EFFECTS OF SODIUM GLUCOSE CO-TRANSPORTER-2 INHIBITORS BY DIABETES STATUS AND LEVEL OF ALBUMINURIA: A COLLABORATIVE META-ANALYSIS

Short title: Net absolute effects of SGLT2i

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Key Points (limit 100 words)

Question: What are the relative and absolute effects of SGLT2 inhibitors in the large trials once stratified by a urine albumin:creatinine ratio (uACR) threshold of 200 mg/g, after stratifying by diabetes status?

Findings: In this meta-analysis that included 58,816 participants from 8 trials of SGLT2 inhibitors vs placebo, there were net absolute benefits across efficacy outcomes, particularly hospital admission, among patients with and without diabetes, and at both levels of albuminuria. Greater baseline risk in those with uACR ≥200 mg/g may translate to larger absolute benefits on for preventing kidney disease progression

Meaning: These data support removal of stratification by level of albuminuria from guideline recommendations for use of SGLT2 inhibitors in chronic kidney disease and more widespread use.

ABSTRACT

Importance: There is uncertainty about the effects of SGLT2 inhibitors (SGLT2i) in certain types of patients with chronic kidney disease (CKD), with international guidelines offering different strengths of recommendation based on diabetes status and urine albumin:creatinine ratio (uACR) of ≥200 mg/g or <200 mg/g.

Objective: To assess the relative and absolute effects of SGLT2i in participants across the full range of efficacy and serious safety outcomes stratified by diabetes status and uACR.

Data sources: Eight large placebo control trials providing analyses to SMART-C.

Study selection: Trials were included if they: studied an SGLT2i with label indication for use in kidney disease, and reported longitudinal kidney outcomes and baseline data on albuminuria.

Data extraction and synthesis: Data were combined using inverse variance-weighted meta-analysis. Group-specific absolute effects were estimated by applying relevant subgroup-specific relative risks to the event rates in placebo groups.

Main outcomes and measures: We assessed effects on clinical efficacy and safety outcomes, including kidney outcomes, heart failure and other hospitalization, and mortality. We assessed heterogeneity by baseline uACR <200 versus ≥200mg/g separately by diabetes status.

Results: A total of 58,816 participants (mean [SD] age, 64 [10] years; 20,543 (35%) female; 48,946 with diabetes and 9870 without diabetes) were included from 8 large randomized trials of an SGLT2i versus placebo. Allocation to SGLT2i reduced risk of kidney disease progression (33 vs 48 per 1000 patient-years [1000py], hazard ratio [HR] 0.65, 95%

confidence interval 0.60-0.70 in those with diabetes; and 32 vs 46/1000py, HR 0.74, 0.63-0.85 in those without diabetes), acute kidney injury (14 vs 18/1000py, HR 0.77, 0.69-0.87 in diabetes; and 13 vs 18/1000py, HR 0.72, 0.56-0.92 without diabetes), any hospitalization (202 vs 231/1000py, HR 0.90, 0.87-0.92 with diabetes; and 203 vs 237/1000py, HR 0.89, 0.83-0.95 without diabetes), and any death (42 vs 47/1000py, HR 0.86, 0.80-0.91 with diabetes; and 42 vs 48/1000py, HR 0.91, 0.78-1.05 without diabetes). In analyses further stratified by uACR, diabetes-specific hazard ratios were generally similar in participants with uACR ≥200 mg/g versus <200 mg/g (heterogeneity test by uACR for death p=0.03, all other outcomes p>0.10).

Higher absolute risk at uACR ≥200 mg/g meant larger estimated absolute benefits on kidney disease progression were evident in this subgroup. Net absolute benefits were evident for other efficacy outcomes, and particularly hospitalization, in participants with uACR <200 mg/g. Net benefits were clear in analyses restricted to non-heart failure populations and when estimated glomerular filtration rate was <60 mL/min/1.73m^2.

Conclusions and relevance: Within the studied participants, there were clear net absolute benefits of SGLT2i on kidney, hospitalization, and mortality outcomes irrespective of diabetes status and level of uACR.

INTRODUCTION

There are an estimated ~850 million people with chronic kidney disease (CKD) globally,[1] and it is associated with substantial increased risk of kidney failure and cardiovascular disease.[2] Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce risk of kidney failure and/or cardiovascular disease in patients with CKD or heart failure, and are recommended as a standard of care in these conditions.[3-5] To ensure maximum benefits, they should be continued long-term.[6] Despite relevant recommendations for SGLT2 inhibition, this class remains underutilised in clinical practice among participants with CKD, especially in patients without diabetes.[6-9] This may be attributable in part to ongoing uncertainties on the net effects of SGLT2 inhibition in certain subtypes of patient with CKD with an indication for prescription. This is reflected in 2024 international guidance regarding the use of SGLT2 inhibitors in adults with CKD which provided class IA recommendations for most types of patients who were eligible for the different SGLT2 inhibitor trials, but a 2B level recommendation for patients with eGFR 20-45ml/min/1.73m^2 with urine albumin:creatinine ratio (uACR) <200 mg/g. The rationale for that lower level of recommendation was evidence for benefits on CKD progression in participants without diabetes and uACR <200 mg/g being limited to eGFR slope analyses in heart failure trials and a subgroup of one CKD trial (EMPA-KIDNEY).[3,10]

In addition to confirmed benefits on kidney disease progression, SGLT2 inhibitors also reduce risk of cardiovascular death, hospitalization for heart failure, hospitalization for other causes, and acute kidney injury.[10-12] In the United States, individuals with the lowest levels of albuminuria (i.e. A1 levels) represent around two thirds of patients with decreased eGFR,[13,14] and although they may be at lower risk of CKD progression than patients with overt albuminuria, they remain at risk of all other adverse health outcomes which are modifiable with SGLT2 inhibition.[2] Furthermore, the absolute risks of harms associated with SGLT2 inhibition appear to be low, particularly among patients without diabetes.[11] Quantifying net effects of SGLT2 inhibition in patients with different levels of albuminuria

after stratification by diabetes within the totality of information from the large-scale trials is therefore important to explore.

In this collaborative meta-analysis, first we aimed to quantify post-hoc the relative effects of SGLT2 inhibition across the full range of clinical efficacy and relevant serious safety outcomes reported within relevant large placebo-control trials. We then assess net absolute effects within the included trial populations. We focus on subgroups with different strengths of evidence in current CKD guidelines (i.e. by uACR ≥200 mg/g versus <200 mg/g after stratifying by diabetes status) rather than CKD staging categories.

METHODS

The SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART-C) comprises completed randomized, double-blind, placebo-controlled outcome trials with at least 500 participants in each treatment arm and follow-up of at least six months. All trials were subject to relevant regulatory and ethics committee approvals, and participants provided written informed consent. The Consortium is led by an academic steering committee comprising representatives from each of the participating trials. This analysis was restricted to trials evaluating SGLT2 inhibitors with a label indication for CKD progression (canagliflozin, dapagliflozin and empagliflozin).

This meta-analysis included data from eight trials. Three trials enrolled participants with type 2 diabetes at high atherosclerotic cardiovascular risk (EMPA-REG OUTCOME[15], CANVAS Program[16] and DECLARE-TIMI-58[17]), two trials studied participants with heart failure across the spectrum of ejection fraction (EMPEROR-REDUCED[18], EMPEROR-PRESERVED[19]), and three were CKD trials (CREDENCE[20], DAPA-CKD[21], EMPA-KIDNEY[10]). Of the other SMART-C contribution trials, DAPA-HF[22] and DELIVER[23] were excluded due to no baseline information on albuminuria, DAPA-MI[24] and EMPACT-MI[25] were excluded due to no systematic collection of longitudinal kidney outcomes; and SCORED,[26] SOLOIST-WHF[27] and VERTIS-CV[28] were also excluded as sotagliflozin and ertugliflozin do not have a label indication for kidney outcomes. Risk of bias of included studies was assessed using the Cochrane Risk of Bias Version 2 tool.[11,29]

Outcomes

The key objective of these analyses was effect estimation (i.e. there was no hierarchy of outcomes). The categorical CKD progression outcome was a composite kidney disease progression outcome defined as a sustained ≥40% eGFR decline from randomization, kidney failure (i.e. start of maintenance dialysis or receipt of a kidney transplant, or a sustained low eGFR [usually <15 mL/min/1.73m^2]) or renal death. eGFR was calculated

using the race-adjusted 2009 CKD-EPI formula[30]. A ≥40% eGFR decline from randomization is a validated surrogate for kidney failure (see eTable 1 for detailed kidney outcome definitions by trial)[31]. Other efficacy outcomes included adverse events reported using the MedDRA Preferred Term of acute kidney injury (eTable 1), hospitalization for heart failure (excluding urgent heart failure visits), any hospitalization, cardiovascular death (based on individual trial definitions), non-cardiovascular death, and any death. Myocardial infarction and stroke were not included due to no clear evidence for benefit in our previous meta-analysis.[32] Safety outcomes were limited to the key complications that previous individual trials or meta-analyses have indicated are potentially caused by SGLT2 inhibition (i.e. ketoacidosis, lower limb amputation, serious urinary tract infection and bone fracture).[16,33]

Additionally, we evaluated effects on the annualized rate of decline in eGFR (eGFR slope), another surrogate of CKD progression.[34,35] Continuous analyses of eGFR slope provide additional statistical sensitivity compared to the categorical kidney disease progression outcome, and is useful to evaluate subgroup effects on CKD progression . To account for the acute reversible dip in eGFR that occurs after initiation of an SGLT2 inhibitor,[36] we emphasize the effect of SGLT2 inhibitors on chronic eGFR slope. Chronic slope was defined as the difference in annualized rate of change in eGFR between SGLT2 inhibitor and placebo groups, calculated from the first post-randomization eGFR measurement, typically occurring within three months of randomization to final follow-up. Total slope includes all eGFR measurements from randomization to final follow-up. Neither of these slope methods consider the reversibility of the acute dip (i.e. post-treatment eGFR measurements are not included in analyses; see eMethods).

Subgroups

We evaluated treatment effects in analyses stratified by diabetes and then by uACR ≥200 mg/g versus <200 mg/g. This mirrors the stratification used for different strengths/classes of

218 recommendation for use of SGLT2 inhibitors in CKD (these differ from KDIGO conventional
219 thresholds for staging which have thresholds at 30 and 300 mg/g).[3]
220
221 *Sensitivity analyses*
222 To account for differences in types of patients represented by trials, sensitivity analyses
223 were conducted restricting analyses to participants with eGFR <60 mL/min/1.73m^2,
224 participants with eGFR <60 mL/min/1.73m^2 in the presence of heart failure, and excluding
225 heart failure trials, and considering the influence of CANVAS results on amputation risk.
226
227 *Statistical methods*
228 We followed the statistical methods implemented in previous SMART-C collaborative meta-
229 analyses.[11,32,37] Two-stage meta-analysis was conducted with outcome definitions
230 harmonized across trials. We compared characteristics of participants at baseline across the
231 aforementioned diabetes and uACR categories. Treatment effects were obtained from
232 individual trials using intention-to-treat analyses and pooled using inverse variance weighted
233 (IVW) meta-analysis (i.e. adopts a common fixed effect across trials). Our previous meta-
234 analysis stratified by diabetes status has shown no important differences between included
235 trials for the estimates of treatment effect for each efficacy and mortality outcome.[11] If
236 multiple doses of an SGLT2 inhibitor were included in a trial, these groups were combined
237 and compared to matching placebo. For categorical clinical outcomes, Cox regression
238 models used covariate stratification as pre-specified in each trial. We obtained summary
239 effect estimates, overall, and according to baseline diabetes and uACR by pooling log-
240 transformed hazards ratios (HRs). We assessed effect modification by baseline uACR <200
241 versus ≥200mg/g separately by diabetes status using standard X^2 tests for heterogeneity on
242 the stratified pooled estimates. Two-sided p values <0.05 were considered statistically
243 significant, but were interpreted in the context of the multiple exploratory tests performed and
244 the absence of individual participant-level data from every trial. Participants with missing
245 values of uACR are included in overall rows but not in subgroups by albuminuria.

Absolute benefits and harms of SGLT2 inhibitors versus placebo per 1000 patient-years were then estimated by diabetes status and uACR. Hypothetical absolute risk reductions and increases for a given event rate were estimated by applying the diabetes status-specific HRs and their 95% confidence intervals (CIs) to the corresponding mean event rates in the placebo groups (first event only) without considering any error in the estimate of rate.

Effects on chronic and total eGFR slope were estimated using two-slope mixed-effects linear spline model with unstructured covariance using methods that have been previously reported[37] (https://github.com/SGLT2-Trialists-Consortium/smartc-egfr-slope). We obtained combined estimates of slopes in each treatment group and the absolute difference between them using IVW averages of the trial-specific estimates. As in previous studies, relative differences were emphasized as they control for any differences in baseline risk.[36,38] They are calculated by dividing the IVW estimate of the absolute difference and its 95% confidence interval by the IVW estimate of the mean slope in the placebo group.

Analyses were performed and validated directly on trial datasets for the four empagliflozin trials and meta-analysed summary statistics provided from the other trials using SAS software, version 9.4 (SAS Institute) by the University of Oxford. Reporting followed PRISMA guidance (https://www.equator-network.org/reporting-guidelines/prisma/).

RESULTS

Eligible trial characteristics

The present analysis from eight large randomized clinical trials comprised 59,354 participants (eFigure 1 & eTable 2), including 34,322 participants randomized into trials of type 2 diabetes at high risk of atherosclerotic cardiovascular disease, 9718 participants randomized into trials of heart failure, and 15,314 participants randomized into CKD trials. Two included trials (CREDENCE, DAPA-CKD) enrolled only participants with albuminuria (uACR >300 mg/g and ≥200 mg/g, respectively) and four trials included only participants with diabetes (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE). All eight included trials were considered low risk of bias, with <1% loss to follow-up for mortality (eTable 3).

Of the included trial population, a uACR measurement was available for a total of 58,816 participants (99.1%). Of this population, 48,946 participants (83.2%) had a history of diabetes, and 17,088 participants (29.1%) had baseline uACR ≥200 mg/g. eGFR was highest among participants with diabetes and albuminuria <200 mg/g, (77.8 ± 20.8 mL/min/1.73m^2) and lowest amongst participants with uACR <200 mg/g without diabetes (42.3±16.6 mL/min/1.73m^2) (Table 1).

Relative effects on efficacy outcomes by diabetes status

Overall, kidney disease progression occurred in 2,917 participants with diabetes (5.9%) and 708 participants without diabetes (7.2%); acute kidney injury occurred in 1,127 participants (2.6%) and 261 participants (2.6%) with and without diabetes, respectively; any hospitalisation occurred in 18,486 participants (37.5%) and 3087 participants (31.2%) with and without diabetes; and death from any cause occurred in 3807 participants (7.7%) with diabetes and in 790 participants (8.0%) without diabetes.

Compared to placebo, allocation to SGLT2 inhibition reduced the hazard of kidney disease progression by 35% (hazard ratio [HR] 0.65, 95%CI 0.60-0.70; Figure 1) among participants with diabetes and 26% (HR 0.74, 0.63-0.85) among participants without diabetes, without evidence of heterogeneity by diabetes status (P for heterogeneity [P-het] by diabetes status=0.15).

Compared to placebo, allocation to SGLT2 inhibition reduced the hazard of acute kidney injury to a similar extent in participants with and without diabetes, by 23% (HR 0.77, 0.69-0.87) and 28% (HR 0.72, 0.56-0.92), respectively (P-het by diabetes status=0.61; Figure 1). Similarly, the risk of hospitalization for heart failure was reduced by SGLT2 inhibition by 32% (HR 0.68, 0.62-0.74) and 25% (HR 0.75, 0.63-0.88), and any hospitalization reduced by 10% (HR 0.90, 0.87-0.92) and 11% (HR 0.89, 0.83-0.95), in participants with and without diabetes respectively, without evidence of effect modification by diabetes status (Figure 1, eFigure 2). The effects of SGLT2 inhibition on cardiovascular and non-cardiovascular death separately and combined were also not modified by diabetes status (P-het by diabetes status >0.1 for all these outcomes; Figure 1, eFigure 2).

Relative effects on efficacy outcomes by uACR after stratification by diabetes status

Among participants with diabetes, there was no evidence that the effect of SGLT2 inhibition on kidney disease progression differed between participants with uACR <200 mg/g and participants with uACR ≥200 mg/g (HR for uACR <200 mg/g 0.65, 0.56-0.75; HR for uACR ≥200 mg/g 0.65, 0.59-0.71; P-het by uACR=0.95; Figure 1). Similarly, the effect of SGLT2 inhibition on kidney disease progression among participants without diabetes did not differ by the presence or absence of uACR ≥200 mg/g (HR for uACR <200 mg/g 0.88, 0.64-1.23; HR for uACR ≥200 mg/g 0.71, 0.60-0.84; P-het by uACR=0.24; Figure 1).

There was no evidence that the diabetes-specific HRs were modified by baseline uACR category for acute kidney injury, hospitalization for heart failure, any hospitalization,

cardiovascular death, nor non-cardiovascular death (P-het tests by uACR all >0.1; Figure 1, eFigure 2). When considering death from any cause among participants with diabetes, there was some evidence that the magnitude of relative effect of SGLT2 inhibition was greater among participants with uACR ≥200 mg/g versus <200 mg/g (HR 0.78, 0.80-0.91 versus 0.90, 0.83-0.98; P-het by uACR=0.03; Figure 1, eFigure 2).

Relative effects on safety outcomes

Allocation to SGLT2 inhibition approximately doubled the hazard of ketoacidosis (HR 2.29, 1.42-3.71) among participants with diabetes, without evidence of differential effect by uACR status (Figure 2). Ketoacidosis was too infrequent among participants without diabetes to estimate an HR or test for heterogeneity by diabetes or by uACR status. The HR for lower limb amputation, serious urinary tract infection, and bone fracture among participants with diabetes did not differ statistically from the HRs for participants without diabetes (P-het by diabetes >0.3 for all outcomes); nor did the effect of SGLT2 inhibition on these outcomes differ by baseline uACR within each diabetes stratum (Figure 2).

Absolute effects on clinical outcomes within the trial populations

Because kidney disease progression occurred at a greater rate among participants with uACR ≥200 mg/g than among participants with uACR <200 mg/g in both participants with and without diabetes, predicted absolute benefit was correspondingly greater among those with uACR ≥200 mg/g. We estimate 31 (SE 2) and 24 (SE 5) fewer participants with kidney disease progression outcomes per 1000 treated for one year when uACR was ≥200 mg/g with and without diabetes, respectively. This compares to 4 (SE 0.3) and 4 (SE 0.9) fewer participants with such outcomes per 1000 treated for a year when uACR was <200 mg/g (Figure 3). Absolute benefits for all efficacy outcomes were evident among participants with and without diabetes and in participants above and below a uACR of 200 mg/g, with substantially fewer hospitalizations for heart failure or for other causes (Figure 3, eTable 5). The predicted absolute number of safety outcomes resulting from use of SGLT2 inhibition

were notably smaller than the corresponding total absolute benefits for each subgroup, and particularly among participants without diabetes, and were irrespective of albuminuria status (Figure 3; eTable 5).

Effects on eGFR slope analyses

eGFR slope-based analyses found that allocation to SGLT2 inhibition reduced the chronic annual rate of decline of eGFR in participants both with and without diabetes, though the magnitude was greater among participants with diabetes (58% relative reduction in chronic eGFR slope; 95%CI 54-61%) than among participants without diabetes (43% relative reduction, 35-52%; P-het by diabetes status=0.0019; Figure 4).

Within each diabetes stratum, there was no difference in the relative effect of SGLT2 inhibitors on chronic eGFR slopes in participants with uACR <200 mg/g compared to participants with uACR ≥200 mg/g (P-het by uACR among participants with and without diabetes=0.21 and 0.23, respectively; Figure 4). A similar pattern was observed in analyses using the total eGFR slope (Figure 4).

Sensitivity analyses

Relative effects were generally consistent in a range of sensitivity analyses. Clear net absolute benefits were evident in analyses limited to participants with an eGFR <60 mL/min/ 1.73m^2, and in the presence of heart failure plus eGFR <60 mL/min/1.73m^2 (eFigures 3-7). After exclusion of heart failure populations, absolute net benefits remained substantial despite smaller absolute effects on cardiovascular death or hospitalization for heart failure (eFigure 8).

DISCUSSION

The overarching objective was to explore the impact of diabetes status and albuminuria on the net absolute effects of SGLT2 inhibition on the range of clinical efficacy and relevant serious safety outcomes reported within large placebo-control trials. Relative benefits for kidney disease progression, acute kidney injury, hospitalization for any cause, and cardiovascular death were generally similar in analyses stratified by diabetes status and then by baseline uACR category. When absolute benefits were considered, higher baseline risk of kidney disease progression at uACR ≥200 mg/g meant substantially larger absolute benefits for this outcome were evident compared to participants with uACR <200mg/g. Nevertheless, there were substantial absolute benefits on other efficacy outcomes irrespective of level of albuminuria, with particularly large absolute benefits on risk of hospitalization, both for heart failure and for other causes, in all subgroups. Diabetes status did not importantly modify net absolute benefits in participants with a uACR <200mg/g, and absolute benefits on hospitalization remained substantial even when uACR was <200mg and after exclusion of participants from the heart failure trials. The absolute risks of serious harm were largely limited to patients with diabetes, and were substantially outweighed by the cardiorenal, hospitalization and mortality benefits.

The large absolute benefits of SGLT2 inhibitors on hospitalization have been shown to lead to cost-effectiveness in patients with CKD irrespective of diabetes status and level of albuminuria in analyses of several SGLT-2 inhibitor trials including EMPA-KIDNEY, DAPA-CKD and DECLARE-TIMI 58.[39,40] The widespread use of SGLT2 inhibitors in CKD could lead to major reduction in kidney failure and hospitalization globally, thus improving efficiency for healthcare services. The presented evidence offers an opportunity for guidelines to be simplified to reduce arguably unnecessary stratification of recommendations by diabetes status and by uACR, and consequently maximize implementation of appropriate SGLT2 inhibition. Patients with low levels of albuminuria represent the vast majority of patients with decreased eGFR.[13,14] Guidelines focusing on only one potential benefit of SGLT2 inhibition

(e.g. kidney disease progression outcomes alone) will overlook the major absolute benefits on other important clinical outcomes among this large group of patients, including reduction in hospitalizations and mortality. Availability of generic SGLT2 inhibitors now and in the near future will help facilitate more equitable use globally, improve cost-effectiveness further, and help achieve the objectives of a 2025 World Health Organization (WHO) resolution. This resolution has recognized that the burden of non-communicable diseases globally can be reduced through promotion of kidney health and strengthening prevention and control of kidney disease.[41] Strengthening prevention may include use of generic SGLT2 inhibitors in earlier stages of CKD (e.g. stage G3A1), a group not included in CKD trials due to slow CKD progression rate. The global prevalence of early CKD is high, and the clinical care of early CKD usually takes place in primary care and non-nephrology specialities. Such patients are at increased risk of hospitalization, as well as adverse kidney and cardiovascular outcomes, and assessing the potential cost-effectiveness of treating early CKD long-term should be considered in future health economic research.[2,42]

The strengths of this meta-analysis include the availability of the full range of clinical efficacy and serious safety outcomes, including a standardized kidney disease progression outcome, and the ability to explore eGFR slope analyses in ~60,000 participants recruited into the eight large placebo-controlled SGLT2 inhibitor trials.

Limitations

The first study limitation was that uACR was not available for a subset of the large placebo-controlled trials of SGLT2 inhibition, precluding their inclusion. Second, the tests for heterogeneity for categorical outcomes have low power. For example, effect modification by diabetes status on eGFR slope was not detected using the categorical kidney disease progression outcome. Third, our hypothetical absolute effect estimates for categorical events and eGFR slopes are specific to the recruited trial populations, and not adjusted for potential confounders nor competing risks. Such adjustments would have required individual

participant level data from every trial. The presented absolute effect estimates should be interpreted as the hypothetical absolute effects of treatment with SGLT2 inhibition in a group of 1000 patients with a given baseline risk (in this case, a baseline risk equal to that of placebo-allocated participants from relevant populations in the included trials). As relative estimates of effect appear generalizable, in routine clinical practice, absolute effects of SGLT2 inhibitors for individuals could be estimated by calculating a patient's absolute risk for a clinical outcome using a validated risk score, and then applying the relative effect estimate for the outcome from the present meta-analysis. This method could also be applied to eGFR slopes. Other meta-analysis have demonstrated the reversibility of the acute eGFR dip, so we emphasis chronic eGFR slope over total slope when explaining benefits of SGLT2 inhibitors to patients.[36] Larger effects on chronic rate of eGFR decline were evident in patients with diabetes versus not, with SGLT2 inhibition reducing the rate of eGFR decline by about three-fifths and two-fifths respectively, irrespective of level of albuminuria. These two statistics provide a simple method to explain the beneficial effect of initiating an SGLT2 inhibitor on kidney function over time when introducing eGFR-by-time plots.

Conclusions

In summary, the relative benefits of SGLT2 inhibitors on kidney outcomes, mortality, and hospitalization in the reported large trials are similar in patients irrespective of diabetes status or baseline uACR ≥200 versus <200 mg/g. Within the included trial populations, participants with higher uACR experience larger absolute kidney disease progression benefits. Nevertheless, among participants with a uACR <200mg/g, net absolute benefits in participants without diabetes appear similar to participants with diabetes. The absolute risks of any harm (mainly ketoacidosis)) are substantially smaller than the absolute benefits, and largely limited to patients with diabetes. These data should encourage widespread utilization of SGLT2 inhibitors in patients with CKD irrespective of diabetes status and level of albuminuria.

CONTRIBUTIONS

WG Herrington & N Staplin conceived the meta-analysis and developed its analytical strategy. B Neuen and HL Heerspink coordinate the SMART-Consortium (www.smart-c.net). All authors contributed to interpretation and manuscript review. N Staplin & WG Herrington are responsible for the decision to submit for publication. N Staplin performed analyses. WG Herrington, AJ Roddick and N Staplin wrote the first draft of the manuscript.

CONFLICT OF INTEREST DISCLOSURES

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TABLES AND FIGURES

Table 1: Baseline characteristics from 8 included trials, by diabetes status and level of albuminuria

	DIABETES		NO DIABETES	
	uACR <200 mg/g	uACR ≥200 mg/g	uACR <200 mg/g	uACR ≥200 mg/g
Number of participants	35853	13093	5875	3995
Demographics				
Age at randomization (years)	65 (8)	64 (9)	70 (11)	57 (15)
Sex				
Male	22886 (64%)	9046 (69%)	3582 (61%)	2759 (69%)
Female	12967 (36%)	4047 (31%)	2293 (39%)	1236 (31%)
Race*				
N with known data	35832	13089	5846	3991
Asian	5318 (15%)	3322 (25%)	947 (16%)	1718 (43%)
Black	1417 (4%)	650 (5%)	266 (5%)	131 (3%)
White	27803 (78%)	8203 (63%)	4417 (76%)	2039 (51%)
Other	1294 (4%)	914 (7%)	216 (4%)	103 (3%)
Past medical history				
Heart failure trial	3813 (11%)	957 (7%)	4526 (77%)	377 (9%)
Non-heart failure trial - self-report	3664 (10%)	1612 (12%)	163 (3%)	170 (4%)
No heart failure	28376 (79%)	10524 (80%)	1186 (20%)	3448 (86%)
Any prior cardiovascular disease	22506 (63%)	7231 (55%)	4931 (84%)	961 (24%)
Medications				
RAS inhibitors	29177 (81%)	12045 (92%)	4792 (82%)	3646 (91%)
Mineralocorticoid receptor antagonists	3374 (9%)	868 (7%)	2402 (41%)	323 (8%)
GLP-1 receptor agonists	1457 (4%)	587 (4%)	0 (0%)	0 (0%)
Physical findings				
Systolic blood pressure, mean (SD)	133.9 (15.8)	140.9 (17.0)	127.6 (16.6)	134.3 (16.8)
Laboratory findings				
eGFR (mL/min/1.73m²)				
Mean (SD)	77.8 (20.8)	55.8 (22.2)	56.5 (21.1)	42.3 (16.6)
<45	3137 (9%)	4888 (37%)	2061 (35%)	2541 (64%)
≥45 to <60	3893 (11%)	3109 (24%)	1354 (23%)	887 (22%)
≥60	28599 (80%)	5073 (39%)	2460 (42%)	567 (14%)
uACR (mg/g), geometric mean (geometric SD)	15.3 (3.1)	874.2 (2.5)	17.2 (3.3)	815.3 (2.2)

See eTable 2 for summary details of the included trials including baseline characteristics. *Race based on self report. uACR = urinary albumin:creatinine ratio. eGFR = estimated glomerular filtration rate.

Figure legends

Figure 1: Relative effects of SGLT2 inhibitors on selected efficacy outcomes, by diabetes status and level of albuminuria

Kidney disease progression is a composite outcome defined as a sustained ≥40% eGFR decline from randomization, kidney failure (i.e. start of maintenance dialysis or receipt of a kidney transplant, or a sustained low eGFR [usually <15 mL/min/1.73m^2]) or renal death. Acute kidney injury was generally based on reports of adverse events using the MedDRA Preferred Term of Acute Kidney Injury (see eTable 1 for more details). * Participants with missing values of uACR are included in overall rows but not in subgroups by albuminuria, so the sum of the numbers of events and participants by level of uACR may not equal the overall totals. † The mean follow-up time (in years) in the SGLT2i and diabetes, placebo and diabetes, SGLT2i and no diabetes, placebo and no diabetes groups is 3.1, 3.0, 1.7 and 1.6 for kidney disease progression, 2.8, 2.7, 1.9 and 1.9 for acute kidney injury, 2.6, 2.4, 1.6 and 1.5 for any hospitalization, and 3.3, 3.1, 1.9 and 1.9 for any death. The area of each box is proportional to the inverse of the variance of the log hazard ratios. SGLT2i = sodium-glucose co-transporter-2 inhibitor. uACR = urinary albumin:creatinine ratio. Het = heterogeneity.

Figure 2: Relative effect of SGLT2 inhibitors on safety outcomes, by diabetes status and level of albuminuria

Serious refers to the standard definition of a serious adverse event, including death, life-threatening, hospitalization or other important medical event in the opinion of an investigator. * Participants with missing values of uACR are included in overall rows but not in subgroups by albuminuria, so the sum of the numbers of events and participants by level of uACR may not equal the overall totals. † The mean follow-up time (in years) in the SGLT2i and diabetes, placebo and diabetes, SGLT2i and no diabetes, placebo and no diabetes groups is 3.2, 3.0, 1.9 and 1.9 for bone fracture, 3.2, 3.1, 1.6 and 1.9 for lower limb amputation, 3.1, 2.9, 1.9 and 1.9 for serious urinary tract infections and 2.9, 2.9, 1.9 and 1.9 for ketoacidosis. The

hazard ratios for lower limb amputation and bone fracture in all participants (excluding CANVAS) are 1.02 (0.88, 1.19) and 1.04 (0.96,1.14) respectively. The area of each box is proportional to the inverse of the variance of the log hazard ratios. SGLT2i = sodium-glucose co-transporter-2 inhibitor. uACR = urinary albumin:creatinine ratio. Het = heterogeneity.

Figure 3: Hypothetical number of events prevented or caused per 1000 patients treated with an SGLT2 inhibitor for a year, by diabetes status and level of albuminuria (i.e. absolute effects)

As no significant heterogeneity by level of albuminuria were identified in figures 1&2, this absolute risk bar chart represents estimated absolute effects calculated by applying the diabetes subgroup-specific hazard ratio (i.e. estimate of relative effects) to the average event rate in the placebo arms for each subgroup (first event only). The presented numbers can be considered the hypothetical number of events avoided or caused if a population of 1000 patients with the same baseline risk as placebo-allocated participants from the relevant population were to be prescribed an SGLT2 inhibitor for 1 year, together with the standard error of this estimate (calculated from the uncertainty in the hazard ratio in Figures 1&2). The lighter shaded sections of the bars for any hospitalization and any death indicate the number of hospitalizations for heart failure and cardiovascular deaths avoided (see eFigure 2 for details of hazard ratios for these outcomes). eFigures 5, 7 and 8 provide sensitivity analyses restricted to participants with eGFR <60 ml/min/1.73m^2, restricted to participants with eGFR <60 ml/min/1.73m^2 and presence of heart failure and excluding heart failure trials respectively. *Too few ketoacidosis events to estimate absolute effects in the absence of diabetes. The estimated excess absolute risk of amputation per 1000 patient-years in patients with diabetes after excluding CANVAS was 0.1±0.3 for uACR <200 mg/g and 0.4±0.9 for uACR ≥200mg/g. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Figure 4: Effect of SGLT2 inhibitors on chronic and total slopes, by diabetes status and level of albuminuria (relative and absolute differences)

Chronic slope was defined as the difference in annualized rate of change in eGFR between SGLT2 inhibitor and placebo groups, calculated from the first post-randomization eGFR measurement, typically occurring within three months of randomization to final follow-up. Total slope includes all eGFR measurements from randomization to final follow-up (see eMethods for further explanation). The forest plot presents effects on the relative scale and assesses for evidence for effect modification by study treatment. The area of each box is proportional to the inverse of the variance of slope. There is evidence of larger relative effects on chronic slope in patients with diabetes, but no strong evidence of effect modification by level of albuminuria. The bar chart plots absolute differences in eGFR slopes. SGLT2i = sodium-glucose co-transporter-2 inhibitor. uACR = urinary albumin:creatinine ratio. Het = heterogeneity.