Effects of canagliflozin on hyperkalaemia and serum potassium in people with diabetes and chronic kidney disease: Results from the CREDENCE trial

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ABSTRACT

Aims

Hyperkalaemia is a common complication of type 2 diabetes mellitus (T2DM) and limits the optimal use of agents that block the renin-angiotensin aldosterone system, particularly in patients with chronic kidney disease (CKD). In patients with CKD, sodium glucose cotransporter 2 (SGLT2) inhibitors provide cardiorenal protection, but whether they affect the risk of hyperkalaemia remains uncertain.

Methods and Results

The CREDENCE trial randomized 4401 participants with T2DM and CKD to the SGLT2 inhibitor canagliflozin or matching placebo. In this post-hoc analysis using an intention-to-treat approach, we assessed the effect of canagliflozin on a composite outcome of time to either investigator-reported hyperkalaemia or the initiation of potassium binders. We also analysed effects on central laboratory-determined hyper- and hypokalaemia (serum potassium ≥6.0 and <3.5 mmol/L, respectively) and change in serum potassium. At baseline the mean serum potassium in canagliflozin and placebo arms was 4.5 mmol/L; 4395 (99.9%) participants were receiving renin angiotensin system blockade. The incidence of investigator-reported hyperkalaemia or initiation of potassium binders was lower with canagliflozin than with placebo (occurring in 32.7 vs. 41.9 participants per 1000 patient-years; HR 0.78, 95% CI 0.64-0.95, p=0.014). Canagliflozin similarly reduced the incidence of laboratory-determined hyperkalaemia (HR 0.77, 95% CI 0.61-0.98, p=0.031); with no effect on the risk of hypokalaemia (HR 0.92, 95% CI 0.71-1.20, p=0.53). Mean serum potassium over time with canagliflozin was similar to that of placebo.

Conclusion

Among patients treated with RAAS inhibitors, SGLT2 inhibition with canagliflozin may reduce the risk of hyperkalaemia in people with T2DM and CKD without increasing the risk of hypokalaemia.

Key Words: Canagliflozin, SGLT2 inhibitors, hyperkalemia, potassium, type 2 diabetes, chronic kidney disease

Introduction

Hyperkalaemia occurs frequently in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD), increasing in incidence as kidney function declines, and is associated with discontinuation of renin-angiotensin-aldosterone (RAAS) inhibitors due to its potential to cause life threatening arrythmias that are clinically relevant to both physicians and patients.(1-3) In individuals with CKD, the association between serum potassium is U-shaped such that both high and low levels are associated with increased risk of hospitalization and death.(4, 5)

Inhibition of the RAAS system with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is standard of care for people with T2DM and CKD, but these agents are known to increase the risk of hyperkalaemia,(6) contributing at least partly to non-prescription or discontinuation of these agents in routine clinical practice.(7) More recently, the non-steroidal mineralocorticoid receptor antagonist, finerenone, has been shown to reduce the risk of kidney disease progression in people with T2DM and CKD, however these benefits were counterbalanced by an increased risk of hyperkalaemia.(8)

Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of kidney failure and cardiovascular events in people with CKD or heart failure, irrespective of the presence or absence of T2DM.(9-11) In people with preserved kidney function, SGLT2 inhibitors may enhance potassium excretion by the kidney through a combination of increased sodium and water delivery to the distal nephron, enhanced glycosuria and stimulation of aldosterone.(12, 13) However, the effect of SGLT2 inhibitors on serum potassium and risk of hyperkalaemia in people with CKD is uncertain. While initial studies with canagliflozin suggested a possible increased risk of hyperkalaemia in people with T2DM and preserved kidney function, longer term data did not show such risk; however, the effects on the risk of hyperkalaemia remain undefined because few patients in the earlier SGLT2 inhibitor studies had CKD.(14)

We hypothesized that canagliflozin might reduce the risk of hyperkalaemia in people with T2DM and CKD and sought to assess the effect of canagliflozin on a range of potassium related outcomes in this

population at high risk of hyperkalaemia, by conducting a post-hoc analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.

Methods

Data availability

Data from this study will be made available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in the United States and European Union and the study has been completed for 18 months.

Study design and participants

The design, statistical analysis plan and main results of the CREDENCE trial have been published previously.(15, 16) Briefly, CREDENCE was a double-blind, event-driven, randomized, placebo-controlled trial assessing the effect of canagliflozin on major kidney, cardiovascular and safety outcomes in people with T2DM and CKD. The trial was conducted in 695 sites across 34 countries. The trial protocol was approved by local institutional ethics committees at each site and all participants provided written informed consent.

The trial enrolled participants with glycated haemoglobin between 6.5 and 12% who had an estimated glomerular filtration rate (eGFR) of 30-90 mL/min/1.73m^2 and a urinary albumin:creatinine ratio (UACR) of >300 mg/g. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate eGFR. All participants were required to be receiving maximum tolerated or labelled dose of ACE inhibitor or ARB for at least four weeks prior to randomization. Key exclusion criteria included type 1 diabetes, non-diabetic kidney disease, current use of a mineralocorticoid receptor antagonist and serum potassium >5.5 mmol/L at baseline.

Randomization and follow-up procedures

All eligible participants underwent a two-week, single blind, placebo run-in period before being randomized to either canagliflozin 100 mg, or matching placebo once daily. Randomization was performed centrally using a computer-generated randomization schedule and randomly permuted blocks stratified by pre-randomization eGFR (30 to <45, 45 to <60, 60 to <90 mL/min/1.73m^2). All participants, care providers and study investigators were blinded to treatment allocation until the end of the trial.

After randomization, study visits were conducted at weeks 3, 13, and 26 and then alternated between clinic and telephone follow-up at 13-week intervals thereafter. Blood tests for serum potassium were done at each study visit (i.e. every 6 months) and measured at a central laboratory. We identified potassium-related outcomes by searching the CREDENCE trial database, held at The George Institute for Global Health, Sydney, Australia, for (1) investigator reported adverse events, (2) investigator initiated concomitant medications, and (3) central laboratory values. Firstly, we identified spontaneous investigator reported hyperkalaemia and hypokalaemia events by searching the adverse event database. Definitions of hyper- and hypokalaemia were based on the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of “hyperkalaemia”, “blood potassium increased”, hypokalaemia” and “blood potassium decreased”. Secondly, we searched the concomitant medications database to identify new initiation of potassium binders during the trial, including sodium polystyrene sulfonate, calcium polystyrene sulfonate, patiromer or sodium zirconium. Thirdly, we identified hyperkalaemia events using laboratory-based definitions; serious hyperkalaemia was defined as serum potassium ≥6.0 mmol/L and hypokalaemia was defined as <3.5 mmol/L.

Outcomes

In this post-hoc analysis, the main outcome was a composite of investigator reported hyperkalaemia events or initiation of potassium binders. Other potassium-related outcomes included investigator reported hyperkalaemia events; initiation of potassium binders; hyperkalaemia, defined as a serum potassium ≥6.0 mmol/L; investigator reported hypokalaemia; hypokalaemia, defined as serum potassium <3.5 mmol/L; and mean difference in serum potassium over time. In sensitivity analyses, we defined hyperkalaemia and hypokalaemia using ≥ 5.5 mmol/L and <4.0mmol/L cut-off values, respectively.

Statistical analysis

We compared characteristics of participants according to baseline serum potassium values using Chi Square and ANOVA tests for categorical and continuous variables, respectively.

The effect of canagliflozin on the main outcome of investigator reported hyperkalaemia events or initiation of potassium binders was assessed using Kaplan Meier analysis and Cox regression models with stratification by screening eGFR categories. We used a similar approach for other dichotomous secondary outcomes. The primary analytical approach was done using the intention-to-treat principle, with on-treatment analysis done as sensitivity analyses. The on-treatment dataset was defined as all randomized participants followed for up to 30 days after the last dose, which was pre-specified for safety analyses in the primary trial report. We assessed the consistency of the effect on the main outcome across a range of clinically relevant participant characteristics including age, sex, screening eGFR, UACR, duration of diabetes, history of heart failure, cardiovascular disease, diuretic use, baseline serum potassium; P-interaction values were obtained using likelihood ratio tests comparing nested models with and without subgroup by treatment interaction terms with no adjustment for multiplicity.

To assess the impact of concomitant medication use that may have affected serum potassium levels during the trial, we evaluated the use of potassium sparing diuretics (spironolactone, eplerenone, amiloride, or triamterene), mineralocorticoid receptor antagonists (spironolactone or eplerenone), loop diuretics (frusemide, torsemide, bumetanide, etacrynic acid) and discontinuation of RAAS blockade during follow-up across canagliflozin and placebo arms.

The mean difference in serum potassium over time between canagliflozin and placebo arms was assessed using linear mixed effects models that included all post-baseline data up to week 182. The model included categorical covariates for randomized treatment allocation, visit, screening eGFR, treatment by visit interaction and two continuous covariates: baseline serum potassium and baseline

potassium-by-visit interaction. The variance-covariance matrix was assumed to be unstructured, i.e., purely data dependent.

In additional exploratory analyses, we assessed the association between baseline serum potassium levels and adverse outcomes as well as the effect of canagliflozin versus placebo on key kidney and cardiovascular outcomes. We assessed the association between baseline serum potassium levels and kidney and cardiovascular outcomes (doubling of serum creatinine, kidney failure, kidney or cardiovascular death; doubling of serum creatinine, kidney failure or kidney death; cardiovascular death, myocardial infarction or stroke; and cardiovascular death or hospitalization for heart failure) using multivariable Cox regression analysis adjusted for age, sex, race, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body-mass index, systolic blood pressure, glycated haemoglobin, eGFR, log-transformed urinary albumin-to-creatinine ratio, HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, and randomised treatment (canagliflozin or placebo). We assessed the effect of canagliflozin on these outcomes according to baseline serum potassium levels using Cox regression models stratified by screening eGFR, as has been done previously.(17) P-interaction values were obtained from the relevant model using the same approach as for the main potassium outcome.

All p-values were two-sided and 0.05 was used as the level of significance. Analyses were done using SAS (version 9.4) and Stata (version 15).

Results

CREDENCE included 4401 participants of whom 4397 (99.9%) had serum potassium measured at baseline. The mean baseline serum potassium was 4.5 mmol/L (SD 0.5) in both canagliflozin and placebo arms. Few participants were receiving potassium sparing diuretics at baseline (20 [0.9%] and 15 [0.7%] respectively for canagliflozin and placebo arms). Of these, 24 (0.5%) were receiving a mineralocorticoid receptor antagonist at baseline. Potassium binder use at baseline was also uncommon (15 [0.7%] and 11

[0.5%] for canagliflozin and placebo treated participants, respectively), with no participants receiving novel agents (i.e. patiromer or sodium zirconium) at baseline or during follow-up.

The number of participants with serum potassium <4, 4-4.5, >4.5-5.0 and >5.0 mmol/L at randomization was 582 (13.2%), 1849 (42.0%), 1303 (29.6%) and 663 (15.1%), respectively. 151 (3.4%) participants had a baseline serum potassium >5.5 mmol/L. The distribution of serum potassium values at baseline are displayed in Figure S1. Participants with higher levels of baseline potassium were more likely to have a lower eGFR, longer duration of diabetes, and history of microvascular complications and peripheral vascular disease (Table 1).

Over a median follow up of 2.6 years, 179 (8.1%) canagliflozin-treated participants and 226 (10.3%) placebo-treated participants experienced the composite outcome of investigator reported hyperkalaemia or initiation of potassium binders. Canagliflozin reduced the risk of the composite outcome by 22% (32.7 vs. 41.9 participants per 1000 patient-years; HR 0.78, 95% CI 0.64-0.95, p=0.014; Figure 1). A similar effect was observed for investigator reported hyperkalaemia alone (HR 0.82, 95% CI 0.67-1.01, p=0.063). Initiation of potassium binders occurred less frequently in the canagliflozin compared to placebo arm (HR 0.66, 95% CI 0.46-0.95, p=0.027). Canagliflozin reduced the incidence of central laboratory-determined serum potassium ≥6 mmol/L (HR 0.77, 95% CI 0.61-0.98, p=0.031). The effects of canagliflozin on hyperkalaemia-related outcomes are summarized in Figure 2. Results were similar in on-treatment sensitivity analysis, with statistically significant results observed for both investigator-reported and laboratory-defined hyperkalaemia (Table S1). No clear effect on hyperkalaemia was observed when defined as a central laboratory determined serum potassium level ≥5.5 mmol/L (HR 0.93, 95% CI 0.83-1.04, p=0.21). In the majority of cases of investigator reported hyperkalaemia (84%), randomized treatment remained unchanged, though drug interruption or withdrawal occurred more commonly in placebo treated participants (Table S2).

The effect of canagliflozin on serum potassium over time is displayed in Figure 3. Mean serum potassium levels increased in both canagliflozin and placebo arms during the trial. There was no significant

difference in mean serum potassium levels between canagliflozin and placebo treated participants over the duration of the trial (placebo-subtracted difference 0.00039 mmol/L, 95% CI -0.018 to 0.019, p=0.97; Figure 3). Effects were similar across different levels of baseline potassium (P-interaction=0.95; Table S3).

There were some differences in the use of medications affecting serum potassium across canagliflozin and placebo arms. In addition to the more frequent initiation of potassium binders in placebo treated participants (Figure 2), loop diuretic use was also more common in placebo-treated participants post-randomization (Figure S2), as was discontinuation of RAAS blockade (Figure S3). However there was no difference in the use of potassium sparing diuretics and mineralocorticoid receptor antagonists across canagliflozin and placebo arms, which were initiated in less than 4% of participants after randomization (Figure S4-5).

The incidence of investigator reported hypokalaemia and of serum potassium <3.5 mmol/L was low overall (Figure 4). Canagliflozin did not increase the risk of investigator reported hypokalaemia events (HR 1.20, 95% CI 0.71, 2.04, p=0.50), with similar findings observed for central laboratory measured potassium <3.5 mmol/L (HR 0.92, 95% CI 0.71, 1.20, p=0.53; Figure 4). Canagliflozin also did not increase the risk of hypokalaemia defined as a serum potassium <4.0 mmol/L (HR 0.92, 95% CI 0.82-1.02; p=0.13).

The effect of canagliflozin on the composite outcome of investigator reported hyperkalaemia or initiation of potassium binders was broadly consistent across a range of baseline characteristics, including age, sex, history of heart failure, established cardiovascular disease, baseline serum potassium, eGFR, UACR and diuretic use (all P-interaction >0.05; Figure 5). In an additional analysis, the effect of canagliflozin on hyperkalemia defined as central laboratory serum potassium $\geq$6.0 mmol/L was similar in participants with baseline eGFR 30-60 mL/min/1.73 and 60-90 mL/min/1.73m^2 (HR 0.82, 95% CI 0.65, 1.03 and HR 0.69, 95% CI 0.47, 1.02; P-interaction=0.46).

In additional analyses we explored both the association between serum potassium levels and adverse outcomes and the consistency of the effect of canagliflozin on kidney and cardiovascular outcomes across different levels of baseline serum potassium. We observed a U-shaped association between serum potassium levels and kidney and cardiovascular outcomes such that serum potassium levels <4.0 and >5.0 mmol/L were associated with increased risk of adverse outcomes (Figure S6). There was some evidence that the magnitude of benefit with canagliflozin was greater at higher levels of baseline serum potassium levels for the primary endpoint in the CREDENCE trial (a composite outcome of kidney failure, doubling of serum creatinine, cardiovascular or kidney death; P-interaction=0.03; Table S4). However, the effect of canagliflozin on the kidney-specific composite outcome of kidney failure, doubling of serum creatinine or kidney death was consistent across different levels of baseline serum potassium (P-interaction=0.31), as were effects on key cardiovascular outcomes, including cardiovascular death or hospitalization for heart failure (P-interaction=0.14; Table S4).

Discussion

Individuals with T2DM and CKD experience a high rate of hyperkalaemia, which can result in discontinuation of kidney protective therapies, hospitalization and life-threatening arrythmias.(18) In this post-hoc analysis of the CREDENCE trial, we observed that canagliflozin reduced the risk of investigator reported hyperkalaemia or initiation of potassium binders compared to placebo, with a similarly significant reduction in risk of central laboratory-determined hyperkalaemia, defined as a serum potassium ≥6.0 mmol/L. The lower risk of hyperkalaemia with canagliflozin is notable since it was observed on a background of near universal use of ACE inhibitors or ARBs as mandated for entry into the CREDENCE trial.

The validity of our findings is strengthened by results from completed T2DM cardiovascular outcome and heart failure trials of other agents within the class. In EMPA-REG OUTCOME, the risk of hyperkalaemia was lower with empagliflozin versus placebo (incident rate ratio 0.57, 95% CI 0.42-0.77).(19) The incidence of investigator reported hyperkalaemia was also numerically lower in the cardiovascular outcome trials for canagliflozin (CANVAS Program)(20) and dapagliflozin (DECLARE-TIMI 58).(21) In the

DAPA-HF trial, in which more than two-third of participants were receiving mineralocorticoid receptor antagonists at baseline, dapagliflozin significantly reduced the incidence of serious hyperkalaemia, defined as serum potassium >6.0 mmol/L (HR 0.64, 95% CI 0.42-0.99), with greater benefit in those receiving mineralocorticoid receptor antagonists at baseline.(22) Our results extend these observations to people with T2DM and CKD, who are at higher risk of serious hyperkalaemia. Importantly, the effects of canagliflozin on hyperkalaemia outcomes did not appear to be explained by the differential concomitant use of potassium sparing diuretics or mineralocorticoid receptor antagonists during the trial, which were similar in both treatment arms. Indeed, the reduction in risk of hyperkalaemia with canagliflozin was observed despite more frequent initiation of potassium binders, use of loop diuretics and discontinuation of RAAS blockade over time in the placebo arm, which would be expected to lower serum potassium and limit our ability to detect effects on hyperkalaemia.

The lower risk of hyperkalaemia with canagliflozin in people with T2DM and CKD contrasts with agents that inhibit the RAAS system, which are known to increase the risk of hyperkalaemia. While ACE inhibitors and ARBs have formed the foundations of treatment for slowing the progression of kidney disease for almost two decades, their optimal use and dosing in people with CKD has been limited at least partly by hyperkalaemia, especially as kidney function declines. In people with advanced CKD, hyperkalaemia is a major factor influencing the discontinuation of ACE inhibitors and ARBs.(2, 23) Recently, the FIDELIO-DKD trial (Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease) demonstrated that the non-steroidal mineralocorticoid receptor antagonist finerenone can slow the progression of kidney disease and prevent cardiovascular events in people with T2DM and CKD.(8) These benefits, however, were counterbalanced by an increased risk of hyperkalaemia, despite the trial requiring an entry criteria of serum potassium $\leq$4.8 mmol/L, an established risk factor for hyperkalaemia development .(5) A similar challenge exists in the management of patients with heart failure with reduced ejection fraction, where hyperkalaemia limits the use of RAAS blockade and mineralocorticoid receptor antagonists,(24) which are key components of disease modifying pharmacological therapy in this population.(25) Further, the optimal strategy for managing chronic hyperkalaemia remains uncertain; while newer potassium binders may facilitate greater use of RAAS

blockade, there remains concern about the long-term safety of sodium polystyrene sulfonate, especially serious gastrointestinal adverse effects,(26) which remains the most commonly used potassium binder in many parts of the world.

In this context, our study has important implications for the care of people with T2DM and CKD. While clinical practice guidelines now recommend RAAS blockade plus SGLT2 inhibition for most people with T2DM and CKD,(27) the benefits of finerenone on major kidney and cardiovascular outcomes in this population raise questions about whether combination treatment with all three agents should be routinely offered to patients with T2DM and CKD.(8) The risk of hyperkalaemia is also greater in people with T2DM and CKD, compared to non-diabetic kidney disease, in large part due to coexisting type 4 renal tubular acidosis.(28) The effect of canagliflozin on hyperkalaemia may make combined treatment with all three classes of agent more feasible. Additionally, many patients are unable to tolerate RAAS blockade due to hyperkalaemia. A 2019 meta-analysis of CREDENCE and cardiovascular outcome trials observed consistent benefits for kidney outcomes regardless of the baseline use of RAAS blockade.(9) For individuals unable to tolerate RAAS blockade due to hyperkalaemia, treatment with an SGLT2 inhibitor alone may be a reasonable alternative, given the lower risk of hyperkalaemia with these agents.

The mechanisms underpinning the effect of canagliflozin on hyperkalaemia are uncertain. Under normal conditions, key determinants of potassium excretion by the kidney include the rate of sodium and water delivery to the distal nephron and stimulation of aldosterone. In people with T2DM, and in those treated with an SGLT2 inhibitor, glycosuria and the resultant osmotic diuresis also contributes to kaliuresis. By inhibiting SGLT2 in the proximal tubule, canagliflozin increases distal sodium delivery and reabsorption, thus enhancing the electronegative charge in the tubular lumen which drives potassium secretion via the principle cell at the cortical collecting duct.(29) Effects on aldosterone could also affect distal potassium handling although the effects of SGLT2 inhibition on this pathway are complex and not well understood.(12)

Alternatively, the lower incidence of hyperkalaemia may partly reflect preservation of kidney function with canagliflozin, rather than direct effects on sodium-potassium handling by the kidney. The neutral effect on serum potassium over time could support this hypothesis. In both treatment arms, mean serum potassium levels increased during the study, which is likely to reflect loss of kidney function over time, given the study population was enriched for individuals at high risk of kidney disease progression. The separation of the Kaplan Meier curves at approximately 18 months for the composite outcome of investigator reported hyperkalaemia or initiation of potassium binders might also lend support to the notion that reductions in risk of hyperkalaemia were driven by preservation of kidney function. Nevertheless, when the direct effect of canagliflozin on hyperkalaemia was based on a serial central laboratory values, these curves separated much earlier – at 6 months. It could also be argued that the more frequent initiation of potassium binders, use loop diuretics and greater discontinuation of RAAS blockade in placebo treated participants during the trial – all of which lower serum potassium levels – could explain the neutral effects on mean serum potassium over time. It is also important to note that mean changes in serum potassium levels in the overall trial population may also not reflect the true risk of hyperkalaemia; in the FIDELIO-DKD, ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) and VA-NEPHRON D (Veterans Affairs Nephropathy in Diabetes) trials, increases in risk of hyperkalaemia were observed with active treatment despite relatively modest changes in mean serum potassium over time (approximately 0.2 mmol/L).(8, 30, 31)

These results should be interpreted in light of certain limitations. This was a post-hoc analysis of the CREDENCE trial with the inherent drawbacks of such an approach. Hyperkalaemia events were investigator reported, not adjudicated and therefore potentially variable across study sites. With sodium polystyrene sulfonate being available in virtually all countries participating in CREDENCE, initiation of potassium binders was also at the discretion of treating physicians according to local guidelines with no specific recommendations on hyperkalaemia management in the trial protocol. However, the consistency of the effect on investigator reported hyperkalaemia with results based on central laboratory values and in on-treatment sensitivity analyses, as well as with data from other large-scale SGLT2 inhibitor trials provides some reassurance with regards to the robustness of the findings. Newer potassium binders

(patiromer and sodium zirconium cyclosilate) were not prescribed at baseline and were almost seldom used during follow-up by virtue of the fact that these drugs were not registered for use in most countries at the time the trial was conducted. As such, our findings are unlikely to be influenced by the use of these agents. Because serum potassium was measured at six-monthly intervals, we were unable to identify the exact time at which individuals developed hyper- or hypokalaemia. Thus interval censoring and differences in frequency of serial biochemical analyses compared to investigator reported events could have contributed to the time at which Kaplan Meier curves separated for the different hyperkalaemia outcomes. Ultimately, we were unable to address the question of whether canagliflozin reduces the risk of hyperkalaemia through enhanced kaliuresis or other mechanisms as we did not assess fractional excretion of potassium. Regardless of hypothesized mechanisms, confirmation of a cause-and-effect relationship would require a dedicated randomized controlled trial. Finally, due to the exclusion criteria of the CREDENCE trial, whether these findings are generalisable to individuals with non-diabetic CKD or to people with CKD receiving mineralocorticoid receptor antagonists is uncertain.

In summary, canagliflozin may reduce the risk of hyperkalaemia in people with T2DM and CKD without any adverse effect on incident hypokalaemia. Further prospective studies are required to confirm these findings.

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Disclosures

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has received consulting fees from Aegerion, Alnylam, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Corvidia, GlaxoSmithKline, Innovent, Eisai, Eli Lilly, Kowa, Merck, Pfizer, Regeneron, and Sanofi. Prof Charytan has personal fees or fees paid by Janssen Pharmaceuticals to the Baim Institute for work on the CREDENCE trial steering committee. He has received consulting fees from Amgen, Eli Lilly, Fresenius, Gilead, Medtronic/Covidien, Merck, Novo Nordisk, Zoll, AstraZeneca, PLC Medical and Allena Pharmaceuticals, and has received research support from Medtronic and Amgen. R. Edwards is a full-time employee of Janssen Research & Development, LLC. Dr Górriz has received honoraria for lectures Astrazeneca, Mundipharma, Eli Lilly and Novo Nordisk; and for advisory boards from Astrazeneca, Boehringer Ingelheim, Mundipharma and MSD. Prof Jardine was a member of the CREDENCE study steering committee and is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Amgen, Baxter, CSL, Eli Lilly, Gambro, and MSD; has served on advisory boards sponsored by Akebia, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, MSD and Vifor; serves on Steering Committee for trials sponsored by CSL and Janssen; serves on a Steering Committee for an investigator-initiated trial with funding support from Dimerix, spoken at scientific meetings sponsored by Janssen, Amgen, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution. Prof Levin was a member of the CREDENCE study steering committee and a member of the CANVAS and serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); is on the data safety and monitoring board for the NIDDK, Kidney Precision Medicine, University of Washington Kidney Research Institute Scientific Advisory Committee; is funded by the Canadian Institute of Health Research and Kidney Foundation of Canada, outside the submitted work. Prof Neal was a member of the CREDENCE and CANVAS study steering committees and his institution received grant funding support for those trials as well as funding for consultancies done for Janssen, Merck, Mundi Pharma and Mitsubishi Tanabe. Prof De Nicola has received honoraria for lectures Astrazeneca, Mundipharma, and Novo Nordisk; and for advisory boards from Astrazeneca, Boehringer Ingelheim, and Mundipharma. Prof Pollock was a member of the CREDENCE study steering committee and has received honoraria for serving on advisory boards and as a speaker for Merck Sharp & Dohme, AstraZeneca, and Boehringer

Ingelheim/Eli Lilly, and has received personal fees from Johnson and Johnson/Janssen Cilag and Novartis, outside the submitted work. Dr Rosenthal is a full-time employee of Janssen Research & Development, LLC. Prof Wheeler was a member of the CREDENCE study steering committee and has an ongoing consultancy agreement with AstraZeneca and within the last 3 years has received payments for consultancy work and/or speaker fees from Astellas, Amgen, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Napp, Mundipharma, Merck Sharp and Dohme, Tricida and Vifor Fresenius. Prof Mahaffey was co-chair of the CREDENCE study steering committee and the CANVAS steering committee. He has received research support from Afferent, Amgen, Apple Inc., AstraZeneca, Cardiva Medical Inc., Daiichi Sankyo, Ferring, Goo- gle (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health (NIH), Novartis, Sanofi, St. Jude, and Tenax; has served as a consultant (speaker fees for continuing medical education events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi Tanabe, Myokardia, NIH, Novartis, Novo Nordisk, Por- tola, Radiometer, Regeneron, Springer Publishing, and University of California, San Francisco; and has received personal fees from Abbott, Anthos, CSL Behring, Intermountain Health, Mount Sinai, Mundi Pharma, SmartMedics, and Theravance; outside the submitted work. Prof Heerspink was a member of the CREDENCE study steering committee and serves as a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Dimerix, Gilead, GoldFinch, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, and Travere Therapeutics.

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FIGURE LEGENDS

Figure 1. Effects of canagliflozin versus placebo on (A) the composite outcome of investigator reported hyperkalaemia or initiation of potassium binders, (B) investigator reported hyperkalaemia, (C) initiation of potassium binders, and (D) serum potassium ≥6 mmol/L. HR: hazards ratio; CI: confidence interval

Figure 2. Effects of canagliflozin versus placebo on hyperkalaemia related outcomes. †Based on central-laboratory values. HR: hazard ratio; CI: confidence interval.

Figure 3. Mean serum potassium levels over time in canagliflozin and placebo treated participants.

Figure 4: Effects of canagliflozin versus placebo on (a) investigator reported hypokalaemia and (b) serum potassium <3.5 mmol/L. *Based on central-laboratory values

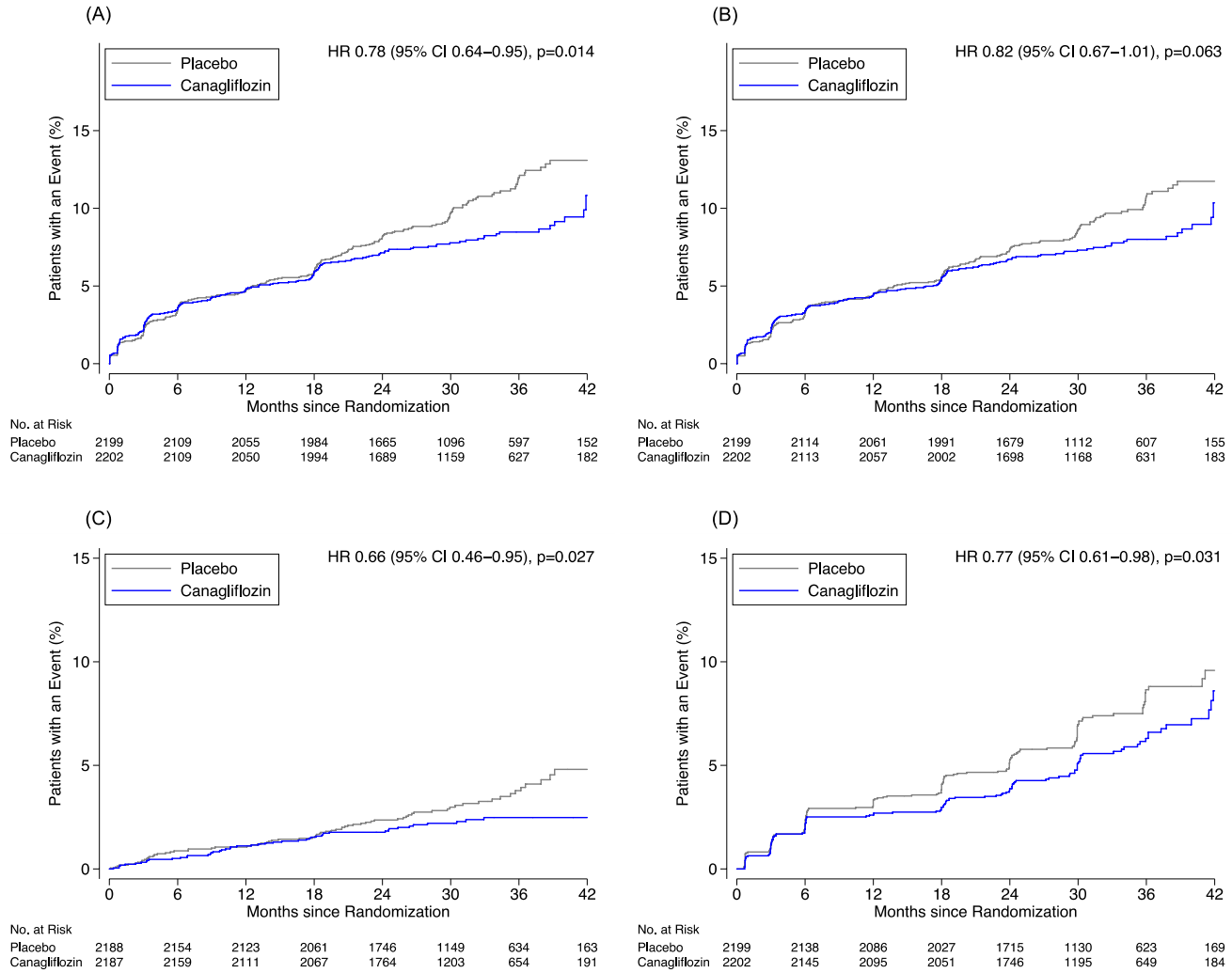
Figure 5. Effects of canagliflozin versus placebo on the primary composite outcome of investigator reported hyperkalaemia or initiation of potassium binders across baseline characteristics. AE, adverse event; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration ratio; UACR, urinary albumin:creatinine ratio. †Race was reported by the patients. The designation “Other” includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Table 1. Participant characteristics in the CREDENCE trial according to baseline serum potassium (mmol/L).

	<4.0 N=582	4.0-4.5 N=1,849	>4.5-5.0 N=1,303	>5.0 N=663	P value
Age	63.5 (9.1)	63.0 (9.2)	63.4 (9.3)	62.0 (9.0)	0.03
Female	176 (30.2)	644 (34.8)	449 (34.5)	224 (33.8)	0.36
Race					<0.001
Asian	101 (17.4)	358 (19.4)	270 (20.7)	148 (22.3)	
Black or African American	59 (10.1)	99 (5.4)	40 (3.1)	26 (3.9)	
Other	39 (6.7)	155 (8.4)	123 (9.4)	51 (7.7)	
White	383 (65.8)	1,237 (66.9)	870 (66.8)	438 (66.1)	
Region					<0.001
Central/South America	111 (19.1)	398 (21.5)	299 (22.9)	133 (20.1)	
Europe	120 (20.6)	369 (20.0)	253 (19.4)	120 (18.1)	
North America	194 (33.3)	500 (27.0)	331 (25.4)	156 (23.5)	
Rest of the world	157 (27.0)	582 (31.5)	420 (32.2)	254 (38.3)	
Current smoker	80 (13.7)	274 (14.8)	202 (15.5)	81 (12.2)	0.55
Heart failure	89 (15.3)	264 (14.3)	178 (13.7)	120 (18.1)	0.22
Diabetes duration	15.3 (8.9)	15.5 (8.4)	16.4 (8.9)	15.9 (8.4)	0.02
Concomitant medications					
Insulin	384 (66.0)	1,194 (64.6)	862 (66.2)	441 (66.5)	0.51
Metformin	327 (56.2)	1,094 (59.2)	772 (59.2)	349 (52.6)	0.17
Statin	405 (69.6)	1,288 (69.7)	895 (68.7)	445 (67.1)	0.25
Antiplatelet	371 (63.7)	1,090 (59.0)	778 (59.7)	383 (57.8)	0.10
Beta-blockers	281 (48.3)	748 (40.5)	490 (37.6)	251 (37.9)	<0.001
Loop diuretics	166 (28.5)	374 (20.2)	249 (19.1)	166 (25.0)	0.23
Microvascular disease					
Retinopathy	189 (32.5)	746 (40.3)	605 (46.4)	340 (51.3)	<0.001
Neuropathy	269 (46.2)	882 (47.7)	645 (49.5)	349 (52.6)	0.01
Atherosclerotic vascular disease					
Coronary artery disease	187 (32.1)	535 (28.9)	387 (29.7)	203 (30.6)	0.86
Cerebrovascular disease	110 (18.9)	284 (15.4)	208 (16.0)	98 (14.8)	0.15
Peripheral vascular disease	106 (18.2)	418 (22.6)	342 (26.2)	180 (27.1)	<0.001
Cardiovascular disease	288 (49.5)	919 (49.7)	681 (52.3)	331 (49.9)	0.46
BMI	32.6 (6.5)	31.6 (6.1)	30.8 (6.0)	30.7 (6.2)	<0.001
Systolic BP	142.2 (16.1)	139.9 (15.4)	140.1 (15.8)	138.2 (15.2)	<0.001
HbA1c	8.2 (1.4)	8.3 (1.3)	8.3 (1.3)	8.2 (1.3)	0.65
Total cholesterol	4.5 (1.2)	4.7 (1.3)	4.7 (1.3)	4.7 (1.3)	0.02
Triglycerides	2.2 (1.5)	2.3 (1.7)	2.2 (1.7)	2.2 (1.5)	0.92
LDL	2.4 (1.0)	2.5 (1.1)	2.5 (1.1)	2.5 (1.1)	0.04
Serum potassium	3.7 (0.2)	4.3 (0.2)	4.8 (0.1)	5.4 (0.3)	<0.001
eGFR, mL/min/1.73m^2	59.0 (17.9)	58.9 (18.3)	55.1 (18.0)	48.3 (16.2)	<0.001
>60	280 (48.1)	852 (46.1)	485 (37.2)	151 (22.8)	
45-<60	156 (26.8)	524 (28.3)	395 (30.3)	190 (28.7)	
<45	146 (25.1)	473 (25.6)	423 (32.5)	322 (48.6)	
UACR, mg/g	924 (447-2050)	874 (447-1697)	953 (489-1907)	965.0 (492-2077)	0.10
≤1000	307 (52.7)	1,023 (55.4)	675 (51.8)	343 (51.8)	
>1000-<3000	193 (33.2)	648 (35.1)	469 (36.0)	233 (35.2)	
≥3000	82 (14.1)	178 (9.6)	159 (12.2)	87 (13.1)	

Data are presented as mean (SD) or median (IQR) for continuous measures, and n (%) for categorical measures. BMI: body mass index; BP: blood pressure; HbA1c: glycated haemoglobin; LDL: low density lipoprotein; eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio.

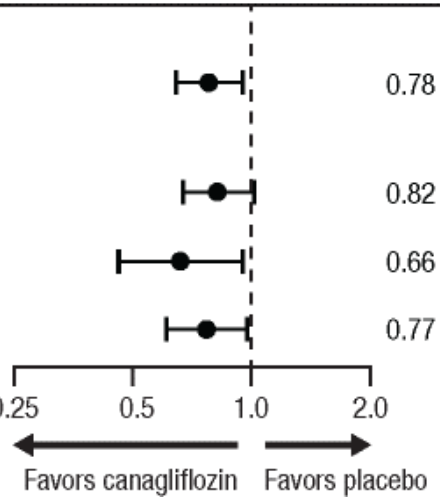
Figure 1. Effects of canagliflozin versus placebo on (A) the composite outcome of investigator reported hyperkalaemia or initiation of potassium binders, (B) investigator reported hyperkalaemia, (C) initiation of potassium binders, and (D) serum potassium ≥6 mmol/L.



HR: hazards ratio; CI: confidence interval.

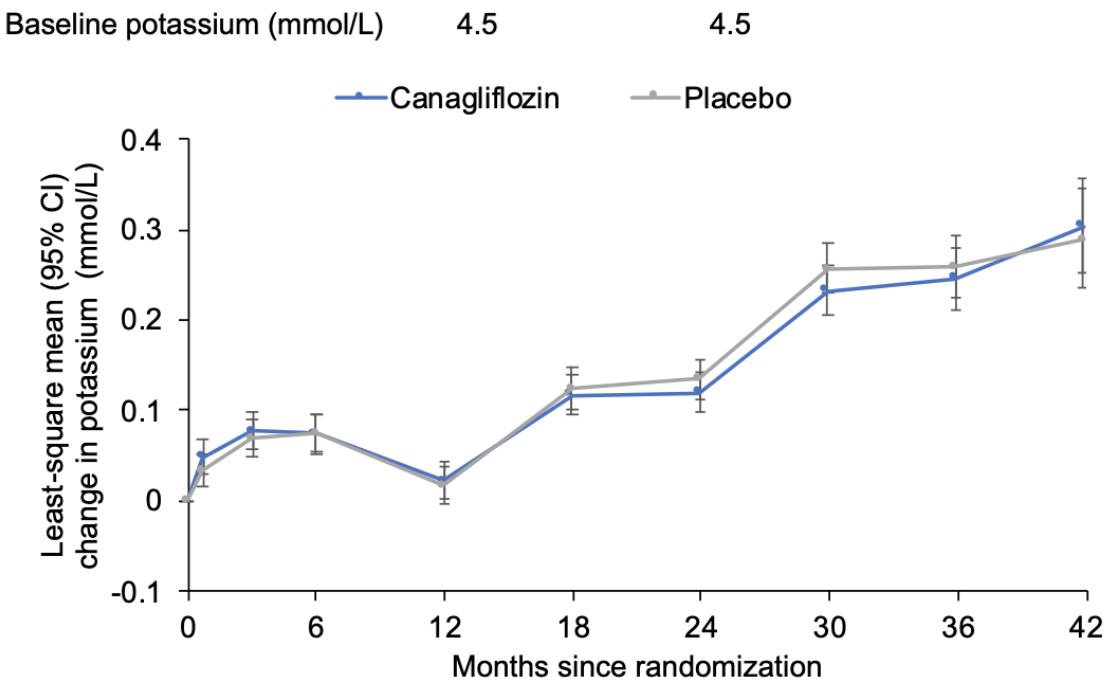
Figure 2. Effects of canagliflozin versus placebo on hyperkalaemia related outcomes.

	Participants with an event		Participants with an event per 1000 patient-years			
	Canagliflozin	Placebo	Canagliflozin	Placebo	HR (95% CI)*	*P* value
The primary composite outcome of investigator-reported hyperkalemia or initiation of potassium binders	179	226	32.7	41.9	0.78 (0.64, 0.95)	0.01
Investigator-reported hyperkalemia	169	203	30.7	37.4	0.82 (0.67, 1.01)	0.06
Initiation of potassium binder	48	72	8.5	12.9	0.66 (0.46, 0.95)	0.03
Potassium ≥6 mmol/L†	121	154	21.6	27.9	0.77 (0.61, 0.98)	0.03



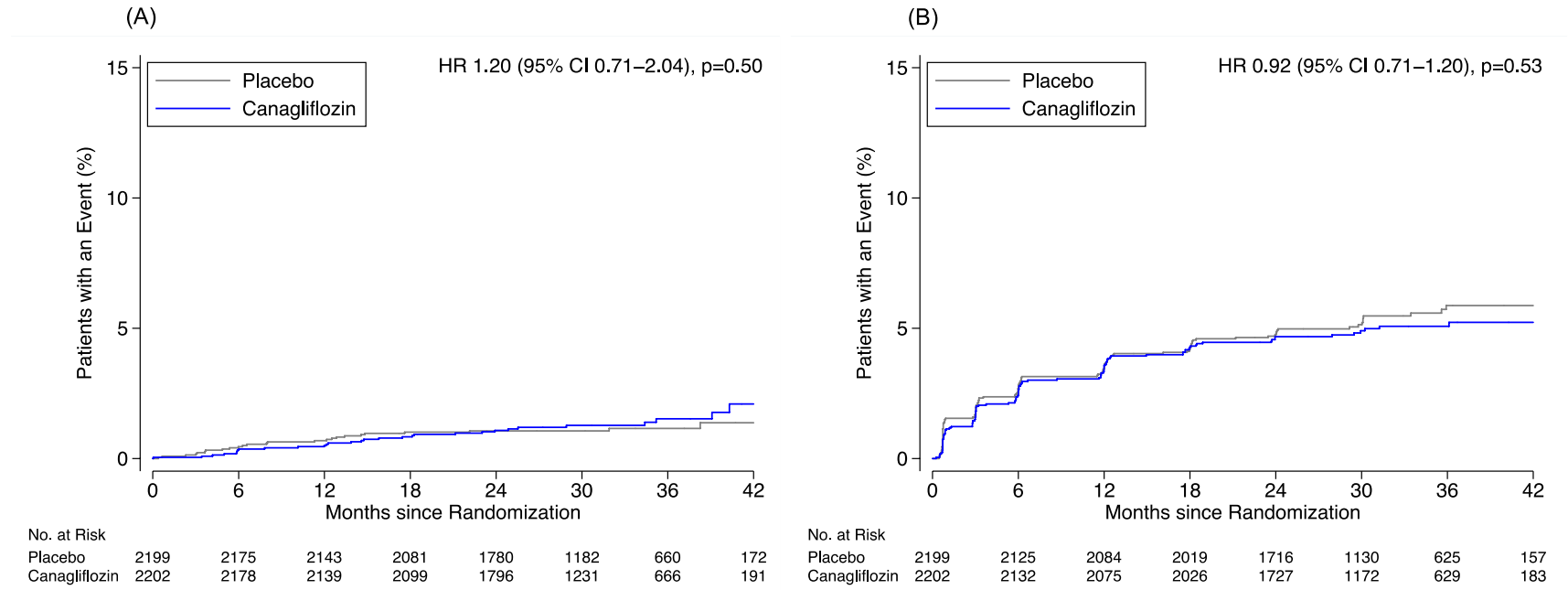
†Based on central-laboratory values. HR: hazard ratio; CI: confidence interval.

Figure 3. Mean serum potassium levels over time in canagliflozin and placebo treated participants.



No. of Patients								
Placebo	2187	2006	1972	1816	1726	1151	691	252
Canagliflozin	2184	2022	2004	1883	1801	1229	727	273

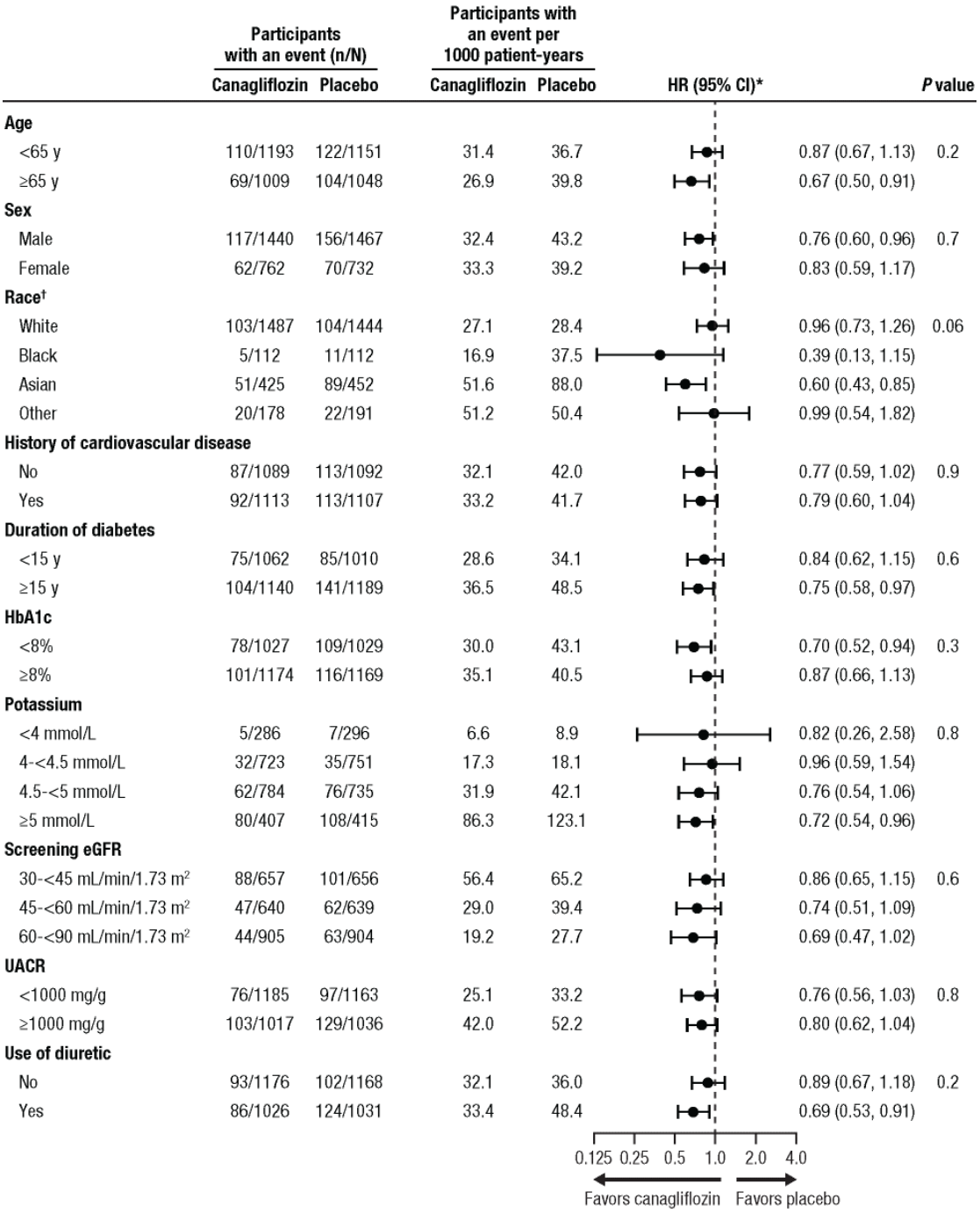
Figure 4: Effects of canagliflozin versus placebo on (a) investigator reported hypokalaemia and (b) serum potassium <3.5 mmol/L.



	N		Events per 1000 patient-years			
	Cana	Placebo	Cana	Placebo	HR (95% CI)	P value
Investigator reported hypokalaemia	30	25	5.2	4.4	1.20 (0.71, 2.04)	0.50
Serum potassium <3.5 mmol/L*	107	116	19,3	21.1	0.92 (0.71, 1.20)	0.53

*Based on central-laboratory values

Figure 5. Effects of canagliflozin versus placebo on the composite outcome of investigator reported hyperkalaemia or initiation of potassium binders across baseline characteristics.



AE, adverse event; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration ratio; UACR, urinary albumin:creatinine ratio. †Race was reported by the patients. The designation "Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Supplementary appendix

Figure S1. Distribution of serum potassium at baseline in canagliflozin and placebo treated participants

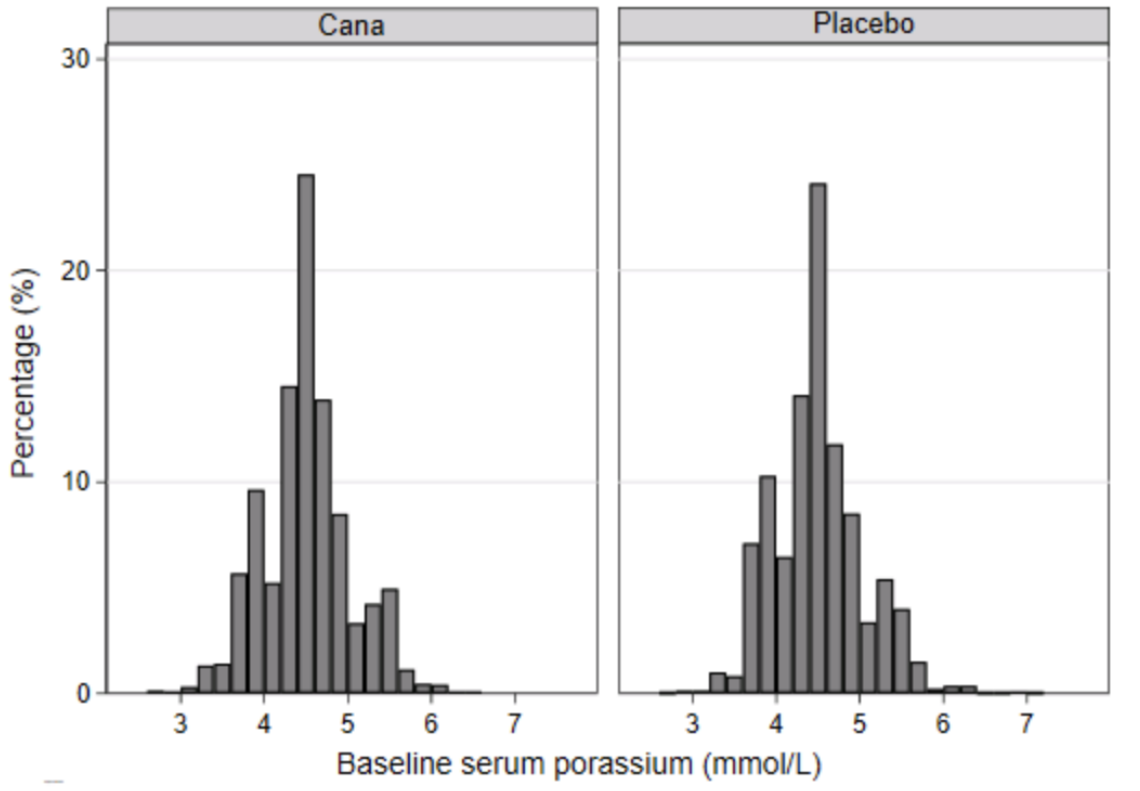


Figure S2: Use of loop diuretics in canagliflozin and placebo treated participants post randomization

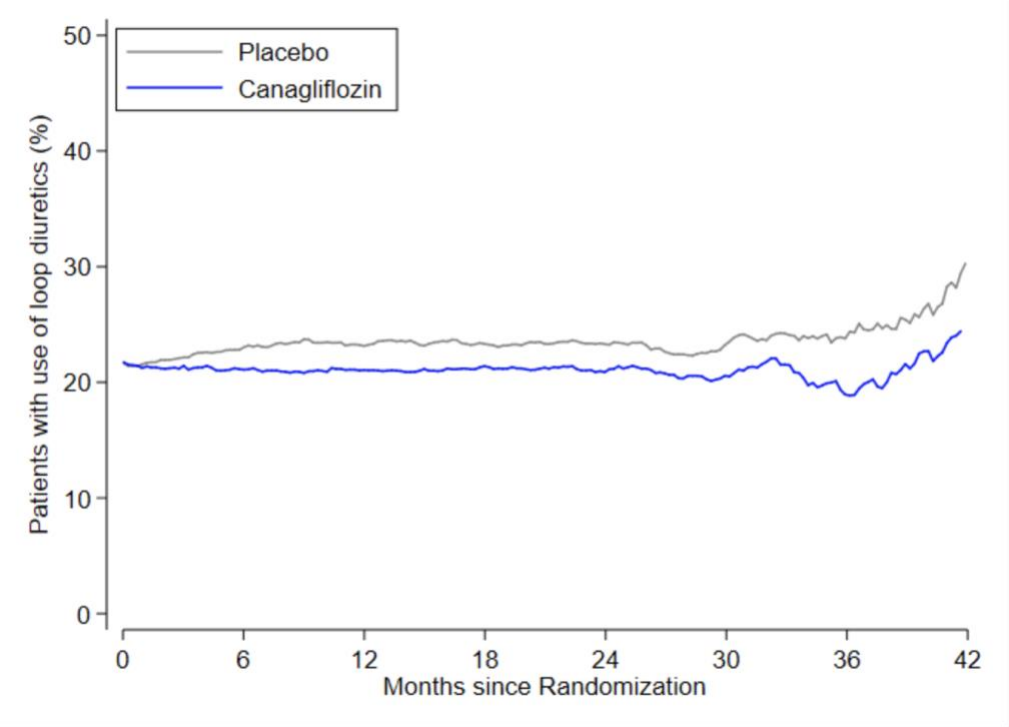
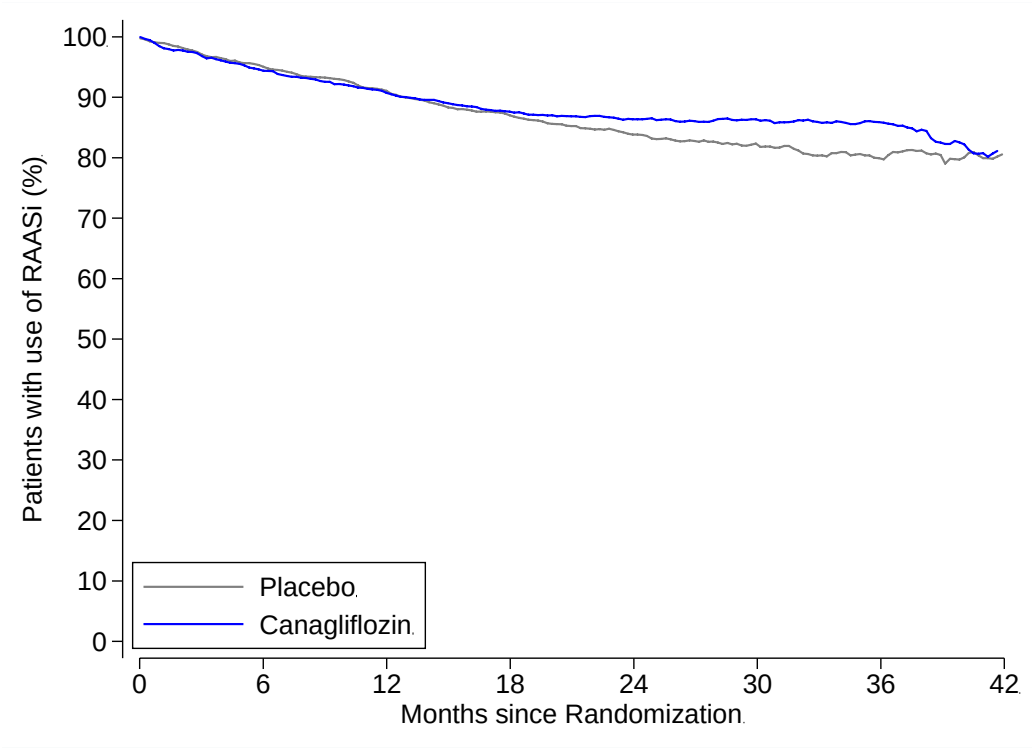


Figure S3: Use of ACE inhibitors and ARBs in canagliflozin and placebo treated participants post-randomization



ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker

Figure S4: Use of potassium sparing diuretics (spironolactone, eplerenone, amiloride, or triamterene) in canagliflozin and placebo treated participants post randomization

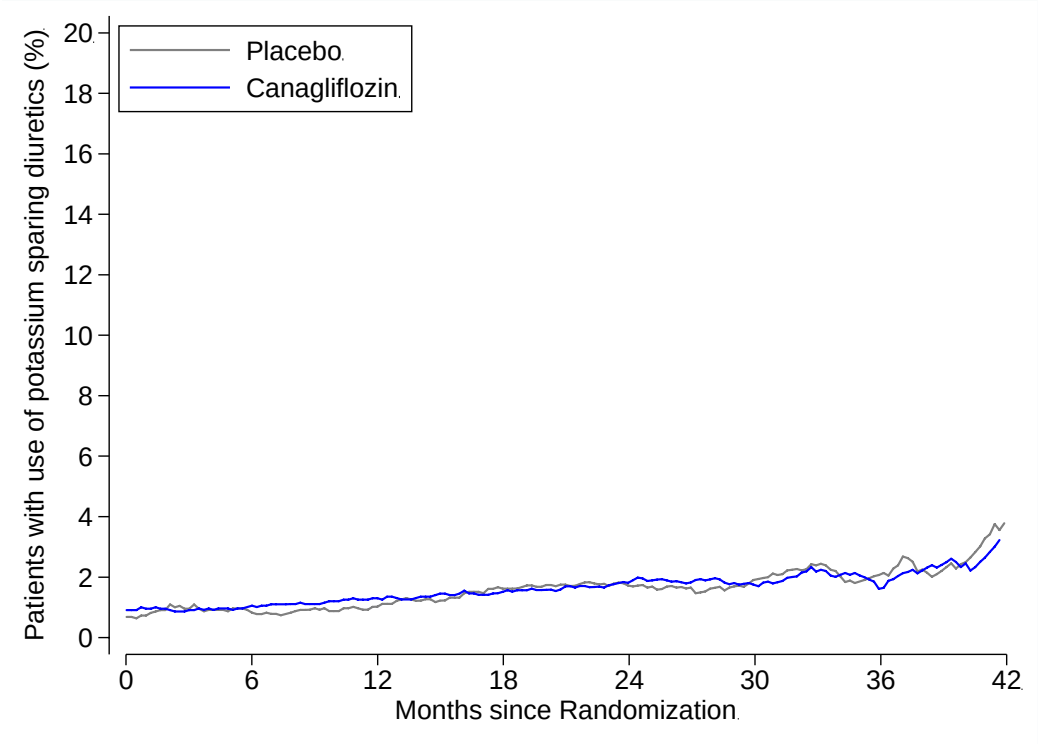
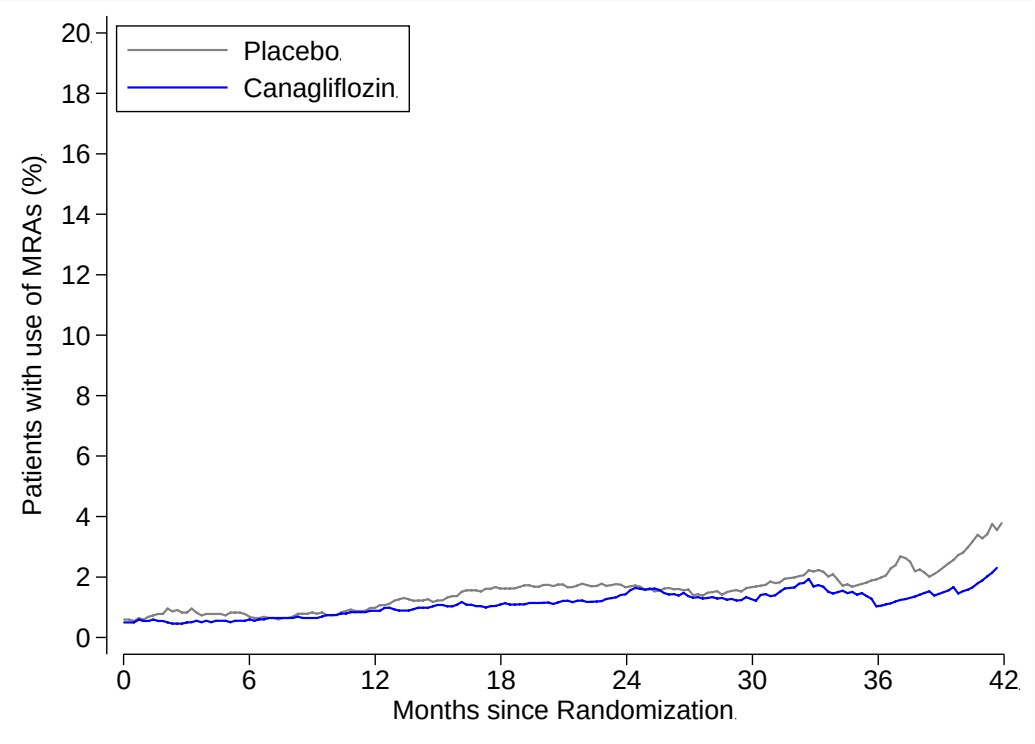
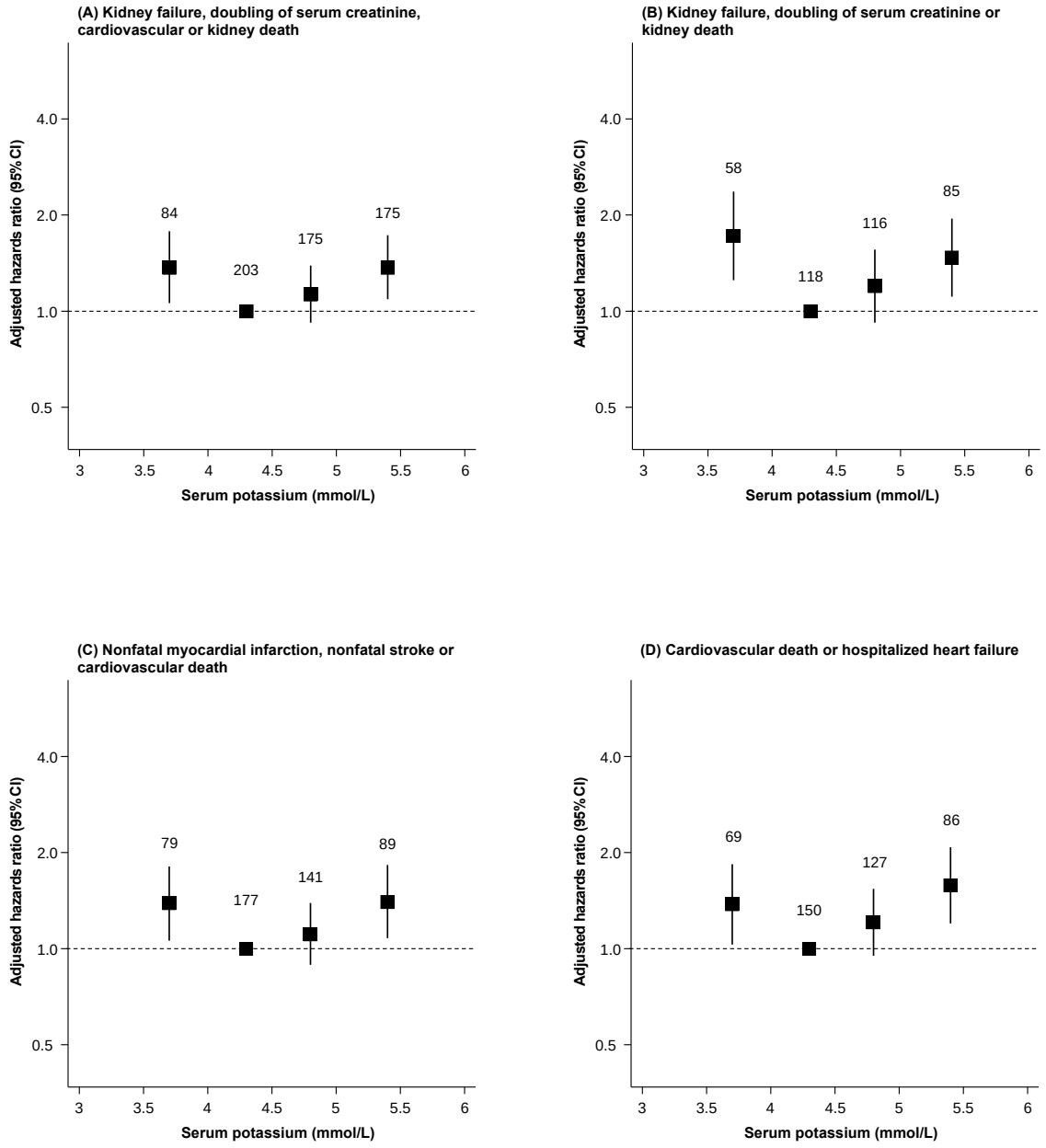


Figure S5: Use of mineralocorticoid receptor antagonists (spironolactone or eplerenone) in canagliflozin and placebo treated participants post randomization



MRAs: mineralocorticoid receptor antagonists.

Figure S6. Association of baseline serum potassium with kidney and cardiovascular outcomes



Numbers above each data point represent the number of participants experiencing an event. Hazard ratios (95% CI) for each category of baseline serum potassium are displayed with 4-4.5mmol/L as the reference category. All models were adjusted for age, sex, race, current smoking, history of hypertension, history of heart failure, duration of diabetes, history of cardiovascular disease, body-mass index, systolic blood pressure, glycated haemoglobin, eGFR, log-transformed urinary albumin-to-creatinine ratio HDL cholesterol, LDL cholesterol, log-transformed triglycerides, diuretic use, and randomised treatment (canagliflozin or placebo). CI: confidence interval.

Table S1: On-treatment analysis of the effects of canagliflozin versus placebo on hyperkalaemia related outcomes

	N		Events per 1000 patient-years			
	Cana	**Placebo**	**Cana**	**Placebo**	**HR (95% CI)**	**P value**
Composite outcome of investigator reported hyperkalaemia or initiation of potassium binders	160	198	32.8	42.3	0.77 (0.63, 0.95)	0.016
Investigator reported hyperkalaemia	151	181	30.9	38.5	0.80 (0.65, 0.99)	0.045
Initiation of potassium binder	42	60	8.4	12.4	0.67 (0.45, 1.00)	0.051
Potassium ≥6 mmol/L*	107	138	21.6	29.1	0.74 (0.57, 0.95)	0.018

*Based on central laboratory values. CI: confidence interval.

Table S2: Drug action for investigator reported hyperkalaemia

	Total	Canagliflozin	Placebo
Number of patients with hyperkalaemia events, n (%)	332 (7.6)	151 (6.9)	181 (8.2)
Drug action			
Drug interrupted, n (%)	17 (5.1)	7 (3.9)	10 (6.6)
Drug withdrawn, n (%)	9 (2.7)	4 (2.2)	5 (3.3)
Dose not changed, n (%)	279 (84.0)	156 (86.2)	123 (81.5)
Not applicable, n (%)	26 (7.8)	13 (7.2)	13 (8.6)
Unknown, n (%)	1 (1)	1 (0.6)	0 (0)

Table S3: Mean change in serum potassium over time by baseline potassium levels.

Baseline potassium	N Cana/Placebo	Mean baseline potassium (mmol/L [SD])		LS mean change in potassium (mmol/L [SE])		Difference (95% CI)	P interaction
		Cana	Placebo	Cana	Placebo		
<4.0	283/295	3.7 (0.2)	3.7 (0.2)	0.47 (0.02)	0.47 (0.02)	-0.0028 (-0.054, 0.048)	0.95
4.0-4.5	912/927	4.3 (0.2)	4.3 (0.2)	0.28 (0.01)	0.27 (0.01)	0.0043 (-0.022, 0.031)	
>4.5-5.0	671/626	4.8 (0.1)	4.8 (0.1)	0.037 (0.01)	0.042 (0.01)	-0.0049 (-0.038, 0.028)	
>5.0	318/339	5.4 (0.3)	5.4 (0.3)	-0.35 (0.02)	-0.35 (0.02)	-0.0026 (-0.057, 0.051)	

SD: standard deviation; SE: standard error

Table S4. Effects of canagliflozin versus placebo on kidney and cardiovascular outcomes according to baseline potassium

	Events per 1000 patient-years					
	Cana	**Placebo**	**Cana**	**Placebo**	**HR (95% CI)**	**P interaction**
Doubling of serum creatinine, kidney failure, kidney or cardiovascular death						0.03
<4.0	44	40	59.4	51.9	1.21 (0.79-1.86)	
4-4.5	86	117	36.1	49.0	0.72 (0.55-0.96)	
>4.5-5.0	71	104	41.3	66.2	0.61 (0.45-0.83)	
>5.0	44	79	53.4	96.6	0.53 (0.47-0.77)	
Doubling of serum creatinine, kidney failure, or kidney death						0.31
<4.0	28	30	37.8	38.9	1.04 (0.62-1.74)	
4-4.5	44	74	18.5	31.0	0.58 (0.40-0.85)	
>4.5-5.0	49	67	28.5	42.6	0.65 (0.45-0.95)	
>5.0	32	53	38.8	64.9	0.56 (0.36-0.88)	
Cardiovascular death, myocardial infarction, or stroke						0.06
<4.0	41	38	56.1	49.9	1.15 (0.74-1.79)	
4-4.5	82	95	34.9	40.0	0.87 (0.65-1.17)	
>4.5-5.0	64	77	37.7	49.0	0.77 (0.55-1.07)	
>5.0	30	59	36.4	72.4	0.50 (0.32-0.78)	
Cardiovascular death or hospitalization for heart failure						0.14
<4.0	34	35	45.8	45.9	1.03 (0.64-1.65)	
4-4.5	62	88	26.0	36.9	0.70 (0.51-0.97)	
>4.5-5.0	55	72	32.0	45.4	0.70 (0.49-1.00)	
>5.0	28	58	33.4	70.0	0.46 (0.29-0.73)	

HR: hazards ratio; CI: confidence interval.