4)	−51.8 (−71.1 to − 19.7)
Change from baseline compared with placebo		−45.8 (−67.3 to − 10.1)	−28.1 (−55.5–16.1)
Change from baseline UACR, adjusted for SBP	−33.3 (−56.9–3.1)	−61.9 (−76.0 to − 39.4)	−49.6 (−68.2 to − 20.1)
Change from baseline compared with placebo		−42.8 (−63.9 to − 9.5)	−24.4 (−50.9–16.4)
Change from baseline UACR, adjusted for BW	−34.9 (−59.3–4.0)	−58.8 (−75.5 to − 30.8)	−46.2 (−67.6 to − 10.6)
Change from baseline compared with placebo		−36.7 (−62.6–7.0)	−17.3 (−49.1–34.3)

Table 3. Adverse events and serious adverse events

	Placebo (n = 69)	Dapagliflozin 5 mg (n = 58)	Dapagliflozin 10 mg (n = 93)
≥1 AE	58 (84.1)	53 (91.4)	79 (84.9)
≥1 SAE	21 (30.4)	13 (22.4)	24 (25.8)
AEs leading to study drug discontinuation	20 (29.0)	13 (22.4)	21 (22.6)
AEs of special interest			
Hypoglycemia[a]	26 (37.7)	25 (43.1)	29 (31.2)
Urinary tract infection	10 (14.4)	6 (10.3)	9 (9.7)
Genital infection	1 (1.4)	3 (5.2)	4 (4.3)
Renal function	9 (13.0)	4 (6.9)	24 (25.8)
Volume depletion	5 (7.2)	5 (8.6)	7 (7.5)
SAE of special interest			
Urinary tract infection	0	1 (1.7)	0
Genital infection	0	0	0
Renal function	4 (5.8)	1 (1.7)	1 (1.1)
Volume depletion	1 (1.4)	0	1 (1.1)

n (%) of adverse events (AEs) and serious adverse events (SAEs).
[a]Total subjects with hypoglycemia.

The mechanisms by which SGLT2 inhibitors reduce body weight, BP and albuminuria in the absence of glycemic effects are unknown. It is plausible that the reduction in glucose filtration resulting from a reduced eGFR decreases the capacity of SGLT2 inhibitors to inhibit glucose reabsorption. Yet, it remains unclear why other effects persist in patients with impaired kidney function. Such patients may have an increased sensitivity to the mild natriuretic/osmotic diuresis induced by dapagliflozin. The DAPASALT trial (NCT03152084), designed to investigate the mechanism of natriuretic–diuretic effects of dapagliflozin in patients with preserved and impaired kidney function, will provide more insight into this issue.

The observed reductions in eGFR, albuminuria and BP resulting from treatment with SGLT2 inhibitors are thought to be a clinical manifestation of increased sodium delivery to the macula densa, which in turn reduces tubuloglomerular feedback and decreases intraglomerular pressure. In many primary and secondary kidney diseases, for example, focal segmental glomerulosclerosis, immunoglobulin A (IgA) nephropathy, hypertensive nephrosclerosis and obesity-induced nephropathy, maladaptive functional renal hemodynamic changes are thought to occur, including increases in renal blood flow, GFR and filtration fraction [25]. In these conditions, administration of SGLT2 inhibitors could potentially restore tubuloglomerular feedback, leading to a reduction in the afferent arterial tone and intraglomerular pressure, which can favorably affect long-term renal prognosis. Hence the increase in the prevalence of non-diabetic kidney disease in many parts of the world, together with the lack of glycemic effects of dapagliflozin in patients with CKD Stages 3b–4, makes SGLT2 inhibitors an attractive adjunctive therapy to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in the broader CKD population.

The overall proportion of adverse events in our study was similar among patients in the dapagliflozin and placebo groups, but there were more renal adverse events in patients treated with dapagliflozin. However, there was no increase in the overall serious renal adverse events and no increase in serious acute renal failure events in the dapagliflozin group compared with the placebo group. In addition, randomized placebo-controlled trial data also indicate that the risk of acute kidney injury (AKI) is not increased during SGLT2 inhibition [5, 26]. Moreover, a recent registry study reported that SGLT2 use in patients with type 2 diabetes who were managed in two large health systems was not associated with an increased risk of AKI [27]. These results are in contrast to the observational reports from clinical practice that were sent to the US Food and Drug Administration (FDA) suggesting that SGLT2 inhibitors increase the risk of AKI. In response to these reports, the FDA recently strengthened their AKI warning for SGLT2 inhibitors [28]. Ongoing large randomized controlled trials in patients with CKD will provide more definitive evidence as to whether SGLT2 inhibitors cause AKI.

Our study showed increased phosphate levels with SGLT2 inhibition. The clinical relevance of this effect is unknown. It has been speculated that this increase in phosphate may precipitate fractures, but recent data with dapagliflozin in patients with type 2 diabetes indicate no increased fracture risk or increased rate of bone turnover as assessed by biomarkers [15, 29, 30].

Our results extend prior findings demonstrating that the effects of SGLT2 inhibitors on HbA1c levels in patients with type 2 diabetes and more severe CKD is attenuated, while effects on other renal and cardiovascular risk markers persist [6]. We report for the first time the effects of SGLT2 inhibition in a subgroup of patients with CKD Stages 3b–4 over a 102-week follow-up. The previous studies including patients with Stage 3 CKD and a small group of patients with Stage 4 CKD produced similar reductions in UACR, BP and body weight, but during a shorter follow-up period [6, 8]. In contrast to the previous studies, which showed a decline in eGFR during SGLT2 inhibition, we observed no change in eGFR in the dapagliflozin treatment arms and an increase in the placebo arm. This is likely to reflect regression towards the mean, because we specifically selected patients with an eGFR <45 mL/min/1.73 m^2 at the baseline visit and, as observed in the placebo arm, the eGFR regressed to the mean at the next visit. For that reason, we also reported the mean eGFR change with dapagliflozin relative to placebo. Finally, we observed that a large proportion of the treatment effect of dapagliflozin on UACR remained present after adjustment for changes in HbA1c, systolic BP or body weight. This finding is in line with previous studies with dapagliflozin and empagliflozin [4, 31].

A limitation of this study was the relatively small study population. Second, the majority of the population was at relatively low risk of renal endpoints, as reflected by the large number of patients with normoalbuminuria. This likely explains the slow rate of eGFR decline both in the placebo and dapagliflozin treatment groups. Not all of the studies in this pooled analysis examined the effects of both dapagliflozin 5 and 10 mg. The data on dapagliflozin 10 mg came primarily from two studies in patients at high cardiovascular risk, while the data on dapagliflozin 5 mg came from a clinical trial in patients with predominantly Stages 3a–b CKD. This difference in background characteristics in the populations may have influenced the safety comparison between dapagliflozin 5 and 10 mg.

In conclusion, dapagliflozin did not decrease HbA1c in patients with type 2 diabetes and Stages 3b–4 CKD in this post hoc analysis. However, it decreased UACR, BP and body weight without major side effects. These actions of dapagliflozin support the need for a large outcome trial in this population to confirm long-term safety and efficacy in reducing adverse clinical endpoints.

AUTHORS' CONTRIBUTIONS

C.C.J.D. and H.J.L.H. designed the study and wrote the first draft of the manuscript. D.C.W., B.V.S. and C.D.S.

contributed to data collection, data interpretation and critical revisions of the manuscript. V.C. analyzed the data and contributed to critical revision of the manuscript.

CONFLICT OF INTEREST STATEMENT

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

REFERENCES

1. Bailey RA, Wang Y, Zhu V et al. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. BMC Res Notes 2014; 7: 415

2. Afkarian M, Sachs MC, Kestenbaum B et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013; 24: 302–308

3. Heerspink HJ, Perkins BA, Fitchett DH et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016; 134: 752–772

4. Heerspink HJ, Johnsson E, Gause-Nilsson I et al. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin–angiotensin blockers. Diabetes Obes Metab 2016; 18: 590–597

5. Wanner C, Inzucchi SE, Lachin JM et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016; 375: 323–334

6. Barnett AH, Mithal A, Manassie J et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014; 2: 369–384

7. Kohan DE, Fioretto P, Tang W et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 2014; 85: 962–971

8. Yale JF, Bakris G, Cariou B et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab 2014; 16: 1016–1027

9. Ferrannini E, Ramos SJ, Salsali A et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010; 33: 2217–2224

10. Bailey CJ, Gross JL, Pieters A et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010; 375: 2223–2233

11. Strojek K, Yoon KH, Hruba V et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab 2011; 13: 928–938

12. Rosenstock J, Vico M, Wei L et al. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012; 35: 1473–1478

13. Wilding JP, Woo V, Soler NG et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med 2012; 156: 405–415

14. Jabbour SA, Hardy E, Sugg J et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014; 37: 740–750

15. Bolinder J, Ljunggren O, Johansson L et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab 2014; 16: 159–169

16. Cefalu WT, Leiter LA, de Bruin TW et al. Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Diabetes Care 2015; 38: 1218–1227

17. Henry RR, Murray AV, Marmolejo MH et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012; 66: 446–456

18. Leiter LA, Cefalu WT, de Bruin TW et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc 2014; 62: 1252–1262

19. Edelman SV. Importance of glucose control. Med Clin North Am 1998; 82: 665–687

20. European Medicines Agency. Jardiance. EPAR product information, August 2017. http://www.ema.europa.eu/docs/en_GB/document_library/ EPAR_-_Product_Information/human/002677/WC500168592.pdf (20 December 2017, date last accessed)

21. European Medicines Agency. Forxiga. EPAR product information, July 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_ Information/human/002322/WC500136026.pdf (20 December 2017, date last accessed)

22. European Medicines Agency. Invokana. EPAR product information, July 2017. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_ -_Product_Information/human/002649/WC500156456.pdf (20 December 2017, date last accessed)

23. Vlotides G, Mertens PR. Sodium–glucose cotransport inhibitors: mechanisms, metabolic effects and implications for the treatment of diabetic patients with chronic kidney disease. Nephrol Dial Transplant 2015; 30: 1272–1276

24. Heerspink HJ, Kropelin TF, Hoekman J et al. Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. J Am Soc Nephrol 2015; 26: 2055–2064

25. Helal I, Fick-Brosnahan GM, Reed-Gitomer B et al. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol 2012; 8: 293–300

26. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377: 644–657.

27. Nadkarni GN, Ferrandino R, Chang A et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care 2017; 40: 1479–1485

28. US Food and Drug Administration. Canagliflozin (Invokana, Invokamet) and Dapagliflozin (Farxiga, Xigduo XR): Drug Safety Communication—Strengthened Kidney Warnings. 2016. https://www.fda.gov/Safety/Med Watch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm 506554.htm (20 December 2017, date last accessed)

29. Egger A, Kraenzlin ME, Meier C. Effects of incretin-based therapies and SGLT2 inhibitors on skeletal health. Curr Osteoporos Rep 2016; 14: 345–350

30. Blevins TC, Farooki A. Bone effects of canagliflozin, a sodium glucose cotransporter 2 inhibitor, in patients with type 2 diabetes mellitus. Postgrad Med 2017; 129: 159–168

31. Cherney DZI, Zinman B, Inzucchi SE et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017; 5: 610–621