Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized controlled trials

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Clinical perspective

What is new?

- In this meta-analysis of nearly 50,000 participants from clinical outcome trials of SGLT2 inhibitors in people with type 2 diabetes at high cardiovascular risk and/or with CKD, SGLT2 inhibitors reduced the risk of serious hyperkalemia (serum potassium ≥6.0 mmol/L) with no increased risk of hypokalemia
- The lower risk of hyperkalemia with SGLT2 inhibitors was broadly consistent across a range of participant characteristics, including different levels of kidney function, albuminuria, history of heart failure, and concomitant use of diuretics.

What are the clinical implications?

- Hyperkalemia increases the risk of life-threatening arrythmias, limiting the optimal use of renin-angiotensin-aldosterone system (RAAS) inhibitors and mineralocorticoid receptor antagonists in people with type 2 diabetes with CKD and/or heart failure, especially as kidney function declines
- The reduction in risk of serious hyperkalemia with SGLT2 inhibitors may enable greater use of RAAS inhibitors in people with type 2 diabetes with CKD and/or heart failure

ABSTRACT

Background

Hyperkalemia increases risk of cardiac arrhythmias and death and limits the use of renin-angiotensin-aldosterone system (RAAS) inhibitors and mineralocorticoid receptor antagonists (MRAs), which improve clinical outcomes in people with chronic kidney disease (CKD) and/or systolic heart failure. Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiorenal events in people with type 2 diabetes at high cardiovascular risk or with CKD. However, their effect on hyperkalemia has not been systematically evaluated.

Methods

A meta-analysis was conducted using individual participant data from randomized, double-blind, placebo-controlled clinical outcome trials with SGLT2 inhibitors in people with type 2 diabetes at high cardiovascular risk and/or with CKD, in which serum potassium levels were routinely measured. The primary outcome was time to serious hyperkalemia, defined as central laboratory determine serum potassium ≥6.0 mmol/L, with other outcomes including investigator-reported hyperkalemia events and hypokalemia (serum potassium ≤3.5 mmol/L). Cox regression analyses were performed to estimate treatment effects from each trial with hazards ratios (HR) and corresponding 95% CI pooled using random effects models to obtain summary treatment effects, overall and across key subgroups.

Results

Results from six trials were included comprising 49,875 participants assessing four SGLT2 inhibitors. 1,754 participants developed serious hyperkalemia and an additional 1,119 investigator-reported hyperkalemia events were recorded. SGLT2 inhibitors reduced the risk of serious hyperkalemia (HR 0.84, 95% CI 0.76-0.93), an

effect consistent across studies (P-heterogeneity=0.71). The incidence of investigator-reported hyperkalemia was also lower with SGLT2 inhibitors (HR 0.80, 95% CI 0.68-0.93; P-heterogeneity=0.21). Reductions in serious hyperkalemia were observed across a range of subgroups including baseline kidney function, history of heart failure, RAAS inhibitor, diuretic and MRA use. SGLT2 inhibitors did not increase the risk of hypokalemia (HR 1.04, 95% CI 0.94-1.15; P-heterogeneity=0.42).

Conclusion

SGLT2 inhibitors reduce the risk of serious hyperkalemia in people with type 2 diabetes at high cardiovascular risk and/or with CKD, without increasing the risk of hypokalemia.

INTRODUCTION

Hyperkalemia can occur in people with type 2 diabetes, especially in those with chronic kidney disease (CKD), and is clinically important because it can lead to life-threatening arrythmias.[1,2] In patients with CKD and/or systolic heart failure, renin-angiotensin-aldosterone system (RAAS) inhibitors and mineralocorticoid receptor antagonists (MRAs) are cornerstones of disease modifying therapies to prevent kidney disease progression and heart failure hospitalizations.[3,4] However, these agents frequently cause hyperkalemia, leading to treatment discontinuation, compromising the use of these agents in routine clinical practice, particularly in people with more advanced CKD.[5]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of kidney disease progression and cardiovascular events and extend survival in people with type 2 diabetes and CKD, and independent of diabetes status in patients with heart failure.[6-8] SGLT2 inhibitors may increase distal sodium and water delivery, enhancing the electronegative charge in the tubular lumen that regulates potassium excretion in the distal nephron.[9] Small studies of relatively short duration collectively suggest that SGLT2 inhibitors may reduce the risk of hyperkalemia in people with type 2 diabetes.[10] However, the long-term effect of these agents in preventing hyperkalemia in large clinical trials that recruited heterogeneous patient cohorts with varying background therapies has not been systematically evaluated.

It was hypothesized that SGLT2 inhibitors might reduce the risk of serious hyperkalemia, and therefore a meta-analysis was conducted of randomized, double-

blind, placebo-controlled, clinical outcome trials with SGLT2 inhibitors in people with type 2 diabetes at high cardiovascular risk and/or with CKD.

METHODS

A meta-analysis using individual participant data was conducted of SGLT2 inhibitor randomized, double-blind, placebo-controlled, event-driven clinical outcome trials that enrolled people with type 2 diabetes at high cardiovascular risk and/or with CKD in which serum potassium levels were routinely measured. A literature search of PubMed and MedLine from January 1 2000 to July 1 2021 identified the following trials: EMPA-REG OUTCOME,[11] CANVAS Program (CANVAS and CANVAS-R trials),[12] DECLARE-TIMI 58,[13] VERTIS-CV,[14] CREDENCE[15] and DAPA-CKD.[16] High cardiovascular risk was defined in these trials as either established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors. CKD was defined by the presence of albuminuria based on urinary albumin:creatinine ratio derived from spot urine samples. Only participants with type 2 diabetes were included, and therefore participants without type 2 diabetes who were enrolled in DAPA-CKD were excluded, and data from trials in populations with heart failure with reduced ejection fraction, DAPA-HF and EMPEROR-Reduced, that enrolled participants independent of diabetes status were not included in the primary analyses, but were analyzed and reported in sensitivity analyses.[17,18] Data from trials of sotagliflozin, a combined SGLT1/SGLT2 inhibitor, were also excluded given the differing mechanism of action.

The primary outcome in this meta-analysis was serious hyperkalemia, defined as time-to-first central laboratory determined serum potassium level ≥6.0 mmol/L. The effect of SGLT2 inhibition on time-to-first investigator-reported hyperkalemia was

also assessed. Mild hyperkalemia, defined as central laboratory determined serum potassium ≥5.5 mmol/L was assessed as a sensitivity analysis. Time-to-first central laboratory determined hypokalemia, defined as a serum potassium ≤3.5 mmol/L, and mean change in serum potassium from baseline over time were also assessed.

The effects of SGLT2 inhibitors on the primary and other potassium-related outcomes were analyzed overall and according to the following baseline participant characteristics: glycated hemoglobin (≤8 and >8%), estimated glomerular filtration rate ([eGFR] <60 and ≥60 ml/min/1.73 m^2), urine albumin-to-creatinine ratio ([UACR] <30 and ≥30 mg/g), history of heart failure, use of RAAS inhibitors, diuretics, and MRAs.

Investigators from each of the eligible trials analyzed individual participant data according to the outcome definitions previously described. This was done to ensure that statistical methods and outcomes definitions were applied consistently across all the studies. In each individual trial, the effects of SGLT2 inhibitors were assessed on time-to-first serum potassium ≥6.0 mmol/L and other potassium outcomes using the intention-to-treat population and included all central laboratory values following randomization until the last available measure. Treatment effects from each study, obtained from Cox proportional hazard regression models and expressed as hazards ratios with corresponding 95% confidence intervals (CI), were pooled using the random effects model with the Mantel-Haenszel test. Heterogeneity in treatment effects across trials was assessed using I^2 and P-heterogeneity values obtained from the same random effects model. Heterogeneity in treatment effect estimates across baseline participant subgroups was also assessed using P-heterogeneity values

obtained from a random effects meta-regression approach with restricted maximum likelihood. Mean change in serum potassium from baseline over time was assessed by calculating weighted mean differences and 95% CIs in serum potassium levels at baseline, week 52, 104, 156 and 208, applying an inverse variance random effects model.

In a sensitivity analysis for the primary outcome, we included data from two randomized, double-blind, placebo-controlled clinical outcome trials that recruited participants with heart failure and reduced ejection fraction, irrespective of diabetes status (DAPA-HF and EMPEROR-Reduced) to assess the robustness of our findings in a broader patient population.[19,20]

Analyses were performed using SAS version 9.4, STATA version 16.1 and RevMan version 5.

RESULTS

Data from six randomized, double-blind, placebo-controlled, event-driven clinical outcome trials of four SGLT2 inhibitors were included for analyses, comprising 49,875 participants with median follow up of 2.4 to 4.2 years (Table 1). Four trials were cardiovascular outcome trials conducted in populations with type 2 diabetes at high cardiovascular risk: EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58 and VERTIS-CV. These four trials recruited participants with differing proportions of individuals with established atherosclerotic cardiovascular disease: 44.1% in DECLARE-TIMI 58 to 100% in EMPA-REG OUTCOME and VERTIS-CV. Two trials were primary kidney outcome trials in populations with type 2 diabetes and

albuminuric CKD: CREDENCE and DAPA-CKD, in which most participants had an eGFR <60 with UACR >300 mg/g in CREDENCE and UACR >200 mg/g in DAPA-CKD and all were treated with maximally tolerated or labelled dose of a RAAS inhibitor at baseline if tolerated.

The prevalence of CKD and heart failure, as well as background use of RAAS inhibitors and diuretic therapy varied across the trials (Table 1). The proportion of participants with an eGFR <60 mL/min/1.73 m^2 at baseline varied from 7.4% in DECLARE-TIMI 58 to 88% in DAPA-CKD. Most participants in the cardiovascular outcome trials had a UACR <30 mg/g at baseline (60.4% in EMPA-REG OUTCOME to 70.2% in the CANVAS Program), whilst all participants in CREDENCE and DAPA-CKD had a UACR ≥30 mg/g. The prevalence of heart failure at baseline ranged from 10.1% in DECLARE-TIMI 58 to 23.7% in VERTIS-CV. More than 80% of participants in the cardiovascular outcome trials were treated with RAAS inhibitors at baseline, while virtually all participants in CREDENCE and DAPA-CKD received this treatment by virtue of the inclusion criteria of the kidney outcome trials. A substantial portion of participants in both kidney and cardiovascular outcome trials were receiving diuretic therapy at baseline (40.6% in DECLARE-TIMI 58 to 50.4% in DAPA-CKD). Use of MRAs varied from 0.5% in CREDENCE to 8.2% in VERTIS-CV.

Across all included trials, 1,754 participants developed serious hyperkalemia and 1,119 investigator-reported hyperkalemia events were recorded. The incidence of serious hyperkalemia was substantially higher in the kidney outcome trials (27.9 and 65.3 events per 1000 patient-years in placebo treated participants in CREDENCE and DAPA-CKD respectively; Figure 1) in comparison to the cardiovascular outcome

trials (between 9.2 and 21.2 events per 1000 patient-years in placebo treated participants; Figure 1).

SGLT2 inhibitors reduced the risk of serious hyperkalemia by 16% (HR 0.84, 95% CI 0.76-0.93; Figure 1), an effect consistent across trials (P-heterogeneity=0.71). This effect was unchanged in a sensitivity analysis that included data from DAPA-HF and EMPEROR-Reduced, two randomized trials in people with heart failure with reduced ejection fraction with and without type 2 diabetes (HR 0.82, 95% CI 0.75-0.90, P-heterogeneity=0.65; Figure S1). In an additional sensitivity analysis, the incidence of mild hyperkalemia (central laboratory determine serum potassium ≥5.5 mmol/L) was also modestly lower with SGLT2 inhibitors (HR 0.91, 95% CI 0.84-0.99, P-heterogeneity=0.02; Figure S2). SGLT2 inhibitors reduced the risk of investigator-reported hyperkalemia events by 20%, an effect consistent across trials (HR 0.80, 95% CI 0.68-0.93; P-heterogeneity=0.21; Figure 2).

The incidence of serious hyperkalemia was higher in participants with eGFR <60 mL/min/1.73 m^2, a history of heart failure and in those using MRAs at baseline (Table S1). The relative effect of SGLT2 inhibitors on serious hyperkalemia was consistent across different levels of HbA1c, eGFR, UACR, history of heart failure, and use of MRAs and diuretic therapy (all P-heterogeneity ≥0.19; Figure 3). The beneficial effect of SGLT2 inhibition on serious hyperkalemia appeared larger in participants not receiving RAAS inhibitors at baseline (P-heterogeneity=0.002; Figure 3) but was separately statistically significant for those receiving and not receiving RAAS inhibitors (Figure 3). Additional analyses of the two kidney outcome trials, CREDENCE and DAPA-CKD, using more granular eGFR categories (eGFR <45, 45-

<60 and ≥60 mL/min/1.73 m^2) demonstrated considerably higher incidence of serious hyperkalemia with worsening kidney function (event rates in placebo treated participants increasing across lower eGFR categories from 14.2 to 46.4 and 30.0 to 86.5 per 1000 patient-years in CREDENCE and DAPA-CKD respectively), and consistent relative risk reductions for hyperkalemia for SGLT2 inhibitors across all eGFR categories (P-heterogeneity =0.27; Figure 4). In further sensitivity analyses, the inclusion of data from two trials in populations with heart failure with reduced ejection fraction (DAPA-HF and EMPEROR-Reduced) yielded consistent results for subgroup analyses by heart failure status and use of MRAs (both P-heterogeneity ≥0.57; Figure S3). Similarly consistent findings were observed across subgroups for the outcome of investigator reported hyperkalemia (Figure S4 and Table S2).

SGLT2 inhibitors did not affect the risk of central laboratory determined hypokalemia (HR 1.04, 95% 0.94-1.15; Figure 5), a lack of effect consistent across trials (P-heterogeneity=0.42). Individuals receiving diuretics experienced a high rate of hypokalemia (Table S3). The neutral effect of SGLT2 inhibitors on central laboratory determined hypokalemia was consistent across a range of participant characteristics, including those receiving diuretics (P-heterogeneity ≥0.13; Figure 6 and Table S3).

The mean difference in serum potassium from baseline was modestly lower in participants randomized to SGLT2 inhibition compared to placebo at annual visits up to 4 years post-randomization (Figure 7 and Table S4).

DISCUSSION

In this meta-analysis of SGLT2 inhibitor trials enrolling participants with type 2 diabetes at high cardiovascular risk and/or with CKD, using individual patient level data, we observed that SGLT2 inhibitors consistently reduced the risk of serious hyperkalemia, defined as central laboratory-determined serum potassium ≥6.0 mmol/L, with a similarly significant reduction in the incidence of investigator reported hyperkalemia events. Additionally, no increased risk of hypokalemia was observed. Relative risk reductions were broadly consistent across a range of clinically important subgroups, including baseline kidney function, history of heart failure and use of MRAs and diuretics, and similar for different studies and agents within the class. Given that people with type 2 diabetes with CKD and/or heart failure are at substantially higher risk of serious hyperkalemia, absolute reductions in hyperkalemia with SGLT2 inhibitors are likely to be larger in these populations. These findings have important implications for the care of people with type 2 diabetes with CKD and/or heart failure, given that hyperkalemia is a major factor limiting the optimal use of RAAS inhibitors, which form the basis of disease modifying therapy in these populations.[21,22]

This study extends previous work that suggested that SGLT2 inhibitors might reduce the risk of hyperkalemia. A previous meta-analysis of randomized trials observed that the risk of hyperkalemia was lower with SGLT2 inhibitors compared with placebo in people with type 2 diabetes.[10] However, this meta-analysis included generally small studies of short duration and did not assess serial, centrally measured serum potassium levels. Data from the CREDENCE trial demonstrated that the SGLT2 inhibitor canagliflozin reduced the incidence of investigator reported hyperkalemia events or the initiation of potassium binders in people with type 2 diabetes and

CKD.[9] However, whether benefits for hyperkalemia are similar for different agents within the SGLT2 inhibitor class and consistent across heterogenous populations with varying background risk and concomitant therapies has been uncertain. This study provides substantive evidence that SGLT2 inhibition reduces the risk of serious hyperkalemia across diverse subgroups of individuals with type 2 diabetes, without increasing the risk of hypokalemia.

People with type 2 diabetes are prone to hyperkalemia, particularly when using RAAS inhibitors, at least partly due coexisting type 4 renal tubular acidosis.[23] There are at least three possible mechanisms by which SGLT2 inhibitors might prevent the development of hyperkalemia. Firstly, SGLT2 inhibitors might increase the rate of sodium and water delivery to the distal nephron, which are key regulators of potassium handling by the kidney.[24] Enhanced sodium reabsorption at the principal cell in the cortical collecting duct increases the electronegative charge in the tubules which promotes potassium excretion. Secondly, aldosterone is another key regulator of potassium handling by the kidney, and there is some evidence that SGLT2 inhibitors may modestly increase aldosterone, therefore promoting kaliuresis, at least in the short term.[25-27] Thirdly, the reduction in incidence of hyperkalemia with SGLT2 inhibitors may be due to preservation of kidney function rather than any direct effects on tubular function per se. Finally, reductions in hyperkalemia with SGLT2 inhibition may be due to as yet unrecognized mechanism outside of the kidney.

The beneficial effect of SGLT2 inhibitors on serious hyperkalemia contrasts with RAAS inhibitors and MRAs, which increase the risk of hyperkalemia, raising the possibility that SGLT2 inhibitors may enable more optimal use of these therapies. In

CKD, hyperkalemia is a major factor limiting the optimal use and dosing of RAAS inhibitors. Similarly in heart failure, use of MRAs is limited partly due to hyperkalemia, especially as kidney function declines. The FIDELIO and FIGARO trials recently demonstrated that finerenone, a selective non-steroidal MRA, slows the progression of CKD and prevent cardiovascular events in people with type 2 diabetes and albuminuric CKD.[28] However, like steroidal MRAs, finerenone also increased the risk of hyperkalemia. The benefits of finerenone raise the question of what therapies form the standard-of-care for people with type 2 diabetes and CKD, for whom major international clinical practice guidelines recommend combination use of RAAS inhibitors and SGLT2 inhibitors.[29-31] In FIDELIO, reductions in albuminuria were similar in those receiving and not receiving SGLT2 inhibitors, suggesting additional benefits of finerenone when combined with SGLT2 inhibitors. Additionally, the incidence of hyperkalemia with finerenone was lower in those receiving SGLT2 inhibitors, suggesting a potential safety advantage of combining both agents.[32] In this context, the results of this meta-analysis raise the possibility that SGLT2 inhibitors could facilitate greater use of RAAS inhibitors and MRAs for people with CKD and/or heart failure, therefore potentially further improving cardiorenal outcomes for people with type 2 diabetes.

The main strength of these analyses lies in the use of individual participant data, ensuring consistency in methodology and outcome definitions and allowing time-to-event analyses. While a lower incidence of investigator reported hyperkalemia events was previously reported in EMPA-REG OUTCOME and CREDENCE,[9,33] the use of serial, centrally measured serum potassium analyses to assess the effect on hyperkalemia provides greater confidence with respect to the robustness of the

conclusions. Another strength is the inclusion of the largest number of individuals with CKD of any SGLT2 inhibitor study to date - almost all of whom were treated with RAAS inhibitors - who are among those at highest risk for serious hyperkalemia. Finally, the large sample size and long follow-up duration increased the precision of effect estimates and allowed the examination of the consistency of effects across multiple clinically relevant subgroups.

These analyses have limitations that need to be considered when interpreting these findings. While background use of RAAS inhibitors was universally high, there were relatively few participants receiving MRAs (CREDENCE excluded these individuals due to early concerns about the risk of hyperkalemia with canagliflozin). However, sensitivity analyses incorporating published data from EMPEROR-Reduced and DAPA-HF indicate that the benefits of SGLT2 inhibitors on serious hyperkalemia were similar regardless of MRA use. Because of the differences in trial follow-up procedures, we were unable to identify the exact time at which individuals developed hyperkalemia. Further work evaluating the time frame over which SGLT2 inhibitors reduce the risk of hyperkalemia may yield additional insights into the relative contribution of different mechanisms (preservation of kidney function versus direct effects on tubular potassium handling. Finally, the effects of SGLT2 inhibitors on incident hyperkalemia in people without diabetes, as well as the mechanisms underpinning these benefits are not known and are clearly an important area for future study.

In summary, SGLT2 inhibitors reduce the risk of serious hyperkalemia in people with type 2 diabetes at high cardiovascular risk or with CKD without increasing the risk of hypokalemia.

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Tables and figures

Table 1. Baseline characteristics of included SGLT2 inhibitor cardiovascular and kidney outcome trials people in people with type 2 diabetes at high cardiovascular risk and/or with chronic kidney disease

Figure 1. Effects of SGLT2 inhibitors on serious hyperkalemia (central laboratory determined serum potassium ≥6.0 mmol/L)

Figure 2. Effect of SGLT2 inhibitors on time to first investigator-reported hyperkalemia event

Figure 3. Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory determined serum potassium ≥6.0 mmol/L) according to baseline participant characteristics

Figure 4. Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory determined serum potassium ≥6.0 mmol/L) across the spectrum of kidney function in CREDENCE and DAPA-CKD

Figure 5. Effect of SGLT2 inhibitors on hypokalemia (central laboratory determined serum potassium ≤3.5 mmol/L)

Figure 6. Effect of SGLT2 inhibitors on hypokalemia (central laboratory determined serum potassium ≤3.5 mmol/L) according to baseline participant characteristics

Figure 7. Mean change from baseline in serum potassium over time

Table 1. Baseline characteristics of included SGLT2 inhibitor cardiovascular and kidney outcome trials in people with type 2 diabetes at high cardiovascular risk and/or with chronic kidney disease

	CANVAS Program (n=10142)	CREDENCE (n=4401)	DAPA-CKD[±] (n=2906)	DECLARE-TIMI 58 (n=17160)	EMPA-REG OUTCOME (n=7020)	VERTIS CV (n=8246)
SGLT2 inhibitor	Canagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Median follow-up (years, IQR)	2.4 (2.0, 6.0)	2.6 (2.1, 3.1)	2.4 (2.1, 2.7)	4.2 (3.9, 4.4)	3.1 (2.2, 3.6)	3.0 (0.1, 5.9)[†]
Women (%)	3633 (35.8)	1494 (33.9)	965 (33.2)	6422 (37.4)	2004 (28.5)	2477 (30.0)
Mean age (years, SD)	63.3 (8)	63.0 (9)	64.4 (10)	63.8 (7)	63.1 (9)	64.4 (8)
Established CV disease (%)	6656 (65.6)	2220 (50.4)	1281 (44.1)	6974 (40.6)	7020 (100)	8246 (100)
History of heart failure (%)	1461 (14.4)	652 (14.8)	361 (12.4)	1724 (10.0)	706 (10.1)	1958 (23.7)
Mean HbA1c (%, SD)	8.2 (0.9)	8.3 (1.3)	7.8 (1.7)	8.3 (1.2)	8.1 (0.8)	8.2 (0.9)
eGFR <60ml/min/1.73m^2* (%)	2039 (20.1)	2631 (59.8)	2558 (88.0)	1265 (7.4)	1819 (25.9)	1807 (21.9)
UACR ≥30 mg/g (%)	3026 (29.8)	4401 (100)	2905 (100)	5199 (30.3)	2782 (39.6)	3247 (39.4)
Use of RAAS inhibitors (%)	8116 (80.0)	4395 (99.9)	2852 (98.1)	13950 (81.3)	5666 (80.7)	6686 (81.1)
Use of MRAs (%)	192 (1.9)	35 (0.8)	171 (5.9)	762 (4.4)	441 (6.3)	673 (8.2)
Use of diuretics (%)	4490 (44.3)	2057 (46.7)	1465 (50.4)	6967 (40.6)	3035 (43.2)	3539 (43.2)

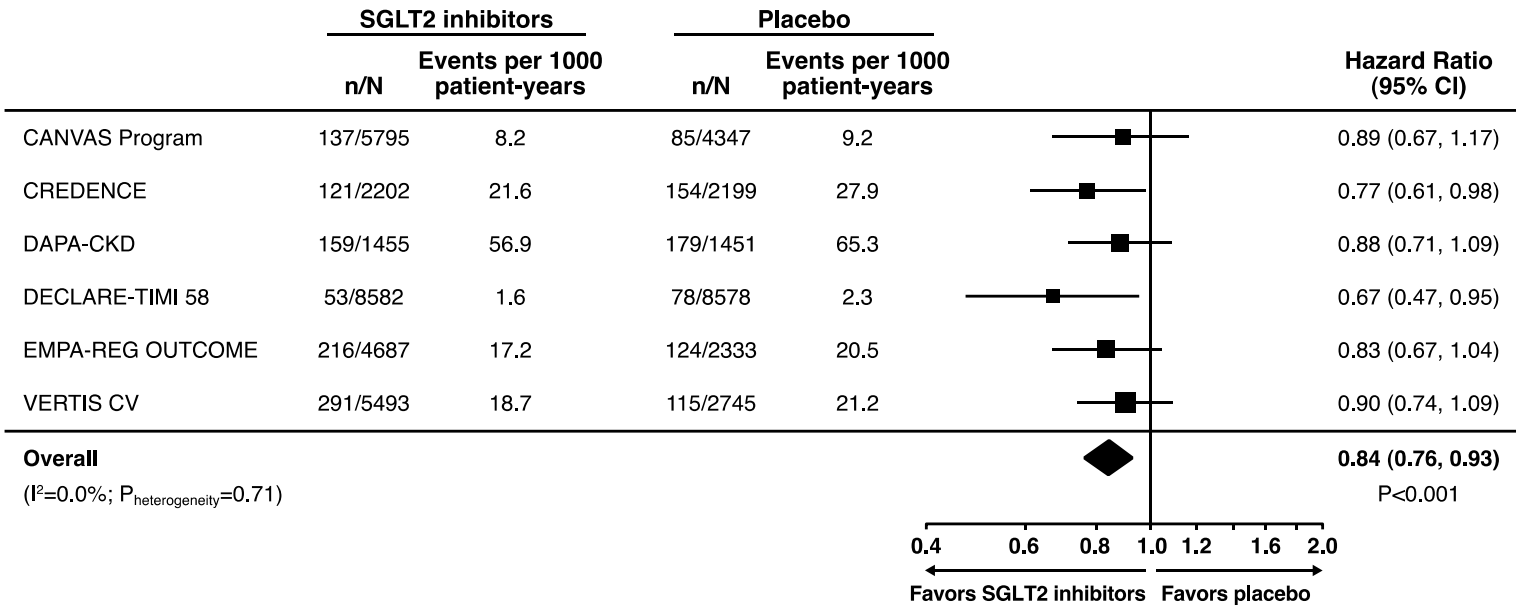
Abbreviations: CANVAS: Canagliflozin Cardiovascular Assessment Study; CREDENCE: Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DAPA-CKD: Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE-TIMI 58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; SGLT2, sodium-glucose cotransporter 2; VERTIS CV: Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease; IQR: interquartile range; SD: standard deviation; CV: cardiovascular; HbA1c: glycated hemoglobin; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; RAAS: renin–angiotensin-aldosterone system; MRAs: mineralocorticoid receptor antagonists;.

*Based on the MDRD (Modification of Diet in Renal Disease equation) equation in the CANVAS Program, EMPA-REG OUTCOME and VERTIS CV and on the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation) equation in CREDENCE and DECLARE–TIMI 58.

[†]Range of follow-up

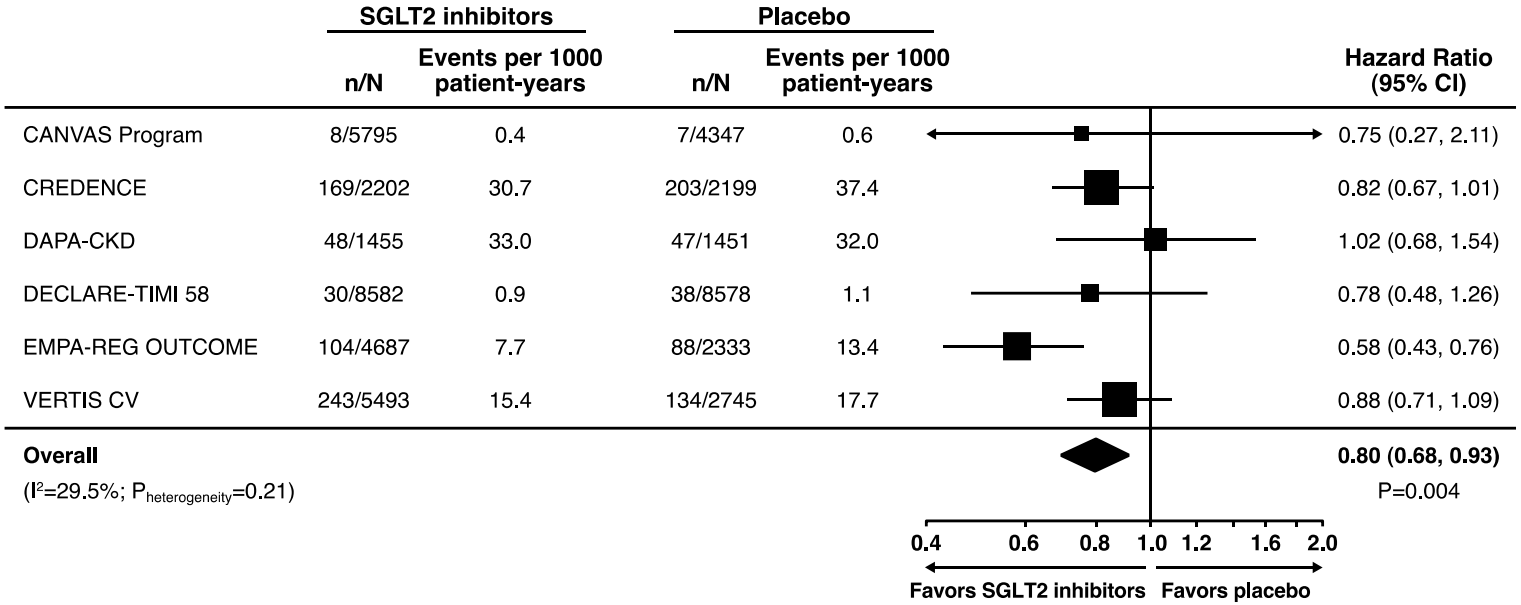
[±] Baseline characteristics for the 2906 (68%) of the DAPA-CKD participants with type 2 diabetes at baseline

Figure 1. Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory determined serum potassium ≥6.0 mmol/L)



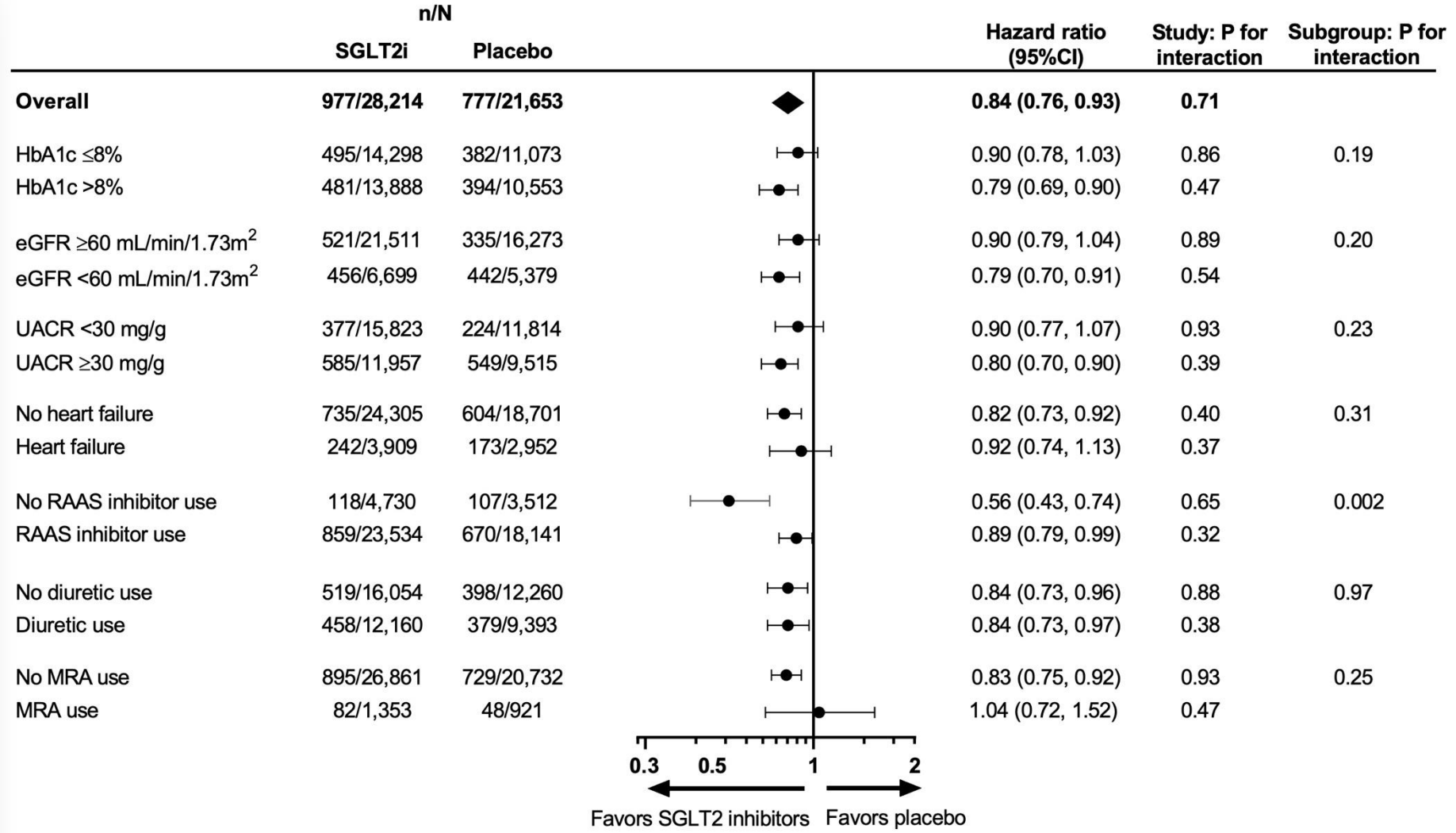
SGLT2: sodium glucose cotransporter 2; CI: confidence interval.

Figure 2. Effect of SGLT2 inhibitors on time to first investigator-reported hyperkalemia event



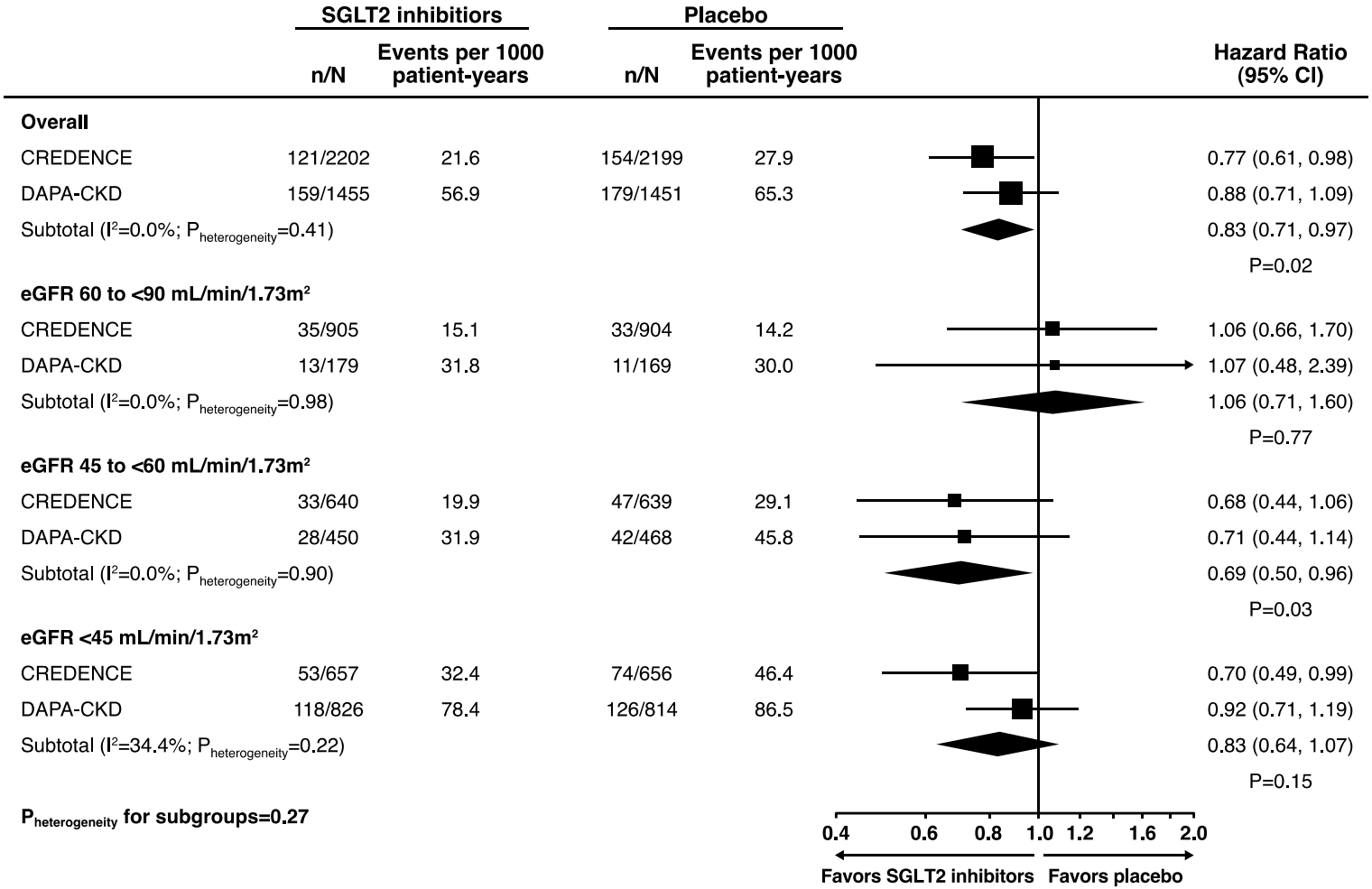
SGLT2: sodium glucose cotransporter 2; CI: confidence interval.

Figure 3. Effect of SGLT2 inhibitors on serious hyperkalemia (serum potassium ≥6.0 mmol/L) according to baseline participant characteristics



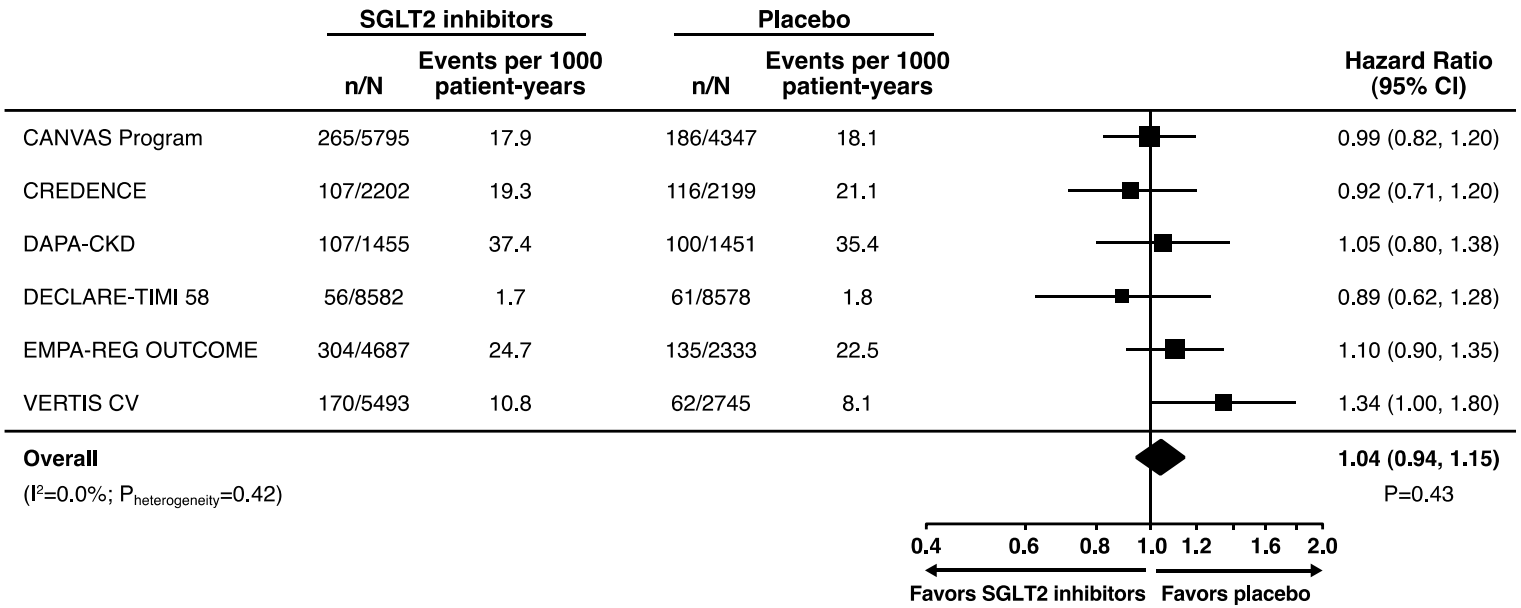
SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio; RAAS: renin-angiotensin-aldosterone system; MRA: mineralocorticoid receptor antagonist.

Figure 4**.** Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory determined serum potassium ≥6.0 mmol/L) across the spectrum of kidney function in CREDENCE and DAPA-CKD



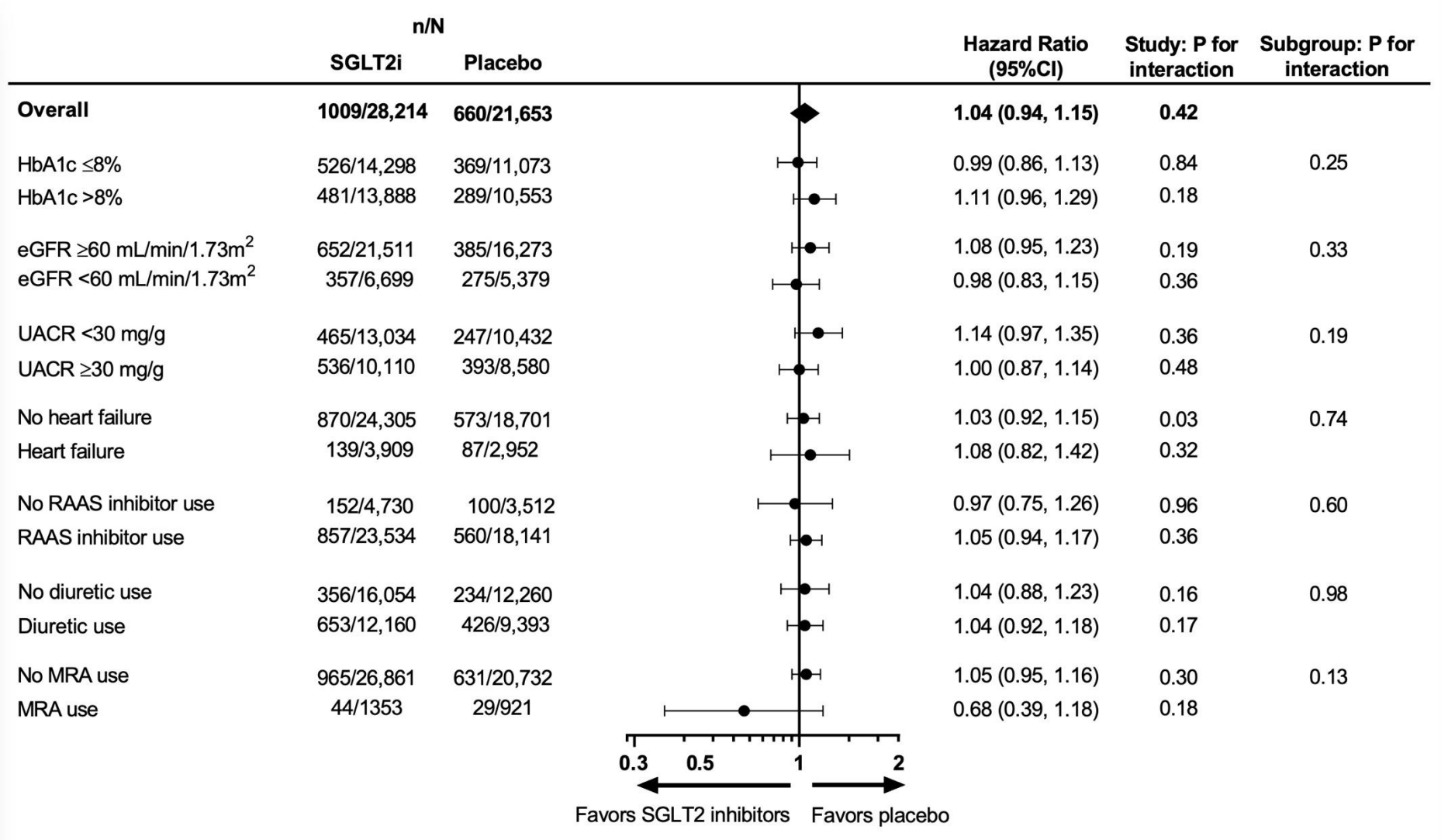
SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval; eGFR: estimated glomerular filtration rate.

Figure 5. Effect of SGLT2 inhibitors on hypokalemia (central laboratory determined serum potassium ≤3.5 mmol/L)



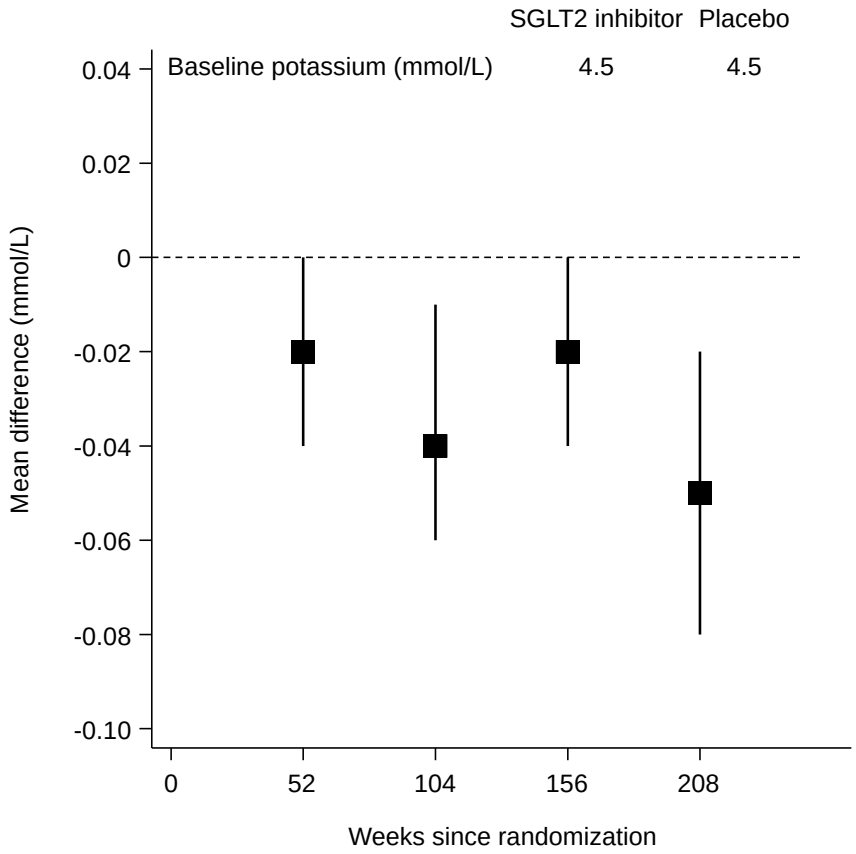
SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval.

Figure 6. Effect of SGLT2 inhibitors on hypokalemia (central laboratory determined serum potassium ≤3.5 mmol/L) according to baseline participant characteristics



SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio; RAAS: renin-angiotensin-aldosterone system; MRA: mineralocorticoid receptor antagonist.

Figure 7. Mean change from baseline in serum potassium over time



Number of participants					
SGLT2 inhibitor	27970	17672	14490	11133	7354
Placebo	21423	11950	9518	4222	5031

SGLT2: sodium glucose cotransporter 2.

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Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized controlled trials

Supplementary appendix

Table S1. Effect of SGLT2 inhibitors on serious hyperkalemia (serum potassium ≥6.0 mmol/L) according to baseline participant characteristics

	SGLT2 inhibitors		Placebo			
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	Hazard ratio (95%CI)	Subgroup: P for interaction
Hba1c ≤8%						0.19
CANVAS Program	59/2744	8.2	36/2089	7.1	0.91 (0.59–1.39)	
CREDENCE	67/1097	23.8	79/1098	28.3	0.83 (0.60–1.15)	
DAPA-CKD	99/943	55.6	113/923	65.6	0.85 (0.65–1.12)	
DECLARE-TIMI 58	23/4372	1.3	30/4367	1.7	0.75 (0.43–1.29)	
EMPA-REG OUTCOME	118/2528	17.5	53/1241	16.4	1.07 (0.78–1.48)	
VERTIS-CV	129/2614	17.3	71/1355	19.3	0.91 (0.68–1.22)	
Subtotal					0.90 (0.78–1.03)	
(I^2=0.0%; $P_{heterogeneity}$=0.86)					p=0.12	
Hba1c >8%						
CANVAS Program	78/3051	10.0	49/2258	9.3	0.86 (0.60–1.25)	
CREDENCE	54/1104	19.4	74/1100	27.1	0.71 (0.50–1.01)	
DAPA-CKD	60/508	59.8	66/519	66.1	0.94 (0.66–1.33)	
DECLARE-TIMI 58	30/4208	1.8	48/4207	3.0	0.62 (0.39–0.98)	
EMPA-REG OUTCOME	98/2157	16.9	71/1092	25.2	0.66 (0.49–0.90)	
VERTIS-CV	161/2860	20.0	86/1377	23.2	0.88 (0.68–1.14)	
Subtotal					0.79 (0.69–0.90)	
(I^2=0.0%; $P_{heterogeneity}$=0.47)					P=0.001	
eGFR ≥60						0.20
CANVAS Program	97/4684	7.9	57/3417	6.9	0.90 (0.65–1.26)	
CREDENCE	35/905	15.1	33/904	14.2	1.06 (0.66–1.70)	
DAPA-CKD	13/179	31.8	11/169	30.0	1.07 (0.48–2.40)	
DECLARE-TIMI 58	45/7975	1.4	60/7919	1.9	0.74 (0.50–1.08)	
EMPA-REG OUTCOME	127/3473	13.4	67/1726	14.6	0.90 (0.67–1.21)	
VERTIS-CV	204/4295	16.3	107/2138	18.0	0.92 (0.73–1.16)	
Subtotal					0.90 (0.79–1.04)	
(I^2=0.0%; $P_{heterogeneity}$=0.89)					p=0.14	
eGFR <60						
CANVAS Program	40/1110	14.9	28/929	13.3	0.93 (0.57–1.53)	
CREDENCE	86/1297	26.1	121/1295	37.7	0.69 (0.53–0.91)	
DAPA-CKD	146/1276	61.2	168/1282	70.8	0.87 (0.69–1.08)	
DECLARE-TIMI 58	8/606	3.4	18/659	7.2	0.46 (0.20–1.06)	
EMPA-REG OUTCOME	89/1212	28.8	57/607	38.6	0.75 (0.54–1.05)	
VERTIS-CV	87/1198	28.9	50/607	34.1	0.87 (0.62–1.23)	
Subtotal					0.79 (0.70–0.91)	
(I^2=0.0%; $P_{heterogeneity}$=0.54)					P=0.001	
UACR <30 mg/g						0.23
CANVAS Program	75/4012	7.2	52/2995	7.2	0.82 (0.57–1.17)	
CREDENCE	2/16	49.6	0/15	NA	NA	
DAPA-CKD	0/1	NA	0/0	NA	NA	
DECLARE-TIMI 58	29/5819	1.3	33/5825	1.4	0.86 (0.52–1.42)	
EMPA-REG OUTCOME	115/2789	15.2	58/1382	15.8	0.94 (0.69–1.29)	
VERTIS-CV	156/3186	17.0	81/1597	18.3	0.94 (0.72–1.23)	
Subtotal					0.90 (0.77–1.07)	
(I^2=0.0%; $P_{heterogeneity}$=0.93)					p=0.24	
UACR ≥30 mg/g						
CANVAS Program	58/1699	13.6	33/1270	11.3	0.91 (0.59–1.42)	
CREDENCE	119/2186	21.4	154/2184	28.1	0.76 (0.60–0.96)	
DAPA-CKD	159/1454	57.0	179/1451	65.3	0.88 (0.71–1.10)	
DECLARE-TIMI 58	23/2611	2.3	45/2588	4.5	0.50 (0.30–0.83)	
EMPA-REG OUTCOME	98/1847	20.2	66/935	28.2	0.72 (0.53–0.99)	
VERTIS-CV	128/2160	21.5	72/1087	25.7	0.86 (0.65–1.15)	
Subtotal					0.80 (0.70–0.90)	
(I^2=3.8%; $P_{heterogeneity}$=0.39)					p<0.001	
Heart failure No						0.31
CANVAS Program	107/4992	8.2	62/3689	7.0	0.90 (0.65–1.24)	
CREDENCE	86/1873	17.9	129/1876	27.3	0.66 (0.50–0.86)	
DAPA-CKD	135/1278	55.0	149/1267	62.0	0.90 (0.71–1.14)	
DECLARE-TIMI 58	41/7730	1.3	62/7706	2.0	0.65 (0.44–0.97)	
EMPA-REG OUTCOME	190/4225	16.6	104/2089	18.9	0.88 (0.69–1.11)	
VERTIS-CV	176/4207	14.6	98/2074	17.3	0.85 (0.67–1.09)	
Subtotal					0.82 (0.73–0.92)	
(I^2=2.4%; $P_{heterogeneity}$=0.40)					P<0.001	
Heart failure Yes						
CANVAS Program	30/803	15.4	23/658	15.5	0.87 (0.50–1.52)	

CREDENCE	35/329	43.8	25/323	31.4	1.37 (0.82–2.29)	
DAPA-CKD	24/177	71.1	30/184	89.3	0.77 (0.45–1.31)	
DECLARE-TIMI 58	12/852	3.7	16/872	4.9	0.78 (0.37–1.65)	
EMPA-REG OUTCOME	26/462	23.1	20/244	37.1	0.60 (0.34–1.08)	
VERTIS-CV	115/1286	33.4	59/671	33.6	1.01 (0.74–1.39)	
Subtotal					0.92 (0.74–1.13)	
(I^2=7.4%; $P_{heterogeneity}$=0.37)					p=0.42	
RAAS inhibitor use No						0.002
CANVAS Program	16/1150	5.4	15/876	7.3	0.51 (0.24–1.11)	
CREDENCE	0/1	NA	1/5	83.3	NA	
DAPA-CKD	4/36	61.0	4/53	42.2	NA	
DECLARE-TIMI 58	8/1605	1.3	11/1605	1.8	0.74 (0.30–1.84)	
EMPA-REG OUTCOME	31/889	12.9	34/465	28.1	0.45 (0.28–0.73)	
VERTIS-CV	59/1049	19.9	42/508	31.0	0.64 (0.43–0.96)	
Subtotal					0.56 (0.43–0.74)	
(I^2=0.0%; $P_{heterogeneity}$=0.65)					p<0.001	
RAAS inhibitor use Yes						
CANVAS Program	121/4645	10.1	70/3471	8.5	1.00 (0.74–1.35)	
CREDENCE	121/2201	21.6	153/2194	27.8	0.77 (0.61–0.98)	
DAPA-CKD	155/1419	56.8	175/1398	66.2	0.87 (0.70–1.07)	
DECLARE-TIMI 58	45/6977	1.6	67/6973	2.4	0.66 (0.45–0.96)	
EMPA-REG OUTCOME	185/3798	18.2	90/1868	18.6	0.98 (0.76–1.26)	
VERTIS-CV	232/4444	18.5	115/2237	19.0	0.99 (0.79–1.24)	
Subtotal					0.89 (0.79–0.99)	
(I^2=14.7%; $P_{heterogeneity}$=0.32)					p=0.04	
Diuretic use No						0.97
CANVAS Program	75/3259	9.0	43/2393	7.6	0.93 (0.63–1.37)	
CREDENCE	64/1176	21.6	73/1168	25.2	0.84 (0.60–1.17)	
DAPA-CKD	66/737	47.3	86/704	65.4	0.72 (0.53–1.00)	
DECLARE-TIMI 58	30/5094	1.5	40/5099	2.0	0.74 (0.46–1.19)	
EMPA-REG OUTCOME	119/2640	16.7	67/1345	18.9	0.86 (0.64–1.17)	
VERTIS-CV	165/3148	18.4	89/1551	20.6	0.90 (0.70–1.17)	
Subtotal					0.84 (0.73–0.96)	
(I^2=0.0%; $P_{heterogeneity}$=0.88)					p=0.01	
Diuretic use Yes						
CANVAS Program	62/2536	9.4	42/1954	9.0	0.84 (0.56–1.25)	
CREDENCE	57/1026	21.6	81/1031	30.8	0.70 (0.50–0.99)	
DAPA-CKD	93/718	66.6	93/747	65.3	1.04 (0.78–1.38)	
DECLARE-TIMI 58	23/3488	1.7	38/3479	2.8	0.59 (0.35–1.00)	
EMPA-REG OUTCOME	97/2047	17.9	57/988	22.7	0.80 (0.58–1.11)	
VERTIS-CV	126/2345	19.2	68/1194	22.0	0.90 (0.67–1.21)	
Subtotal					0.84 (0.73–0.97)	
(I^2=5.4%; $P_{heterogeneity}$=0.38)					p=0.02	
MRA use No						0.25
CANVAS Program	130/5666	8.9	83/4284	8.2	0.87 (0.66–1.15)	
CREDENCE	121/2182	21.8	154/2184	28.1	0.77 (0.61–0.98)	
DAPA-CKD	146/1373	55.3	166/1362	64.4	0.87 (0.69–1.08)	
DECLARE-TIMI 58	51/8215	1.6	70/8183	2.2	0.72 (0.50–1.03)	
EMPA-REG OUTCOME	194/4382	16.5	114/2197	19.9	0.82 (0.65–1.04)	
VERTIS-CV	253/5043	17.6	142/2522	20.8	0.86 (0.70–1.06)	
Subtotal					0.83 (0.75–0.92)	
(I^2=0.0%; $P_{heterogeneity}$=0.93)					P<0.001	
MRA use Yes						
CANVAS Program	7/129	18.5	2/63	11.1	1.46 (0.29–7.24)	
CREDENCE	0/20	NA	0/15	NA	NA	
DAPA-CKD	13/82	84.1	13/89	79.2	1.16 (0.53–2.51)	
DECLARE-TIMI 58	2/367	1.4	8/395	5.4	0.26 (0.05–1.23)	
EMPA-REG OUTCOME	22/305	28.7	10/136	31.7	0.92 (0.44–1.95)	
VERTIS-CV	38/450	32.1	15/223	26.4	1.23 (0.68–2.24)	
Subtotal					1.04 (0.72–1.52)	
(I^2=0.0%; $P_{heterogeneity}$=0.47)					p=0.83	

Table S2. Effect of SGLT2 inhibitors on investigator reported hyperkalemia events according to baseline participant characteristics

	SGLT2 inhibitors		Placebo			
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	Hazard ratio (95%CI)	Subgroup: P for interaction
Hba1c ≤8%						0.88
CANVAS Program	3/2744	0.3	5/2089	0.9	0.47 (0.11–1.99)	
CREDENCE	80/1097	28.7	108/1098	39.7	0.72 (0.54–0.97)	
DAPA-CKD	28/943	30.0	31/923	34.0	0.88 (0.52–1.48)	
DECLARE-TIMI 58	14/4372	0.8	19/4367	1.1	0.72 (0.36–1.44)	
EMPA-REG OUTCOME	58/2528	8.0	43/1241	12.4	0.65 (0.44–0.97)	
VERTIS-CV	111/2614	14.6	51/1355	13.5	1.10 (0.79–1.53)	
Subtotal					0.80 (0.66–0.98)	
(I^2=14.6%; $P_{heterogeneity}$=0.32)					P=0.03	
Hba1c >8%						
CANVAS Program	5/3051	0.5	2/2258	0.4	1.36 (0.26–7.19)	
CREDENCE	89/1104	32.8	94/1100	34.7	0.94 (0.70–1.25)	
DAPA-CKD	20/508	39.0	16/519	31.0	1.29 (0.66–2.55)	
DECLARE-TIMI 58	16/4208	1.0	19/4207	1.2	0.84 (0.43–1.63)	
EMPA-REG OUTCOME	46/2157	7.4	45/1092	14.6	0.50 (0.33–0.76)	
VERTIS-CV	131/2860	16.0	82/1377	21.8	0.74 (0.56–0.98)	
Subtotal					0.80 (0.62–1.03)	
(I^2=42.4%; $P_{heterogeneity}$=0.12)					P=0.08	
eGFR ≥60						0.65
CANVAS Program	2/4684	0.1	5/3417	0.5	0.26 (0.05–1.40)	
CREDENCE	43/905	18.7	58/904	25.4	0.73 (0.50–1.09)	
DAPA-CKD	3/179	17.0	1/169	6.0	2.86 (0.36–58.20)	
DECLARE-TIMI 58	22/7975	0.7	25/7919	0.8	0.86 (0.49–1.53)	
EMPA-REG OUTCOME	51/3473	5.1	40/1726	8.2	0.62 (0.41–0.95)	
VERTIS-CV	165/4295	12.9	92/2138	15.2	0.86 (0.67–1.11)	
Subtotal					0.78 (0.65–0.93)	
(I^2=0.0%; $P_{heterogeneity}$=0.46)					P=0.006	
eGFR <60						
CANVAS Program	6/1110	2.0	2/929	0.9	2.11 (0.42–10.60)	
CREDENCE	126/1297	39.4	145/1295	46.1	0.86 (0.68–1.09)	
DAPA-CKD	45/1276	35.0	46/1282	36.0	0.98 (0.65–1.49)	
DECLARE-TIMI 58	8/606	3.4	13/659	5.2	0.68 (0.28–1.64)	
EMPA-REG OUTCOME	53/1212	15.5	48/607	29.1	0.53 (0.36–0.79)	
VERTIS-CV	78/1198	25.5	42/607	27.8	0.93 (0.64–1.35)	
Subtotal					0.82 (0.65–1.02)	
(I^2=33.6%; $P_{heterogeneity}$=0.18)					p=0.07	
UACR <30 mg/g						0.58
CANVAS Program	2/4012	0.2	4/2995	0.5	0.32 (0.06–1.81)	
CREDENCE	2/16	53.0	2/15	58.1	0.78 (0.58–1.06)	
DAPA-CKD	0/1	0	0/0	0	NA	
DECLARE-TIMI 58	14/5819	0.6	21/5825	0.9	0.66 (0.34–1.30)	
EMPA-REG OUTCOME	44/2789	5.5	32/1382	8.1	0.68 (0.43–1.06)	
VERTIS-CV	115/3186	12.2	68/1597	15.1	0.82 (0.61–1.11)	
Subtotal					0.76 (0.63–0.91)	
(I^2=0.0%; $P_{heterogeneity}$=0.80)					P=0.003	
UACR ≥30 mg/g						
CANVAS Program	6/1699	1.2	2/1270	0.6	2.09 (0.42–10.55)	
CREDENCE	167/2186	30.6	201/2184	37.3	0.82 (0.67–1.01)	
DAPA-CKD	48/1454	33.0	47/1451	32.0	1.02 (0.68–1.54)	
DECLARE-TIMI 58	14/2611	1.4	17/2588	1.7	0.81 (0.40–1.64)	
EMPA-REG OUTCOME	58/1847	11.1	56/935	22.0	0.50 (0.35–0.73)	
VERTIS-CV	118/2160	19.6	61/1087	21.2	0.94 (0.69–1.28)	
Subtotal					0.81 (0.64–1.03)	
(I^2=50.4%; $P_{heterogeneity}$=0.07)					P=0.08	
Heart failure No						0.93
CANVAS Program	6/4992	0.4	7/3689	0.7	0.55 (0.18–1.65)	
CREDENCE	137/1873	29.2	169/1876	36.4	0.81 (0.65–1.01)	
DAPA-CKD	44/1278	34.0	39/1267	31.0	1.12 (0.72–1.75)	
DECLARE-TIMI 58	23/7730	0.7	28/7706	0.9	0.81 (0.47–1.41)	
EMPA-REG OUTCOME	86/4225	7.0	73/2089	12.3	0.57 (0.42–0.78)	
VERTIS-CV	175/4207	14.3	93/2074	16.2	0.90 (0.70–1.15)	
Subtotal					0.80 (0.66–0.96)	
(I^2=38.5%; $P_{heterogeneity}$=0.15)					p=0.02	
Heart failure Yes						
CANVAS Program	2/803	0.8	0/658	0	NA	

CREDENCE	32/329	40.1	34/323	43.5	0.89 (0.55–1.44)	
DAPA-CKD	4/177	23.0	8/184	43.0	0.51 (0.13–1.65)	
DECLARE-TIMI 58	7/852	2.2	10/872	3.1	0.70 (0.27–1.84)	
EMPA-REG OUTCOME	18/462	15.0	15/244	24.9	0.60 (0.30–1.18)	
VERTIS-CV	68/1286	18.9	41/671	22.5	0.85 (0.58–1.25)	
Subtotal					0.79 (0.61–1.03)	
(I^2=0.0%; $P_{heterogeneity}$=0.83)					p=0.08	
RAAS inhibitor use No						0.04
CANVAS Program	0/1150	0	2/876	0.9	NA	
CREDENCE	1/1	1238.1	0/5	0	NA	
DAPA-CKD	2/36	56.0	3/53	57.0	0.98 (0.12–6.22)	
DECLARE-TIMI 58	6/1605	1.0	6/1605	1.0	1.05 (0.34–3.26)	
EMPA-REG OUTCOME	12/889	4.7	22/465	16.8	0.28 (0.14–0.58)	
VERTIS-CV	40/1049	13.1	28/508	19.9	0.66 (0.41–1.07)	
Subtotal					0.56 (0.31–1.03)	
(I^2=46.4%; $P_{heterogeneity}$=0.13)					p=0.06	
RAAS inhibitor use Yes						
CANVAS Program	8/4695	0.5	5/3471	0.5	1.01 (0.32–3.12)	
CREDENCE	168/2201	30.6	203/2194	37.5	0.82 (0.67–1.00)	
DAPA-CKD	46/1419	32.0	44/1398	31.0	1.03 (0.68–1.57)	
DECLARE-TIMI 58	24/6977	0.9	32/6973	1.2	0.74 (0.44–1.26)	
EMPA-REG OUTCOME	92/3798	8.5	66/1868	12.6	0.67 (0.49–0.92)	
VERTIS-CV	203/4444	15.9	106/2237	17.2	0.94 (0.74–1.19)	
Subtotal					0.84 (0.74–0.95)	
(I^2=0.0%; $P_{heterogeneity}$=0.52)					p=0.006	
Diuretic use No						0.53
CANVAS Program	2/3259	0.2	2/2393	0.3	0.61 (0.08–4.41)	
CREDENCE	88/1176	30.3	94/1168	33.0	0.91 (0.68–1.22)	
DAPA-CKD	16/737	22.0	20/704	28.0	0.76 (0.38–1.47)	
DECLARE-TIMI 58	9/5094	0.4	16/5099	0.8	0.56 (0.25–1.27)	
EMPA-REG OUTCOME	53/2640	6.9	39/1345	10.1	0.67 (0.44–1.02)	
VERTIS-CV	141/3148	15.5	76/1551	17.3	0.90 (0.68–1.19)	
Subtotal					0.83 (0.70–0.99)	
(I^2=0.0%; $P_{heterogeneity}$=0.74)					p=0.03	
Diuretic use Yes						
CANVAS Program	6/2536	0.8	5/1954	1.0	0.82 (0.24–2.73)	
CREDENCE	81/1026	31.3	109/1031	42.2	0.74 (0.56–0.99)	
DAPA-CKD	32/718	45.0	27/747	36.0	1.24 (0.74–2.11)	
DECLARE-TIMI 58	21/3488	1.5	22/3479	1.6	0.94 (0.52–1.71)	
EMPA-REG OUTCOME	51/2047	8.8	49/988	18.1	0.50 (0.34–0.74)	
VERTIS-CV	102/2345	15.2	58/1194	18.3	0.85 (0.62–1.18)	
Subtotal					0.79 (0.62–1.00)	
(I^2=43.1%; $P_{heterogeneity}$=0.12)					p=0.05	
MRA use No						0.56
CANVAS Program	6/5666	0.3	7/4284	0.6	0.58 (0.19–1.76)	
CREDENCE	167/2182	30.6	203/2184	37.7	0.81 (0.66–0.99)	
DAPA-CKD	46/1373	34.0	41/1362	30.0	1.12 (0.73–1.72)	
DECLARE-TIMI 58	24/8215	0.7	31/8183	1.0	0.76 (0.45–1.30)	
EMPA-REG OUTCOME	90/4382	7.1	75/2197	12.1	0.59 (0.44–0.81)	
VERTIS-CV	214/5043	14.7	121/2522	17.3	0.86 (0.691.07)	
Subtotal					0.80 (0.68–0.93)	
(I^2=28.4%; $P_{heterogeneity}$=0.22)					p=0.005	
MRA use Yes						
CANVAS Program	2/129	0.4	0/63	0	NA	
CREDENCE	2/20	43.7	0/15	0	NA	
DAPA-CKD	2/82	24.0	6/89	67.0	0.35 (0.05–1.55)	
DECLARE-TIMI 58	6/367	4.3	7/395	4.7	0.92 (0.31–2.75)	
EMPA-REG OUTCOME	14/305	17.1	13/136	39.0	0.40 (0.19–0.84)	
VERTIS-CV	29/450	23.6	13/223	22.5	1.08 (0.56–2.08)	
Subtotal					0.68 (0.38–1.21)	
(I^2=36.5%; $P_{heterogeneity}$=0.19)					p=0.19	

Table S3. Effect of SGLT2 inhibitors on hypokalemia (serum potassium ≤3.5 mmol/L) according to baseline participant characteristics

	SGLT2 inhibitors		Placebo			
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	Hazard ratio (95%CI)	Subgroup: P for interaction
Hba1c ≤8						0.25
CANVAS Program	134/2744	18.8	97/2089	19.3	0.96 (0.74–1.26)	
CREDENCE	50/1097	17.8	60/1098	21.6	0.83 (0.57–1.21)	
DAPA-CKD	68/943	37.2	68/923	38.4	0.97 (0.69–1.36)	
DECLARE-TIMI 58	36/4372	2.1	36/4367	2.1	0.95 (0.60–1.52)	
EMPA-REG OUTCOME	164/2528	24.8	76/1241	24.0	1.06 (0.80–1.39)	
VERTIS-CV	74/2614	9.8	32/1355	8.5	1.16 (0.77–1.76)	
Subtotal					0.99 (0.86–1.13)	
(I^2=0.0%; $P_{heterogeneity}$=0.89)					p=0.84	
Hba1c >8						
CANVAS Program	131/3051	17.0	89/2258	17.0	1.01 (0.77–1.33)	
CREDENCE	57/1104	20.8	56/1100	20.5	1.01 (0.70–1.47)	
DAPA-CKD	39/508	38.0	30/519	28.8	1.28 (0.80–2.07)	
DECLARE-TIMI 58	20/4208	1.2	25/4207	1.5	0.81 (0.45–1.46)	
EMPA-REG OUTCOME	140/2157	24.5	59/1092	20.9	1.16 (0.86–1.58)	
VERTIS-CV	94/2860	11.5	30/1377	7.8	1.49 (0.99–2.24)	
Subtotal					1.11 (0.96–1.29)	
(I^2=0.0%; $P_{heterogeneity}$=0.52)					p=0.17	
eGFR ≥60						0.33
CANVAS Program	206/4684	17.0	140/3417	17.2	1.01 (0.81–1.26)	
CREDENCE	50/905	22.2	40/904	17.6	1.26 (0.83–1.90)	
DAPA-CKD	14/179	34.9	15/169	41.9	0.85 (0.41–1.76)	
DECLARE-TIMI 58	43/7975	1.4	54/7919	1.7	0.76 (0.51–1.14)	
EMPA-REG OUTCOME	214/3473	23.2	95/1726	21.1	1.12 (0.88–1.43)	
VERTIS-CV	125/4295	9.9	41/2138	6.7	1.49 (1.04–2.11)	
Subtotal					1.08 (0.91–1.28)	
(I^2=33.3%; $P_{heterogeneity}$=0.19)					p=0.36	
eGFR <60						
CANVAS Program	59/1110	21.9	46/929	22.0	0.89 (0.60–1.33)	
CREDENCE	57/1297	17.3	76/1295	23.6	0.74 (0.53–1.05)	
DAPA-CKD	93/1276	37.8	85/1282	34.4	1.09 (0.81–1.47)	
DECLARE-TIMI 58	13/606	5.6	7/659	2.8	1.90 (0.75–4.78)	
EMPA-REG OUTCOME	90/1212	29.1	40/607	26.7	1.05 (0.73–1.53)	
VERTIS-CV	45/1198	14.5	21/607	13.8	1.07 (0.64–1.79)	
Subtotal					0.98 (0.82–1.16)	
(I^2=9.3%; $P_{heterogeneity}$=0.36)					p=0.79	
UACR <30						0.19
CANVAS Program	170/4012	16.3	108/2995	15.0	1.08 (0.84–1.38)	
CREDENCE	0/16	NA	0/15	NA	NA	
DAPA-CKD	0/1	NA	0/0	NA	NA	
DECLARE-TIMI 58	33/5819	1.4	38/5825	1.6	0.83 (0.52–1.33)	
EMPA-REG OUTCOME	166/2789	22.3	63/1382	17.3	1.33 (0.99–1.78)	
VERTIS-CV	96/3186	10.4	38/1597	8.4	1.25 (0.86–1.82)	
Subtotal					1.14 (0.97–1.35)	
(I^2=7.1%; $P_{heterogeneity}$=0.36)					p=0.12	
UACR ≥30						
CANVAS Program	92/1699	21.8	72/1270	24.9	0.91 (0.66–1.24)	
CREDENCE	107/2186	19.4	116/2184	21.2	0.92 (0.71–1.20)	
DAPA-CKD	107/1454	37.4	100/1451	35.4	1.06 (0.80–1.39)	
DECLARE-TIMI 58	22/2611	2.2	20/2588	2.0	1.10 (0.60–2.02)	
EMPA-REG OUTCOME	138/1847	29.0	63/1382	17.3	0.92 (0.69–1.23)	
VERTIS-CV	70/2160	11.5	22/1087	7.5	1.55 (0.96–2.50)	
Subtotal					1.00 (0.87–1.14)	
(I^2=0.0%; $P_{heterogeneity}$=0.48)					p=0.95	
Heart failure No						0.74
CANVAS Program	222/4992	17.2	163/3689	18.6	0.93 (0.76–1.15)	
CREDENCE	94/1873	19.9	104/1876	22.1	0.90 (0.68–1.20)	
DAPA-CKD	93/1278	37.0	91/1267	37.0	1.00 (0.75–1.33)	
DECLARE-TIMI 58	47/7730	1.5	55/7706	1.8	0.82 (0.56–1.22)	
EMPA-REG OUTCOME	272/4225	24.3	121/2089	22.2	1.10 (0.89–1.36)	
VERTIS-CV	142/4207	11.7	39/2074	6.7	1.75 (1.23–2.50)	
Subtotal					1.04 (0.87–1.24)	
(I^2=58.7%; $P_{heterogeneity}$=0.03)					p=0.67	
Heart failure Yes						
CANVAS Program	43/803	21.9	23/658	15.4	1.38 (0.82–2.33)	

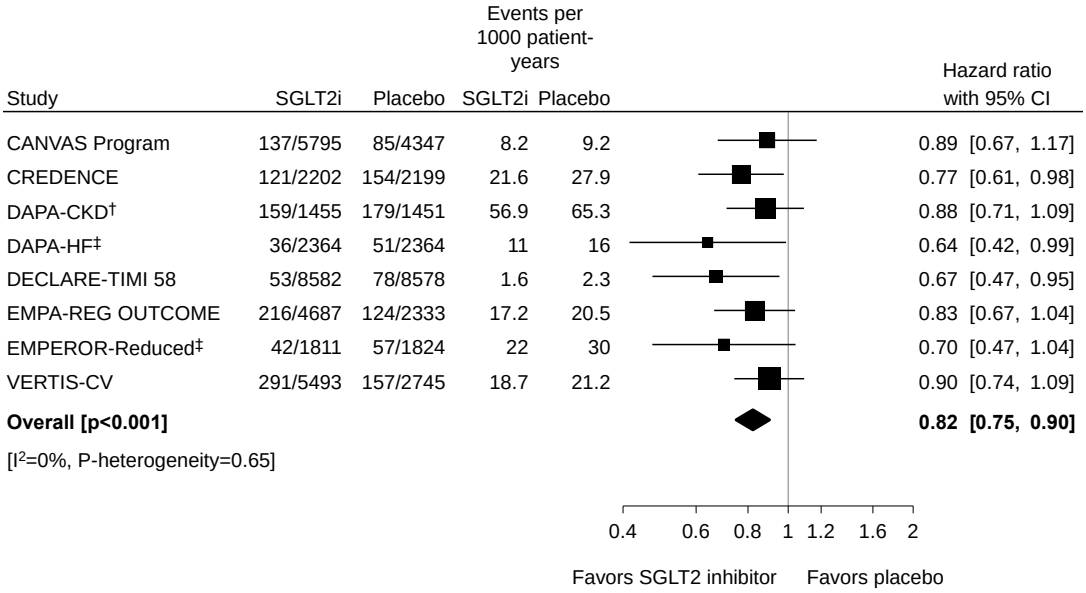
CREDENCE	13/329	15.8	12/323	14.9	1.05 (0.48–2.30)	
DAPA-CKD	14/177	39.9	9/184	24.6	1.58 (0.68–3.68)	
DECLARE-TIMI 58	9/852	2.8	6/872	1.8	1.47 (0.52–4.16)	
EMPA-REG OUTCOME	32/462	28.6	14/244	25.8	1.14 (0.61–2.14)	
VERTIS-CV	28/1286	7.8	23/671	12.6	0.62 (0.36–1.09)	
Subtotal					1.09 (0.81–1.47)	
(I^2=14.6%; $P_{heterogeneity}$=0.32)					p=0.58	
RAAS inhibitor use No						0.60
CANVAS Program	52/1150	17.8	39/876	19.1	0.99 (0.65–1.52)	
CREDENCE	0/1	NA	0/5	NA	NA	
DAPA-CKD	4/36	60.1	3/53	32.1	NA	
DECLARE-TIMI 58	13/1605	2.1	15/1605	2.4	0.84 (0.40–1.78)	
EMPA-REG OUTCOME	57/889	24.4	32/465	26.6	0.95 (0.62–1.47)	
VERTIS-CV	26/1049	8.6	11/508	7.8	1.11 (0.55–2.25)	
Subtotal					0.97 (0.75–1.26)	
(I^2=0.0%; $P_{heterogeneity}$=0.96)					p=0.83	
RAAS inhibitor use Yes						
CANVAS Program	213/4615	17.9	147/3471	17.9	0.98 (0.79–1.21)	
CREDENCE	107/2201	19.3	116/2194	21.1	0.92 (0.71–1.19)	
DAPA-CKD	103/1419	36.8	97/1398	35.5	1.03 (0.78–1.36)	
DECLARE-TIMI 58	43/6977	1.6	46/6973	1.7	0.90 (0.59–1.36)	
EMPA-REG OUTCOME	247/3798	24.7	103/1868	21.5	1.15 (0.91–1.44)	
VERTIS-CV	144/4444	11.3	51/2237	8.2	1.39 (1.01–1.92)	
Subtotal					1.05 (0.94–1.18)	
(I^2=8.8%; $P_{heterogeneity}$=0.36)					p=0.42	
Diuretic use No						0.98
CANVAS Program	76/3259	9.1	51/2393	8.9	1.11 (0.77–1.59)	
CREDENCE	40/1176	13.5	41/1168	14.1	0.96 (0.62–1.48)	
DAPA-CKD	52/737	36.7	35/704	25.5	1.42 (0.93–2.19)	
DECLARE-TIMI 58	17/5094	0.8	20/5099	1.0	0.85 (0.44–1.62)	
EMPA-REG OUTCOME	112/2640	15.7	69/1345	19.6	0.81 (0.60–1.09)	
VERTIS-CV	59/3148	6.4	18/1551	4.0	1.60 (0.95–2.72)	
Subtotal					1.07 (0.86–1.33)	
(I^2=36.9%; $P_{heterogeneity}$=0.16)					p=0.56	
Diuretic use Yes						
CANVAS Program	189/2536	29.3	135/1954	29.7	0.96 (0.77–1.21)	
CREDENCE	67/1026	26.0	75/1031	29.0	0.90 (0.65–1.25)	
DAPA-CKD	55/718	38.0	65/747	44.6	0.85 (0.59–1.22)	
DECLARE-TIMI 58	39/3488	2.8	41/3479	3.0	0.91 (0.59–1.42)	
EMPA-REG OUTCOME	192/2047	36.9	66/988	26.8	1.39 (1.05–1.84)	
VERTIS-CV	111/2345	16.8	44/1194	13.9	1.23 (0.87–1.75)	
Subtotal					1.04 (0.88–1.22)	
(I^2=35.6%; $P_{heterogeneity}$=0.17)					p=0.67	
MRA use No						0.13
CANVAS Program	261/5666	18.1	180/4284	17.9	1.00 (0.82–1.21)	
CREDENCE	106/2182	19.3	115/2184	21.1	0.92 (0.71–1.20)	
DAPA-CKD	99/1373	36.7	91/1362	34.3	1.07 (0.80–1.42)	
DECLARE-TIMI 58	55/8215	1.7	57/8183	1.8	0.94 (0.64–1.36)	
EMPA-REG OUTCOME	283/4382	24.5	134/2197	23.7	1.05 (0.85–1.29)	
VERTIS-CV	161/5043	11.1	54/2522	7.7	1.46 (1.08–1.99)	
Subtotal					1.05 (0.94–1.18)	
(I^2=17.1%; $P_{heterogeneity}$=0.30)					p=0.41	
MRA use Yes						
CANVAS Program	4/129	10.2	6/63	33.3	0.53 (0.13–2.18)	
CREDENCE	1/20	21.2	1/15	27.0	0.28 (0.02–4.71)	
DAPA-CKD	8/82	48.3	9/89	51.6	0.73 (0.26–2.02)	
DECLARE-TIMI 58	1/367	0.7	4/395	2.7	0.25 (0.03–2.20)	
EMPA-REG OUTCOME	21/305	27.3	1/136	3.1	8.41 (1.14–62.25)	
VERTIS-CV	9/450	7.2	8/223	13.8	0.54 (0.21–1.39)	
Subtotal					0.70 (0.33–1.49)	
(I^2=34.9%; $P_{heterogeneity}$=0.18)					p=0.35	

Table S4. Mean change from baseline in serum potassium over time

	SGLT2 inhibitors			Placebo			
Study	Mean	SD	n	Mean	SD	n	Mean difference (95% CI)
Week 52							
CANVAS Program	4.43	0.39	5136	4.43	0.39	3819	0.00 (-0.02, 0.02)
CREDENCE	4.53	0.46	2004	4.52	0.46	1972	0.01 (-0.02, -0.04)
DAPA-CKD	4.75	0.56	1284	4.77	0.59	1252	-0.02 (-0.06, 0.02)
DECLARE-TIMI 58	4.48	0.60	247	4.57	0.67	293	-0.09 (-0.20, 0.02)
EMPA-REG OUTCOME	4.53	0.47	4309	4.57	0.47	2307	-0.04 (-0.06, -0.02)
VERTIS-CV	4.60	0.46	4692	4.64	0.45	2307	-0.04 (-0.06, -0.02)
Total (95% CI)			17672			11950	-0.02 (-0.04, 0.00)
I^2=71%, P-heterogeneity=0.005							P=0.06
Week 104							
CANVAS Program	4.41	0.39	4450	4.43	0.39	3152	-0.02 (-0.04, 0.00)
CREDENCE	4.62	0.47	1801	4.62	0.47	1726	0.00 (-0.03, 0.03)
DAPA-CKD	475	0.57	1113	4.79	0.61	1082	-0.04 (-0.09, 0.01)
DECLARE-TIMI 58	4.58	0.49	280	4.65	0.55	285	-0.07 (-0.16, 0.02)
EMPA-REG OUTCOME	4.54	0.47	3725	4.60	0.47	1775	-0.06 (-0.09, -0.03)
VERTIS-CV	4.61	0.46	3121	4.66	0.49	1498	-0.05 (-0.08, -0.02)
Total (95% CI)			14490			9518	-0.04 (-0.06, -0.01)
I^2=60%, P-heterogeneity=0.03							P=0.001
Week 156							
CANVAS Program	4.37	0.38	2094	4.38	0.37	964	-0.01 (-0.04, 0.02)
CREDENCE	4.75	0.46	727	4.76	0.46	691	-0.01 (-0.06, 0.04)
DAPA-CKD	4.77	0.59	157	4.77	0.62	160	0.00 (-0.13, 0.13)
DECLARE-TIMI 58	4.53	0.48	559	4.63	0.48	320	-0.10 (-0.17, -0.03)
EMPA-REG OUTCOME	4.54	0.47	4439	4.56	0.48	590	-0.02 (-0.06, 0.02)
VERTIS-CV	4.62	0.48	3157	4.65	0.46	1497	-0.03 (-0.06, 0.00)
Total (95% CI)			11133		4222		-0.02 (-0.04, 0.00)
I^2=25%, P-heterogeneity=0.25							P=0.02
Week 208							
CANVAS Program	4.38	0.46	1897	4.40	0.42	843	-0.02 (-0.06, 0.02)
CREDENCE			0			0	Not estimable
DAPA-CKD			0			0	Not estimable
DECLARE-TIMI 58	4.55	0.46	3349	4.60	0.47	3249	-0.05 (-0.07, -0.03)
EMPA-REG OUTCOME	4.54	0.46	371	4.65	0.54	153	-0.11 (-0.21, -0.01)
VERTIS-CV	4.60	0.46	1737	4.67	0.49	786	-0.07 (-0.11, -0.03)
Total (95% CI)							-0.07 (-0.11, -0.03)
I^2=42%, P-heterogeneity=0.16							P=0.0001

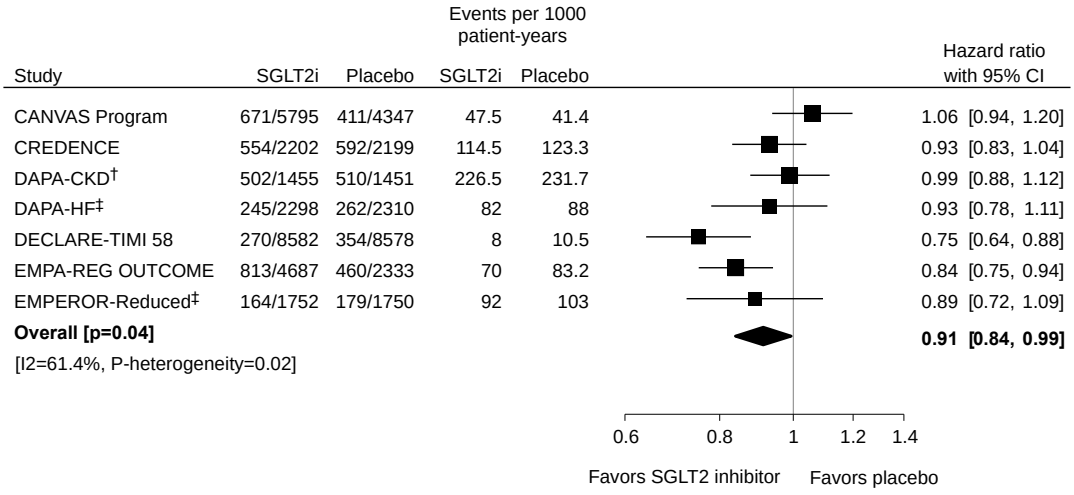
SD: standard deviation; CI: confidence interval.

Figure S1. Effect of SGLT2 inhibitors on serious hyperkalemia (central laboratory determined serum potassium ≥6.0 mmol/L) after including trials in people with heart failure with reduced ejection fraction



SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval.
†DAPA-CKD participants with type 2 diabetes.
‡Serious hyperkalemia was defined as serum potassium >6.0 mmol/L in DAPA-HF and EMPEROR-Reduced, including participants with and without type 2 diabetes.

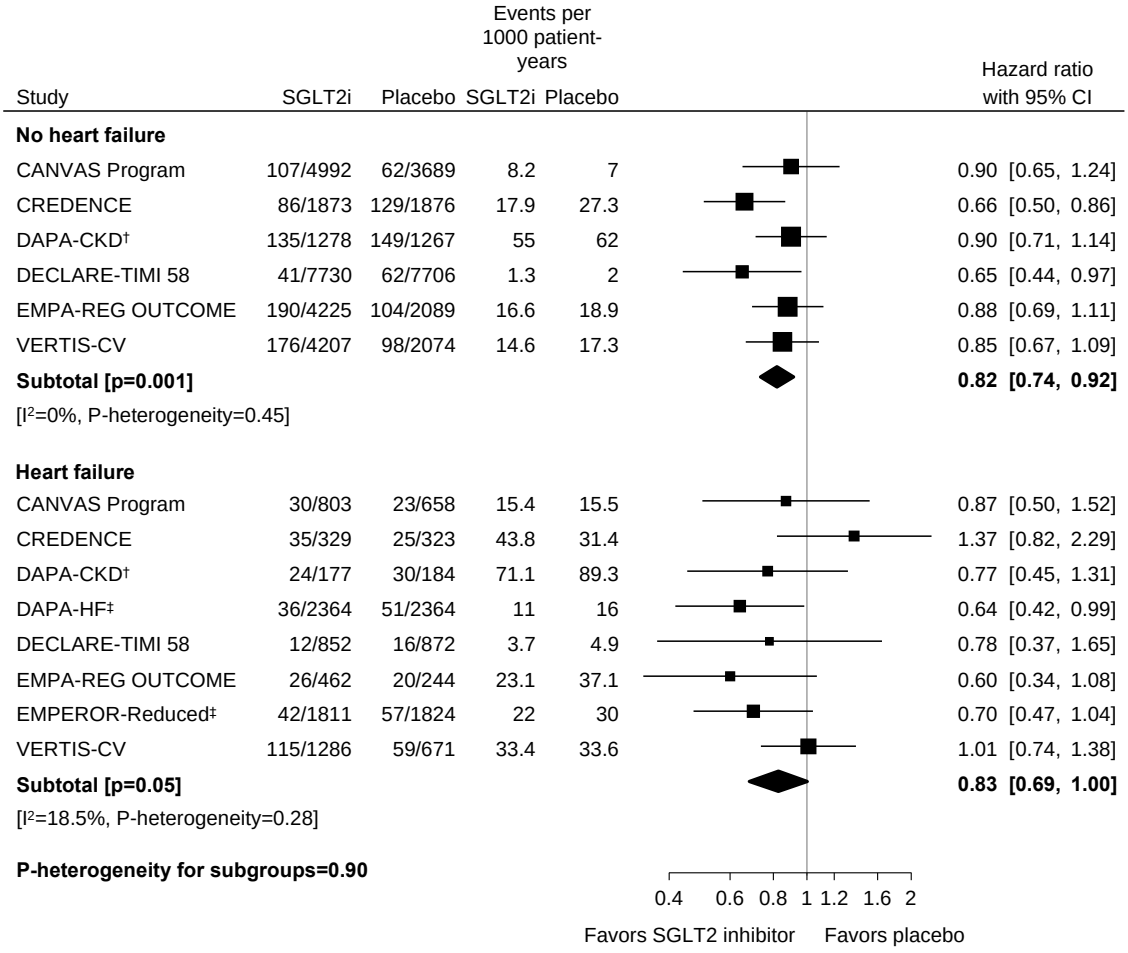
Figure S2. Effect of SGLT2 inhibitors on mild hyperkalemia (central laboratory determined serum potassium ≥5.5 mmol/L), including trials in people with heart failure with reduced ejection fraction



SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval.
†DAPA-CKD participants with type 2 diabetes.
‡Serious hyperkalemia was defined as serum potassium >5.5 mmol/L in DAPA-HF and EMPEROR-Reduced, including participants with and without type 2 diabetes.

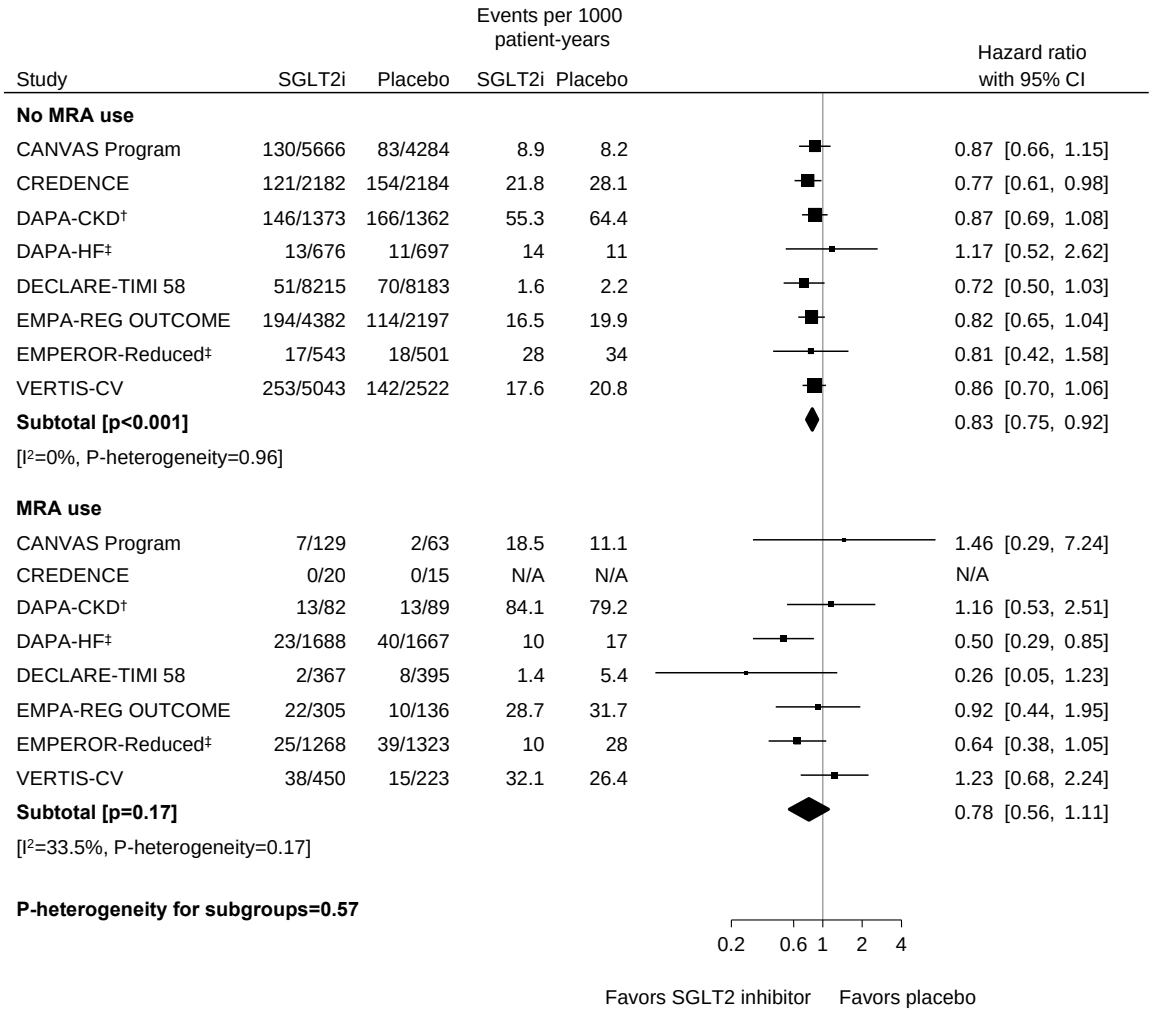
Figure S3. Effect of SGLT2 inhibitors on serious hyperkalemia (serum potassium ≥6.0 mmol/L) according to (A) history of heart failure and (B) baseline use of MRAs after including trials in people with heart failure with reduced ejection fraction

(A)



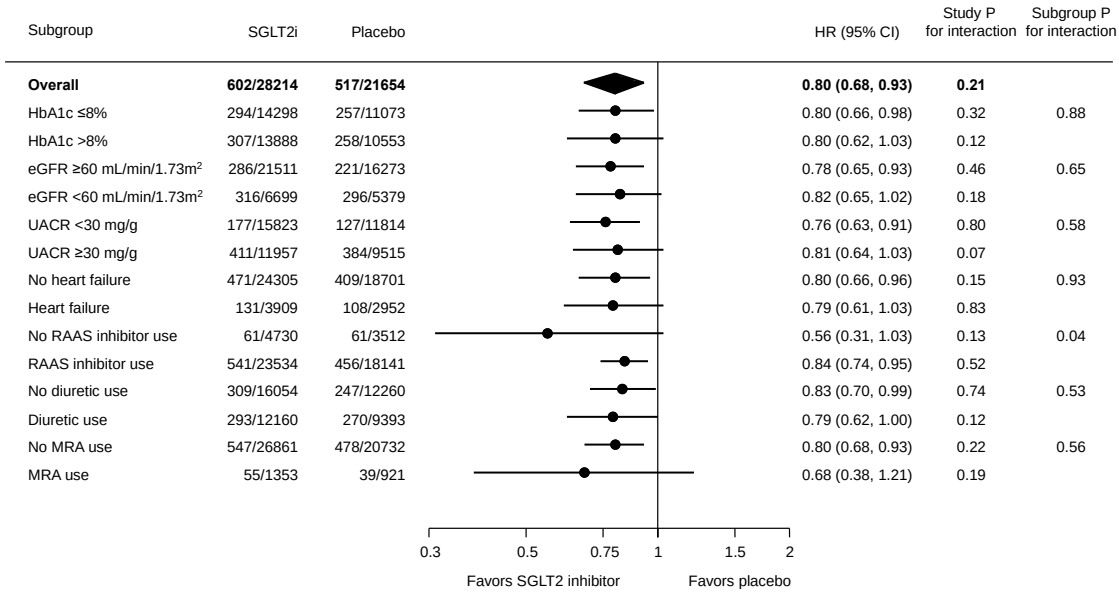
SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval.

(B)



SGLT2i: sodium glucose cotransporter 2 inhibitor; CI: confidence interval; MRA: mineralocorticoid receptor antagonist; N/A: Not available.
†DAPA-CKD participants with type 2 diabetes.
‡Serious hyperkalemia was defined as serum potassium >6.0 mmol/L in DAPA-HF and EMPEROR-Reduced, including participants with and without type 2 diabetes.

Figure S4. Effect of SGLT2 inhibitors on investigator reported hyperkalemia events according to baseline participant characteristics



SGLT2i: sodium glucose cotransporter 2 inhibitor; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio; RAAS: renin-angiotensin-aldosterone system; MRA: mineralocorticoid receptor antagonist; CI: confidence interval.