SGLT2 Inhibitors and Kidney and Cardiac Outcomes According to Estimated GFR and Albuminuria Levels: A Meta-analysis of Randomized Controlled Trials

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Rationale & Objective: There are few data on the absolute effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors, despite their importance in treatment decision making. We investigated absolute treatment effects according to baseline kidney disease status.

Study Design: Meta-analysis.

Study Populations: Adults with type 2 diabetes, chronic kidney disease, or heart failure.

Selection Criteria for Studies: Randomized controlled trials of SGLT2 inhibitors (10 trials to November 20, 2020) for clinical outcomes of kidney disease progression, heart failure events, and major cardiovascular events.

Data Extraction: Publications of 10 trials to November 20, 2020.

Analytical Approach: The incidence rate difference (IRD) between SGLT2 inhibitor and placebo was compared across estimated glomerular filtration rate (eGFR) or urinary albumin-creatinine ratio (UACR) subgroups.

Results: Subgroup analyses included data from seven trials (61,821 participants with diabetes or chronic kidney disease). SGLT2 inhibitor treatment, in eGFR subgroups of <45, 45 to <60, and ≥60 mL/min/1.73 m^2, reduced 16.0, 9.5, and 1.9 heart failure events per 1,000 patient-year, respectively (P < 0.001 for heterogeneity). In urine UACR subgroups of >300, 30 to 300, and <30 mg/g, SGLT2 inhibitors reduced 17.3, 1.4, and 2.2 kidney disease events per 1,000 patient-year, respectively (P < 0.001 for heterogeneity), and 14.8, 8.7, and 2.1 heart failure events per 1,000 patient-year, respectively (P = 0.006 for heterogeneity). The pooled IRDs for major cardiovascular events were also greater in lower eGFR or overt albuminuria subgroups. In secondary analyses, risk differences calculated using pooled baseline and relative risks were comparable to the pooled IRDs, while the relative risk reductions for kidney and heart failure outcomes were consistent across the subgroups. For treatment-related harms, IRDs were similar between eGFR subgroups.

Limitations: Study-level data rather than individual patient data were used.

Conclusions: SGLT2 inhibitor treatment resulted in greater reductions of cardiovascular events in patients with lower eGFR and higher albuminuria and had substantially greater absolute benefits of renoprotection in patients with overt albuminuria than in their counterparts.

Sodium/glucose cotransporter 2 (SGLT2) inhibitors have shown considerable benefits in clinical trials.[1-6] The trials included participants with diabetes mellitus who were at high atherosclerotic cardiovascular disease (CVD) risk or adults with and without diabetes who had heart failure or chronic kidney disease (CKD). In post hoc and meta-analyses, SGLT2 inhibitor treatment was associated with a similar relative risk reduction for kidney and CVD outcomes independent of baseline kidney disease status.[7-9]

In treatment decision making for individual patients, it should be considered whether the overall benefits are worth the potential harms and costs. Given similar relative risk reductions, the absolute benefits will be greater among individuals at higher predicted risk. However, it may not be easy to predict patient risk, and the absolute effects of SGLT2 inhibitor treatment have not yet been sufficiently evaluated. In secondary analyses of the CANVAS program, the absolute effects of canagliflozin on clinical outcomes were not dissimilar among the subgroups stratified by estimated glomerular filtration rate (eGFR),[8] whereas the absolute benefit for kidney outcomes was greater in patients with rather than without albuminuria.[10] A post hoc analysis of the CREDENCE trial also showed that absolute treatment effects on cardiovascular outcomes did not clearly differ among eGFR subgroups, although the absolute renoprotective effects were greater among the lower eGFR subgroups.[11] Briefly, the subgroup analyses were underpowered, and the results were inconclusive. Besides, there remain questions about the risk of treatment-related adverse events in patients with CKD.[12]

To investigate the overall effects of SGLT2 inhibitor treatment according to kidney disease status, this meta-analysis of randomized controlled trials assessed absolute outcome risk differences between SGLT2 inhibitor treatment and placebo according to baseline eGFR and albuminuria levels.

PLAIN-LANGUAGE SUMMARY

There are few data on the absolute effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors despite their importance in clinical practice. In this meta-analysis of randomized controlled trials, the incidence rate difference between SGLT2 inhibitor and placebo was compared across estimated glomerular filtration rate (eGFR) or albuminuria categories. The differences in incidence rates of hospitalized heart failure and major cardiovascular events were greater among lower eGFR and higher albuminuria categories while for kidney disease progression the incidence rate difference was greater in overt albuminuria than in nonalbuminuria. Safety was similar at all eGFR levels. These absolute effect data provide direct evidence that the net benefit of SGLT2 inhibitors is greater in patients with reduced eGFR or overt albuminuria than in their counterparts.

METHODS

Study Selection

This meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[13] We performed a literature search of randomized controlled trials in PubMed and Embase from inception to November 20, 2020 (Item S1). The populations of interest were adults (≥18 years old) with type 2 diabetes and adults with CKD or heart failure regardless of the presence or absence of diabetes. We initially identified 471 publications from our database search, and we screened their titles and abstracts for eligibility, after removal of duplicates. As a result, 18 full articles comprising 10 individual trials for clinical outcomes of kidney disease progression, heart failure, and major cardiovascular events were selected for data extraction (Fig S1). Two investigators reviewed the trial characteristics (Table S1) and independently assessed study quality using the Cochrane Risk of Bias Tool (Table S2). One investigator extracted data using a standardized collection form, and the second investigator checked the data.

Measures of Treatment Effects

We studied the effects of SGLT2 inhibitors for kidney disease progression, heart failure events, major cardiovascular events, mortality, and treatment-related harms. The study outcomes were specified referring to the primary and secondary outcomes in the included trials (Table S3). Kidney disease progression was defined as a composite of substantial decline in eGFR (doubling of serum creatinine or 40% or 50% decline in eGFR), end-stage kidney disease, or death from kidney failure. Heart failure event was defined as heart failure with hospitalization (or a composite of hospitalized heart failure or cardiovascular death). Major cardiovascular events were the composite of myocardial infarction, stroke, or cardiovascular death.

To measure absolute treatment effects, the incidence rate difference (IRD) between SGLT2 inhibitor and placebo and its standard error was collected according to baseline eGFR and urinary albumin-creatinine ratio (UACR). We calculated those with extracted data of events per patient-year and numbers of events. When the data were not available, we used additional data including numbers of patients and average follow-up time in SGLT2 inhibitor treatment and placebo groups or the hazard ratio and 95% confidence interval (CI) between the groups. In addition to the IRD, the incidence rate and standard error in the control group was collected to obtain a meta-analytic estimate of baseline risk. The IRD and incidence rate and their standard errors were calculated on the basis of the Poisson distribution (Items S2 and S3). To measure relative effects, hazard ratios and 95% CIs were extracted and transformed to log values and their standard errors.

Data Analysis

To assess absolute treatment effects of SGLT2 inhibitors, IRDs between SGLT2 inhibitor treatment and placebo were meta-analyzed across the subgroups stratified according to prespecified cutoff values of eGFR (60 and 45 mL/min/1.73 m^2) and UACR (30 and 300 mg/g). We conducted the subgroup analysis including all feasible IRD data. To incorporate incompletely categorized data, the eGFR category of <60 mL/min/1.73 m^2 in the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 Trial) was regarded as an equivalent of 45 to <60 mL/min/1.73 m^2; the participants with an eGFR of <45 mL/min/1.73 m^2 might be rare because the trial enrolled participants with a creatinine clearance (calculated by the Cockcroft-Gault equation) of ≥60 mL/min/1.73 m^2. The eGFR category of <60 mL/min/1.73 m^2 in the VERTIS CV trial was also regarded as an eGFR category of 45 to <60 mL/min/1.73 m^2 because most might have an eGFR of ≥45 mL/min/1.73 m^2. The total participants of the DAPA-CKD trial, which enrolled patients with UACR >200 mg/g, were incorporated as a category of UACR >300 mg/g; however, the incomplete eGFR categories of <45 and 45-75 mL/min/1.73 m^2 in the DAPA-CKD were not used because it was not clear whether the categories were representative of decreased eGFR or severe albuminuria in the absence of counterpart eGFR category (i.e., ≥60 mL/min/1.73 m^2). The trials of participants with established heart failure who had an extreme baseline risk for heart failure event were not included in the subgroup analysis to avoid problems from high-skewed distribution of data.

We also conducted a meta-analysis with subsets of trials, including the trials of established heart failure. In the subsets of trials, we analyzed the outcomes with insufficient subgroup data: namely, all-cause mortality,

Table 1. Baseline Characteristics of Included Trials

	EMPA-REG OUTCOME[1,2,15]	CANVAS Program[3,8,10]	DECLARE-TIMI 58[4,16]	VERTIS CV[17]	SCORED[18]	CREDENCE[5,11]	DAPA-CKD[19]	DAPA-HF[6,20]	EMPEROR-Reduced[21,22]	SOLOIST-WHF[23]
No. of participants	7,020	10,142	17,160	8,246	10,584	4,401	4,304	4,744	3,730	1,222
Participant Characteristics										
Age, y	63.1 ± 8.7	63.3 ± 8.3	63.9 ± 6.8	64.4 ± 8.1	69 [37.0-51.4]	63.0 ± 9.2	61.9 ± 12.1	66.3 ± 10.9	66.9 ± 11.0	69 [63-76]
Women	2,004 (28.5%)	3,633 (35.8%)	6,422 (37.4%)	2,477 (30.0%)	4,754 (44.9%)	1,494 (33.9%)	1,425 (33.1%)	1,109 (23.4%)	893 (23.9%)	412 (33.7%)
Diabetes	7,020 (100.0%)	10,142 (100.0%)	17,160 (100.0%)	8,238 (100.0%)	10,584 (100.0%)	4,401 (100.0%)	2,906 (67.5%)	2,139 (45.1%)	1,856 (49.8%)	1,222 (100%)
Cardiovascular disease										
Atherosclerotic disease	7,020 (100.0%)	6,656 (65.6%)	6,974 (40.6%)	8,238 (100.0%)	5,144 (48.6%)	2,220 (50.4%)	1,610 (37.4%)	NA	NA	NA
History of heart failure	706 (10.1%)	1,461 (14.4%)	1,724 (10.0%)	1,958 (23.8%)	3,283 (31.0%)	652 (14.8%)	468 (10.9%)	4,744 (100.0%)	3,730 (100.0%)	1,222 (100.0%)
LVEF <40.0 %	NA	NA	NA	NA	1,033 (9.8%)	NA	NA	4,744 (100.0%)	3,730 (100.0%)	725 (59.3%)
eGFR										
≥60 mL/min/1.73 m²	5,201 (74.1%)	8,101 (79.9%)	15,894 (92.6%)	6,438 (78.1%)	0 (0.0)	1,809 (41.1%)	454 (11.5%)	2,816 (59.4%)	1,929 (51.7%)	368 (30.2%)
45 to <60 mL/min/1.73 m²	1,249 (17.8%)	1,485 (14.6%)	1,265 (7.4%)[a]	1,805 (21.9%)[a]	5,116 (48.3%)	1,279 (29.1%)	1,328 (30.9%)	1,926 (40.6%)[a]	900 (24.1%)	851 (69.8%)[a]
<45 mL/min/1.73 m²	570 (8.1%)	554 (5.5%)	NA	NA	5,468 (51.7%)	1,313 (29.8%)	2,522 (57.6%)	NA	899 (24.1%)	NA
UACR										
<30 mg/g	4,171 (60.0%)	7,007 (69.8%)	11,644 (69.1%)	NA	3,709 (35.0%)	0 (0.0)	0 (0.0)	NA	2,078 (56.0%)	NA
30 to 300 mg/g	2,013 (29.0%)	2,206 (22.6%)	4,030 (23.9%)	NA	3,589 (33.9%)	0 (0.0)	0 (0.0)	NA	1,236 (33.3%)	NA
>300 mg/g	769 (11.1%)	760 (7.6%)	1,169 (6.9.%)	NA	3,286 (31.0%)	4,401 (100.0%)	4,340 (100.0%)[c]	NA	396 (10.7%)	NA
SGLT2 Inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Sotagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin	Sotagliflozin
Duration of follow-up, median, y	3.1	2.4	4.2	3.0	1.3	2.6	2.4	1.5	1.3	0.8
Baseline risk, per 1,000[b]										
Kidney disease progression	11.5	9.0	7.0	12.0	7.0	40.4	58.0	12.0	30.7	NA

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Included Trials

	EMPA-REG OUTCOME[1,2,15]	CANVAS Program[3,8,10]	DECLARE-TIMI 58[4,16]	VERTIS CV[17]	SCORED[18]	CREDENCE[5,11]	DAPA-CKD[19]	DAPA-HF[6,20]	EMPEROR-Reduced[21,22]	SOLOIST-WHF[23]
Heart failure event	14.5	8.7	8.5	11.0	51.0	25.3	30.0	101.0	155.0	639.0
Major cardiovascular events	43.9	31.5	24.2	40.0	47.5	48.7	NA	NA	NA	NA

Values are mean ± SD, number (percentage), or median [interquartile range] unless otherwise indicated.
Abbreviations: eGFR, estimated glomerular filtration rate; LVEF, left ventricle ejection fraction; NA, not available; UACR, urinary albumin-creatinine ratio. Studies: CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.
[a]The values are the number (percentage) of participants with an eGFR of <60 mL/min/1.73 m².
[b]The baseline risk was the incidence rate per 1,000 patient-year observed in the control group.
[c]The values are the number (percentage) of participants with a UACR of ≥200 mg/g.

components of major cardiovascular events, and treatment-related adverse events. As for adverse events related to treatment with a $P < 0.05$, subgroup analyses were additionally performed using a single cutoff of eGFR 60 or 45 mL/min/1.73 m² or UACR 300 mg/g.

To assess relative effects, we conducted secondary analyses with hazard ratios between SGLT2 inhibitor and placebo across the eGFR or albuminuria subgroups. To obtain a meta-analytic estimate of baseline risk, we also analyzed the incidence rate in the control group according to eGFR or albuminuria levels. Using the meta-analytic relative risk and baseline risk, the risk difference between treatment and control groups was calculated as another index of absolute treatment effect with the assumption of constant event risk (constant hazard) over time.

$$\text{Risk difference per } 1,000 = 1,000 \times \text{baseline risk}$$
$$\times (1 - \text{relative risk})$$

This meta-analysis was conducted using the DerSimonian and Laird random-effects model with Review Manager, version 5.4 (Cochrane Collaboration, 2020). The fixed-effects model was exceptionally used to combine parameter estimates within a trial (eg, combining hazard ratios in eGFR 60 to <90 and ≥90 mL/min/1.73 m² to obtain a hazard ratio for eGFR ≥ 60 mL/min/1.73 m²). We assessed statistical heterogeneity between and within eGFR or albuminuria subgroups using the I^2 statistic and P values. The $I^2 < 40\%$ indicates that heterogeneity may not be important, and $I^2 > 75\%$ may represent considerable heterogeneity.[14] We provided two-sided P values and did not adjust for multiple testing. When statistical heterogeneity was observed within subgroups ($I^2 > 40\%$), we performed sensitivity analyses excluding trials by the heterogeneity in participants' characteristics, outcome definitions, and/or follow-up periods. Further, we did sensitivity analysis restricted to trials that facilitated within-trial comparisons (ie, trials with no missing data in each subgroup of eGFR or albuminuria) to explore the influence of clinical and methodological diversity between trials on the results of the primary analyses.

RESULTS

We identified 10 randomized controlled trials and 71,533 participants (mean age, 64.8 years; and women, 34.4%) including 28,543 (39.9%) with an eGFR of <60 mL/min/1.73 m² and 15,121 (26.4%) with a UACR of >300 mg/g (Table 1). Of the 10 trials, 2 trials were conducted in CKD patients with a UACR of >200 or 300 mg/g, 1 was in CKD patients with an eGFR of <60 mL/min/1.73 m², 3 in established heart failure patients, and the remaining 4 in patients with diabetes at high atherosclerotic CVD risk. Among those, 3 trials enrolled participants regardless of the presence or absence of diabetes.
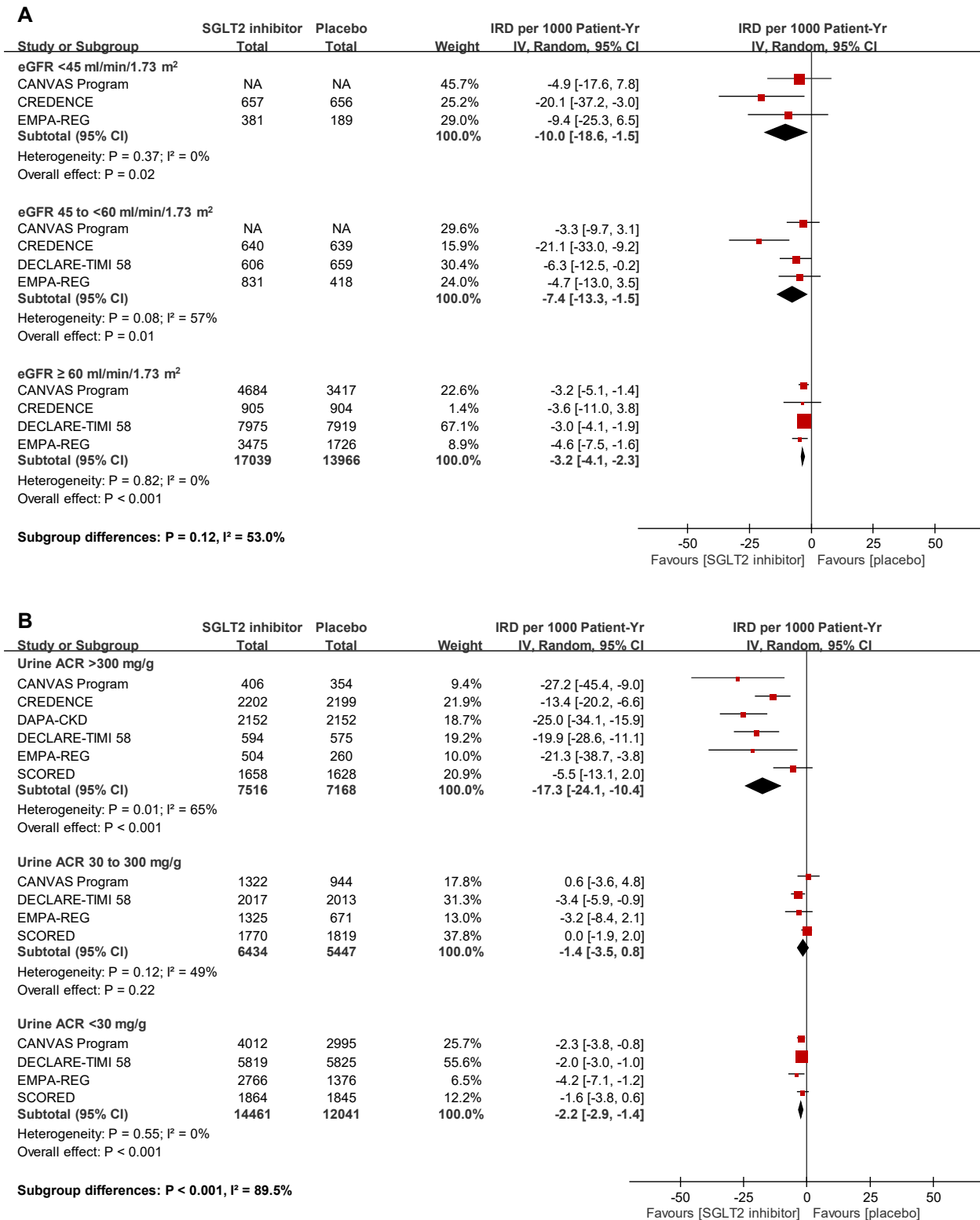
Figure 1. Absolute risk reduction for kidney disease progression according to (A) eGFR or (B) albuminuria levels. The IRDs between SGLT2 inhibitor and placebo were meta-analyzed using the DerSimonian and Laird random-effects model. Kidney disease progression was defined as a composite of 40% decline in eGFR, end-stage kidney disease, or renal death in the CANVAS program and DECLARE-TIMI 58; a composite of 50% decline in eGFR, end-stage kidney disease, or renal death in the DAPA-CKD and the SCORED trials; or a composite of doubling of serum creatinine, end-stage kidney disease, or renal death in the CREDENCE, the EMPA-REG, and the VERTIS CV trials. In the SCORED trial, the composite outcome did not include renal death. Abbreviations: ACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IRD, incidence rate difference; SGLT2, sodium/glucose cotransporter 2.

Subgroup Analysis by eGFR or Albuminuria

Subgroup analyses included data from 7 trials comprising 3 of CKD and 4 of high-risk diabetes. In stratified analyses by eGFR, the absolute risk reduction for kidney disease progression (Fig 1A) appeared to be greater in lower eGFR subgroups with modest heterogeneity (I^2 = 53.0%), but it did not reach statistical significance (P = 0.12). As for heart failure events (Fig 2A), the absolute risk reduction was substantially greater in lower eGFR subgroups: in eGFR subgroups of <45, 45 to <60, and ≥60 mL/min/1.73 m^2, the pooled IRDs between SGLT2 inhibitor and placebo were −16.0, −9.5, and −1.9 events per 1,000 patient-year, respectively (P < 0.001 for heterogeneity, I^2 = 93.5%). The IRDs for major cardiovascular events (Fig 3A) also tended to be greater in lower eGFR subgroups (P = 0.04 for heterogeneity, I^2 = 68.7%). In contrast with the beneficiary effects, IRDs for adverse effects were similar between eGFR subgroups of <60 and ≥60 (Fig 4) and between <45 and ≥45 mL/min/1.73 m^2 (Table S5).

When comparing absolute treatment effects across UACR subgroups, the absolute risk reduction for each outcome was consistently greater in subgroups with a UACR of >300 mg/g than in those without. In UACR subgroups of >300, 30 to 300, and <30 mg/g, the pooled IRDs for kidney disease progression (Fig 1B) were −17.3, −1.4, and −2.2 events per 1,000 patient-year, respectively (P < 0.001 for heterogeneity, I^2 = 89.5%); the IRDs for heart failure events (Fig 2B) were −14.8, −8.7, and −2.1 events per 1,000 patient-year, respectively (P = 0.006 for heterogeneity, I^2 = 80.5%); and the IRDs for major cardiovascular events (Fig 3B) were −15.3, −1.8, and −3.8 events per 1,000 patient-year, respectively (P = 0.01 for heterogeneity, I^2 = 76.7%). For adverse effects, IRDs were similar between UACR subgroups of >300 and ≤300 mg/g except for greater IRD of volume depletion in higher albuminuria (Table S5).

Meta-analysis With Subsets of Trials

We performed meta-analysis with subsets of trials adding the trials of established heart failure (Figs S2-S5). In trials of established heart failure, the absolute risk reduction for heart failure event was markedly great, with a pooled IRD of −72.3 (95% CI, −121.0 to −23.6) events per 1,000 patient-year; the absolute reduction for kidney disease progression was modest, with a pooled IRD of −8.7 (95% CI, −19.5 to 2.0) events per 1,000 patient-year. As for all-cause mortality, the IRDs in subsets of CKD, high-risk diabetes, and established heart failure were −4.9 (−10.2 to 0.4), −3.2 (−5.9 to −0.94), and −13.0 (−23.7 to −2.3) events per 1,000 patient-year, respectively. When we analyzed each component of major cardiovascular events (Figs S6-S8), the IRDs between SGLT2 inhibitor and placebo were minimal for myocardial infarction and stroke in the trials of high-risk diabetes, while the IRDs in the SCORED, a CKD trial, were modest.

When we evaluated adverse events that could potentially be related to SGLT2 inhibitor treatment

(Table S4), the incidence rates of ketoacidosis, volume depletion, limb amputation, and genital infection were higher in SGLT2 inhibitor versus placebo, with pooled IRDs of 0.5 (95% CI, 0.1-0.9), 3.4 (95% CI, 1.0-5.8), 1.2 (95% CI, 0.2-2.3), and 12.0 (95% CI, 5.6-18.4) events per 1,000 patient-year, respectively. Conversely, the incidence rates of any serious adverse events and acute kidney injury were lower in treatment versus control groups, with pooled IRDs of −13.9 (95% CI, −19.6 to −8.2) and −1.5 (95% CI, −2.8 to −0.3) events per 1,000 patient-year, respectively.

Secondary Analyses

When secondary analyses were conducted with hazard ratios between SGLT2 inhibitor and placebo, relative risk reductions for kidney disease progression and heart failure events (Figs S9 and S10) were similar across the eGFR and UACR subgroups. However, the relative risk reduction for major cardiovascular events (Fig S11) was greater in the subgroup with overt albuminuria: the hazard ratios in UACR subgroups of >300, 30-300, and <30 mg/g were 0.74, 0.95, and 0.87, respectively (P = 0.03 for heterogeneity, I^2 = 70.3%). Table 2 shows the pooled estimates of baseline risk, relative risk, risk difference, and IRD according to eGFR or albuminuria levels. The risk differences calculated with meta-analytic baseline risk and relative risk were similar to the IRDs from the primary analyses. The magnitudes of absolute risk reductions for kidney and heart failure outcomes were approximately proportional to the sizes of baseline risks in the eGFR and albuminuria subgroups.

Sensitivity Analyses

In subgroup analyses, modest heterogeneity was observed within a portion of subgroups. As for kidney disease progression, the heterogeneity observed within albuminuria subgroups (Fig 1B) disappeared after excluding the SCORED trial, which had a relatively short follow-up period. Even after that exclusion, the between-albuminuria subgroup heterogeneity persisted (P < 0.001, I^2 = 95.2%). As for heart failure events, the observed heterogeneity within albuminuria subgroups (Fig 2B) disappeared after exclusion of the DAPA-CKD and SCORED trials, which used a composite outcome including cardiovascular death and/or were conducted in patients with reduced eGFR. Even after that, the between-subgroup heterogeneity persisted (P = 0.006, I^2 = 80.7%). Furthermore, we repeated subgroup analyses restricted to trials with no missing data in each subgroup of eGFR and albuminuria (Figs S12-S14; Table S6). The trends of greater absolute risk reductions in subgroups with lower eGFR and those in subgroups with overt albuminuria persisted.

DISCUSSION

In a meta-analysis of 10 randomized clinical trials of SGLT2 inhibitors, the IRD for cardiovascular events was greater at lower eGFR and higher albuminuria levels while for
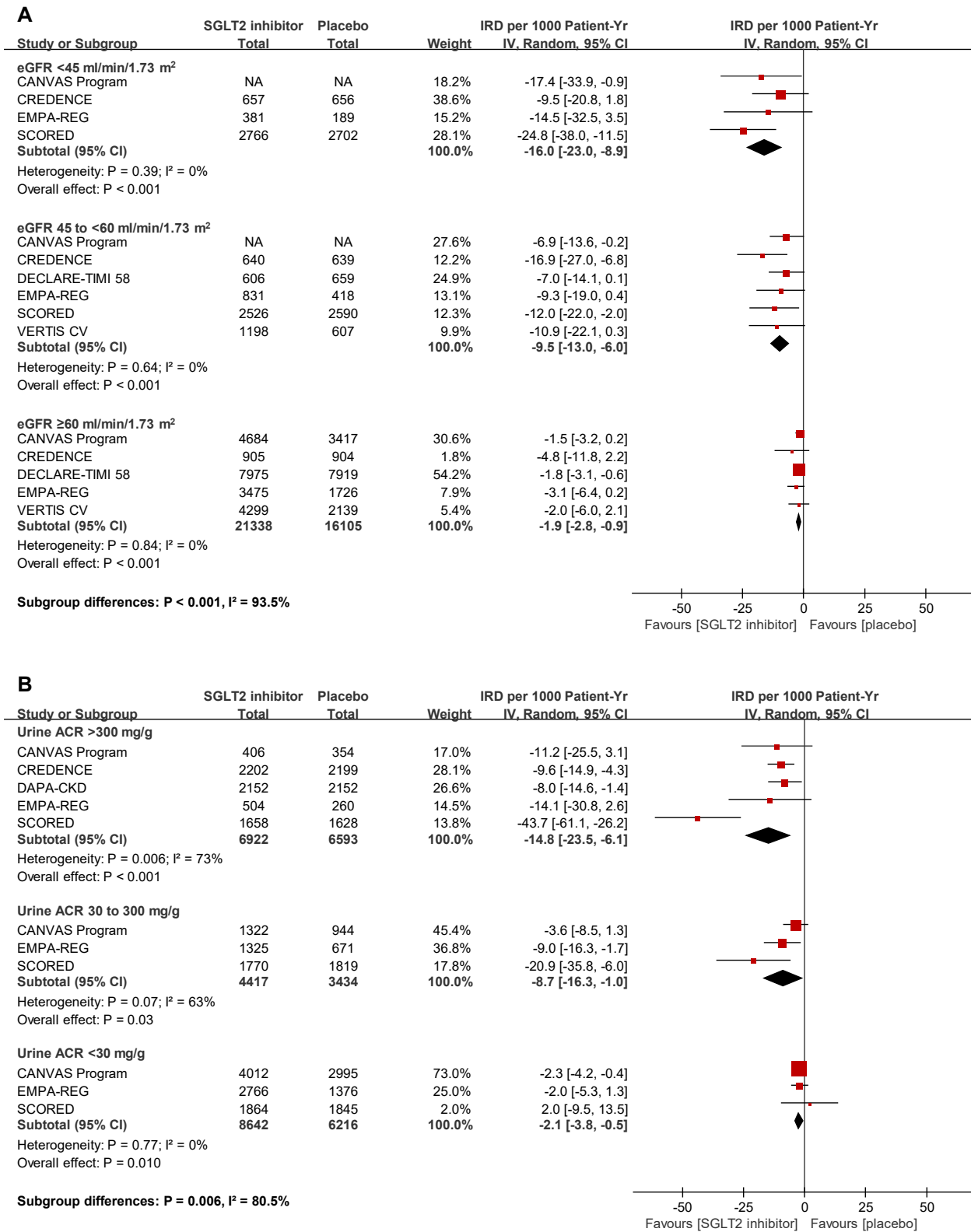
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Study or Subgroup	SGLT2 inhibitor Total	Placebo Total	Weight	IRD per 1000 Patient-Yr IV, Random, 95% CI
eGFR <45 ml/min/1.73 m²				
CANVAS Program	NA	NA	18.2%	-17.4 [-33.9, -0.9]
CREDENCE	657	656	38.6%	-9.5 [-20.8, 1.8]
EMPA-REG	381	189	15.2%	-14.5 [-32.5, 3.5]
SCORED	2766	2702	28.1%	-24.8 [-38.0, -11.5]
Subtotal (95% CI)			100.0%	-16.0 [-23.0, -8.9]
Heterogeneity: P = 0.39; I² = 0%				
Overall effect: P < 0.001				
eGFR 45 to <60 ml/min/1.73 m²				
CANVAS Program	NA	NA	27.6%	-6.9 [-13.6, -0.2]
CREDENCE	640	639	12.2%	-16.9 [-27.0, -6.8]
DECLARE-TIMI 58	606	659	24.9%	-7.0 [-14.1, 0.1]
EMPA-REG	831	418	13.1%	-9.3 [-19.0, 0.4]
SCORED	2526	2590	12.3%	-12.0 [-22.0, -2.0]
VERTIS CV	1198	607	9.9%	-10.9 [-22.1, 0.3]
Subtotal (95% CI)			100.0%	-9.5 [-13.0, -6.0]
Heterogeneity: P = 0.64; I² = 0%				
Overall effect: P < 0.001				
eGFR ≥60 ml/min/1.73 m²				
CANVAS Program	4684	3417	30.6%	-1.5 [-3.2, 0.2]
CREDENCE	905	904	1.8%	-4.8 [-11.8, 2.2]
DECLARE-TIMI 58	7975	7919	54.2%	-1.8 [-3.1, -0.6]
EMPA-REG	3475	1726	7.9%	-3.1 [-6.4, 0.2]
VERTIS CV	4299	2139	5.4%	-2.0 [-6.0, 2.1]
Subtotal (95% CI)	21338	16105	100.0%	-1.9 [-2.8, -0.9]
Heterogeneity: P = 0.84; I² = 0%				
Overall effect: P < 0.001				

Subgroup differences: P < 0.001, I² = 93.5%

IRD per 1000 Patient-Yr IV, Random, 95% CI
-50 -25 0 25 50
Favours [SGLT2 inhibitor] Favours [placebo]

B

Study or Subgroup	SGLT2 inhibitor Total	Placebo Total	Weight	IRD per 1000 Patient-Yr IV, Random, 95% CI
Urine ACR >300 mg/g				
CANVAS Program	406	354	17.0%	-11.2 [-25.5, 3.1]
CREDENCE	2202	2199	28.1%	-9.6 [-14.9, -4.3]
DAPA-CKD	2152	2152	26.6%	-8.0 [-14.6, -1.4]
EMPA-REG	504	260	14.5%	-14.1 [-30.8, 2.6]
SCORED	1658	1628	13.8%	-43.7 [-61.1, -26.2]
Subtotal (95% CI)	6922	6593	100.0%	-14.8 [-23.5, -6.1]
Heterogeneity: P = 0.006; I² = 73%				
Overall effect: P < 0.001				
Urine ACR 30 to 300 mg/g				
CANVAS Program	1322	944	45.4%	-3.6 [-8.5, 1.3]
EMPA-REG	1325	671	36.8%	-9.0 [-16.3, -1.7]
SCORED	1770	1819	17.8%	-20.9 [-35.8, -6.0]
Subtotal (95% CI)	4417	3434	100.0%	-8.7 [-16.3, -1.0]
Heterogeneity: P = 0.07; I² = 63%				
Overall effect: P = 0.03				
Urine ACR <30 mg/g				
CANVAS Program	4012	2995	73.0%	-2.3 [-4.2, -0.4]
EMPA-REG	2766	1376	25.0%	-2.0 [-5.3, 1.3]
SCORED	1864	1845	2.0%	2.0 [-9.5, 13.5]
Subtotal (95% CI)	8642	6216	100.0%	-2.1 [-3.8, -0.5]
Heterogeneity: P = 0.77; I² = 0%				
Overall effect: P = 0.010				

Subgroup differences: P = 0.006, I² = 80.5%

IRD per 1000 Patient-Yr IV, Random, 95% CI
-50 -25 0 25 50
Favours [SGLT2 inhibitor] Favours [placebo]

Figure 2. Absolute risk reduction for heart failure event according to (A) eGFR or (B) albuminuria levels. The IRDs between SGLT2 inhibitor and placebo were meta-analyzed using the DerSimonian and Laird random-effects model. Heart failure event was defined as hospitalized heart failure (or plus urgent visit for heart failure) in the CANVAS program and the CREDENCE, DECLARE-TIMI 58, and EMPA-REG trials; or a composite of hospitalized heart failure or cardiovascular death in the DAPA-CKD, SCORED, and VERTIS CV trials. In the SCORED trial, the outcome measure was the number of total rather than first events. Abbreviations: ACR, urinary albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; IRD, incidence rate difference; SGLT2, sodium/glucose cotransporter 2.
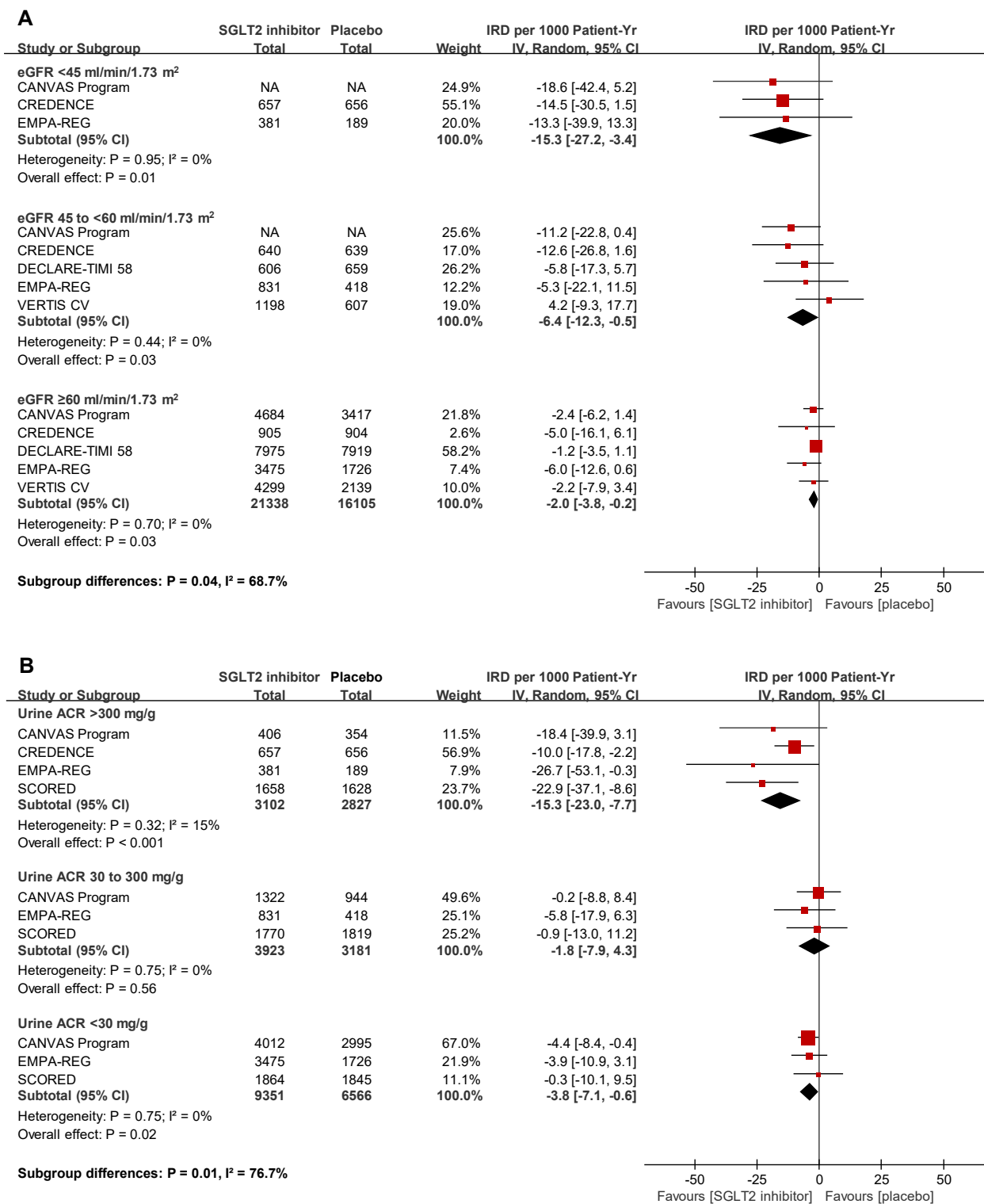
A

Study or Subgroup	SGLT2 inhibitor Total	Placebo Total	Weight	IRD per 1000 Patient-Yr IV, Random, 95% CI
eGFR <45 ml/min/1.73 m²				
CANVAS Program	NA	NA	24.9%	-18.6 [-42.4, 5.2]
CREDENCE	657	656	55.1%	-14.5 [-30.5, 1.5]
EMPA-REG	381	189	20.0%	-13.3 [-39.9, 13.3]
Subtotal (95% CI)			100.0%	**-15.3 [-27.2, -3.4]**
Heterogeneity: P = 0.95; I² = 0%				
Overall effect: P = 0.01				
eGFR 45 to <60 ml/min/1.73 m²				
CANVAS Program	NA	NA	25.6%	-11.2 [-22.8, 0.4]
CREDENCE	640	639	17.0%	-12.6 [-26.8, 1.6]
DECLARE-TIMI 58	606	659	26.2%	-5.8 [-17.3, 5.7]
EMPA-REG	831	418	12.2%	-5.3 [-22.1, 11.5]
VERTIS CV	1198	607	19.0%	4.2 [-9.3, 17.7]
Subtotal (95% CI)			100.0%	**-6.4 [-12.3, -0.5]**
Heterogeneity: P = 0.44; I² = 0%				
Overall effect: P = 0.03				
eGFR ≥60 ml/min/1.73 m²				
CANVAS Program	4684	3417	21.8%	-2.4 [-6.2, 1.4]
CREDENCE	905	904	2.6%	-5.0 [-16.1, 6.1]
DECLARE-TIMI 58	7975	7919	58.2%	-1.2 [-3.5, 1.1]
EMPA-REG	3475	1726	7.4%	-6.0 [-12.6, 0.6]
VERTIS CV	4299	2139	10.0%	-2.2 [-7.9, 3.4]
Subtotal (95% CI)	**21338**	**16105**	100.0%	**-2.0 [-3.8, -0.2]**
Heterogeneity: P = 0.70; I² = 0%				
Overall effect: P = 0.03				

Subgroup differences: P = 0.04, I² = 68.7%

IRD per 1000 Patient-Yr IV, Random, 95% CI
-50 -25 0 25 50
Favours [SGLT2 inhibitor] Favours [placebo]

B

Study or Subgroup	SGLT2 inhibitor Total	Placebo Total	Weight	IRD per 1000 Patient-Yr IV, Random, 95% CI
Urine ACR >300 mg/g				
CANVAS Program	406	354	11.5%	-18.4 [-39.9, 3.1]
CREDENCE	657	656	56.9%	-10.0 [-17.8, -2.2]
EMPA-REG	381	189	7.9%	-26.7 [-53.1, -0.3]
SCORED	1658	1628	23.7%	-22.9 [-37.1, -8.6]
Subtotal (95% CI)	**3102**	**2827**	100.0%	**-15.3 [-23.0, -7.7]**
Heterogeneity: P = 0.32; I² = 15%				
Overall effect: P < 0.001				
Urine ACR 30 to 300 mg/g				
CANVAS Program	1322	944	49.6%	-0.2 [-8.8, 8.4]
EMPA-REG	831	418	25.1%	-5.8 [-17.9, 6.3]
SCORED	1770	1819	25.2%	-0.9 [-13.0, 11.2]
Subtotal (95% CI)	**3923**	**3181**	100.0%	**-1.8 [-7.9, 4.3]**
Heterogeneity: P = 0.75; I² = 0%				
Overall effect: P = 0.56				
Urine ACR <30 mg/g				
CANVAS Program	4012	2995	67.0%	-4.4 [-8.4, -0.4]
EMPA-REG	3475	1726	21.9%	-3.9 [-10.9, 3.1]
SCORED	1864	1845	11.1%	-0.3 [-10.1, 9.5]
Subtotal (95% CI)	**9351**	**6566**	100.0%	**-3.8 [-7.1, -0.6]**
Heterogeneity: P = 0.75; I² = 0%				
Overall effect: P = 0.02				

Subgroup differences: P = 0.01, I² = 76.7%

IRD per 1000 Patient-Yr IV, Random, 95% CI
-50 -25 0 25 50
Favours [SGLT2 inhibitor] Favours [placebo]

Figure 3. Absolute risk reduction for major cardiovascular events according to (A) eGFR or (B) albuminuria levels. The IRDs between SGLT2 inhibitor and placebo were meta-analyzed using the DerSimonian and Laird random-effects model. Major cardiovascular events were the composite of myocardial infarction, stroke, or cardiovascular death. Abbreviations: ACR, urinary albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; IRD, incidence rate difference; SGLT2, sodium/glucose cotransporter 2.
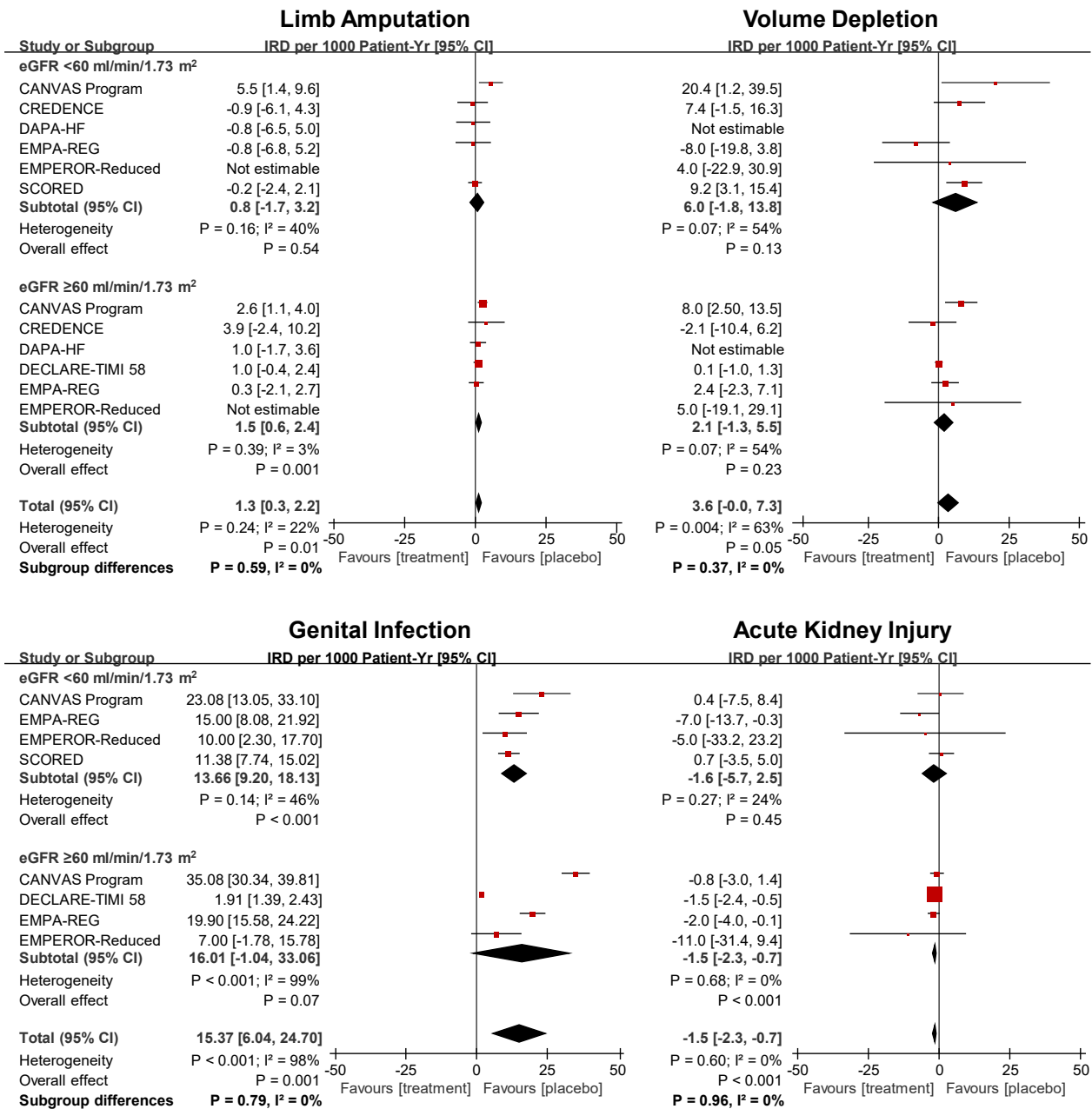
Figure 4. Absolute effects of SGLT2 inhibitors on adverse events (acute kidney injury, genital infection, limb amputation, volume depletion) according to the eGFR level. The IRDs between SGLT2 inhibitor and placebo were meta-analyzed using the DerSimonian and Laird random-effects model. Abbreviations: ACR, urinary albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; IRD, incidence rate difference; SGLT2, sodium/glucose cotransporter 2.

kidney events the IRD was greater at higher albuminuria levels. Safety was similar at all eGFR levels. Compared with previous meta-analyses stratified by baseline kidney function,[9,24] the present study added DAPA-CKD, SCORED, and 4 more trials and analyzed the difference in incidence rate between SGLT2 inhibitor and placebo to investigate absolute treatment effects. This study provides direct evidence that net benefit of SGLT2 inhibitor treatment is greater in populations with reduced eGFR or overt albuminuria than in their counterparts.

To date, most meta-analyses have assessed relative effects of SGLT2 inhibitors, and they reported that the relative benefits were similar independently of baseline kidney disease status,[9,24,25] as also shown in our analysis (Figs S9 and S10). With respect to treatment effect measures, there is empirical evidence that relative effect versus absolute effect measures are more likely to be consistent and generalizable.[26,27] However, knowledge of absolute effects is important for weighing benefits and harms in treatment decision making. The SGLT2 inhibitor trials, which were

Table 2. SGLT2 Inhibitor Versus Placebo Across eGFR and Albuminuria Subgroups

Outcome or Subgroup	No. of Participants (Trials)	Baseline Risk per 1,000[a]	Relative Risk	Risk Difference per 1,000[b]	IRD per 1,000 Patient-Year
Kidney Disease Progression					
eGFR					
<45 mL/min/1.73 m²	2,437 (3)	38.5 (5.6-71.3)	0.69 (0.54-0.89)	11.9	−10.0 (−18.6 to −1.5)
45 to <60 mL/min/1.73 m²	5,278 (4)	20.4 (11.2-29.5)	0.60 (0.46-0.77)	8.1	−7.4 (−13.3 to −1.5)
≥60 mL/min/1.73 m²	31,005 (4)	9.0 (6.3-11.7)	0.56 (0.46-0.67)	4.0	−3.2 (−4.1 to −2.3)
UACR					
>300 mg/g	14,684 (6)	41.2 (28.7-53.7)	0.56 (0.48-0.66)	18.1	−16.7 (−27.0 to −6.4)
30-300 mg/g	11,881 (4)	6.7 (1.9-11.4)	0.72 (0.54-0.94)	1.9	−1.4 (−3.5 to 0.8)
<30 mg/g	26,502 (4)	4.4 (3.1-5.7)	0.49 (0.39-0.62)	2.2	−2.2 (−2.9 to −1.4)
Established heart failure	8,474 (2)	21.0 (2.7-39.3)	0.59 (0.41-0.84)	8.6	−8.7 (−19.5 to 2.0)
Total	70,331 (9)	19.6 (14.5-24.8)	0.61 (0.55-0.68)	7.7	−5.5 (−7.7 to −3.3)
Heart Failure Event					
eGFR					
<45 mL/min/1.73 m²	7,905 (4)	49.4 (14.5-84.3)	0.69 (0.58-0.82)	15.3	−16.0 (−23.0 to −8.9)
45 to <60 mL/min/1.73 m²	12,199 (6)	30.7 (19.1-42.4)	0.69 (0.60-0.81)	9.5	−9.5 (−13.0 to −6.0)
≥60 mL/min/1.73 m²	37,443 (5)	12.2 (8.0-16.4)	0.81 (0.72-0.91)	2.3	−1.9 (−2.8 to −0.9)
UACR					
>300 mg/g	13,515 (5)	46.2 (26.6-65.8)	0.64 (0.57-0.72)	16.6	−14.8 (−23.5 to −6.1)
30-300 mg/g	7,851 (3)	37.5 (7.5-67.5)	0.71 (0.58-0.86)	10.9	−8.7 (−16.3 to −1.0)
<30 mg/g	14,858 (3)	17.6 (7.0-28.2)	0.82 (0.61-1.10)	3.2	−2.1 (−3.8 to −0.5)
Established heart failure	9,696 (3)	285.3 (166.1-404.5)	0.69 (0.62-0.76)	88.4	−72.3 (−121.0 to −23.6)
Total	71,553 (10)	52.1 (41.6-62.6)	0.68 (0.64-0.73)	16.7	−8.7 (−12.3 to −5.1)
Major Cardiovascular Events					
eGFR					
<45 mL/min/1.73 m²	2,437 (3)	62.8 (53.3-72.3)	0.74 (0.60-0.92)	16.3	−15.3 (−27.2 to −3.4)
45 to <60 mL/min/1.73 m²	7,083 (5)	47.6 (43.0-52.2)	0.88 (0.75-1.03)	5.7	−6.4 (−12.3 to −0.5)
≥60 mL/min/1.73 m²	37,443 (5)	26.2 (24.8-27.5)	0.92 (0.86-0.98)	2.1	−2.0 (−3.8 to −0.2)
UACR					
>300 mg/g	5,929 (4)	56.1 (51.2-60.9)	0.74 (0.66-0.84)	14.6	−15.3 (−23.0 to −7.7)
30-300 mg/g	7,104 (3)	41.5 (36.7-46.2)	0.95 (0.82-1.10)	2.1	−1.8 (−7.9 to 4.3)
<30 mg/g	15,917 (3)	28.8 (26.1-31.4)	0.87 (0.77-0.98)	3.7	−3.8 (−7.1 to −0.6)
Total	57,553 (6)	39.1 (30.3-47.9)	0.89 (0.84-0.94)	4.3	−4.0 (−6.4 to −1.5)

Values in parentheses are 95% CI unless otherwise indicated.

Abbreviations: eGFR, estimated glomerular filtration rate; IRD, incidence rate difference; SGLT2, sodium/glucose cotransporter 2; UACR, urinary albumin-creatinine ratio.

[a]Baseline risk was estimated with the meta-analysis of the incidence rate per 1,000 patient-year in the control group on the assumption of constant event risk over time.

[b]Risk difference was calculated as Risk difference = Baseline risk × (1 − Relative risk).

recently conducted including up to 17,000 participants in a trial, were exceptionally large as compared with earlier trials for other purposes. Using clinical outcomes data from the large-sale trials, we could estimate absolute treatment effects according to eGFR and albuminuria levels with acceptable within-subgroup heterogeneity.

In the present study, the absolute risk reductions for kidney and heart failure events were approximately proportional to the baseline risks of the events, while the relative risk reductions were consistent across the subgroups. These beneficial effects of SGLT2 inhibitors are comparable to those of statins on atherosclerotic CVD although statins, unlike SGLT2 inhibitors, have an uncertain effect on kidney disease progression or heart failure outcome.[28-30]

Currently, guidelines recommend predicting individual risk with CVD risk assessment tools and initiating statins in patients at high-predicted risk.[31,32] However, the risk assessment tools, which were developed primarily to predict risks of atherosclerotic CVD, may not be appropriate in decision making for SGLT2 inhibitor treatment. The KDIGO risk matrix can alternatively be considered based on greater absolute benefits in lower eGFR and incremental benefits in overt albuminuria.[33]

In post hoc analyses of trials, the relative benefits of SGLT2 inhibitors were similar across KDIGO categories while the absolute benefit for major cardiovascular events was greater in higher risk categories.[7,34] When considering poor outcomes in heart failure patients and rapidly rising global prevalence of end-stage kidney disease,[35] guidelines and a risk matrix are urgently needed to identify the candidates who are most likely to have a net benefit from SGLT2 inhibitor treatment.

Meanwhile, the relative as well as absolute risk reduction for major cardiovascular events was greater in patients with than without overt albuminuria. Further, the risk reductions for myocardial infarction and stroke were minimal in the trials of high-risk diabetes (Figs S7 and S8). Similarly, in a recent meta-analysis, the beneficial effect of SGLT2 inhibitors on major cardiovascular events was only seen in patients with established atherosclerotic CVD.[24]

The latter could merely reflect a weak beneficial effect of SGLT2 inhibitors on atherosclerotic CVD, or it might indicate true effect modification by albuminuria or CVD status. If the latter is true, it may raise the possibility of different clinical outcomes from a same pharmacological effect (eg, albuminuria-dependent benefits of further blood pressure-lowering by SGLT2 inhibitors) and/or suggest the presence of diverse mechanisms of treatment effects on the atherosclerotic and other cardiorenal diseases. Further research will be required to explore the finding convincingly.

In subgroup analyses, we observed modest within-subgroup heterogeneity in a portion of subgroups. As for kidney disease progression, the within-albuminuria subgroup heterogeneity was derived from the small IRD in the SCORED trial, which had a relatively short duration of follow-up. Substantial decline in eGFR may develop after years, and treatment benefits can be masked initially due to the early, temporary decline in eGFR by SGLT2 inhibitors.[2,5] For heart failure events, the observed within-albuminuria subgroup heterogeneity was derived from the large IRD in SCORED trial, which enrolled participants with reduced eGFR. SGLT2 inhibitors may possibly have a synergistic effect on heart failure outcome in patients with both albuminuria and reduced eGFR. There also is a possibility that the study drug sotagliflozin, a SGLT2 inhibitor with some SGLT1 inhibition, may have an incremental benefit for heart failure events.

There are a number of limitations in this study. First, subgroup analyses are observational in nature, and we used trial-level data rather than individual patient data. The parameters introduced in subgroup analyses were not completely obtained for the subgroups, and it could lead to bias due to missing or non-reporting results. However, we believe that it would not be a case of selective non-reporting or underreporting in such high-profile, large-scale trials.

Next, this meta-analysis was performed assuming that baseline risk was stationary over time, and a violation to the assumption could potentially lead to bias. When we reviewed cumulative incidence curves in each of the included trials, the associations between cumulative incidences and follow-up times were roughly linear. We did not find any curve suggesting severe violations.

Finally, there were differences in participants' characteristics, outcome definitions, follow-up durations, and drugs used across the included trials. Specifically, the CKD trials (CREDENCE, DAPA-CKD, and SCORED) defined substantial decline in eGFR as 50% decline in eGFR or doubling of serum creatinine rather than 40% decline in eGFR. Moreover, the follow-up period of the SCORED trial was relatively short. These might at least not lead to overestimation of kidney-related benefits in CKD trials. Nonetheless, absolute effect estimates could easily be influenced by such differences. It should be considered whether there are potential effect modifiers besides decreased kidney function when treating patients with the use of SGLT2 inhibitors.

In this meta-analysis of SGLT2 inhibitor trials, absolute benefits for cardiovascular outcomes were greater in patients with reduced eGFR or overt albuminuria compared with patients without the condition. Moreover, the absolute renoprotective benefit was substantially greater in the patients with than without overt albuminuria. The absolute benefits for kidney and heart failure outcomes were proportionally associated with the baseline outcome risks, and the relative benefits were consistent across eGFR and albuminuria categories. For major cardiovascular events, relative as well as absolute benefits were greater in patients with than without overt albuminuria. These data may provide helpful information for management of patients with various kidney conditions and decision making for SGLT2 inhibitor treatment.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: PRISMA flow diagram: identification of eligible studies.

Figure S2: Absolute risk reductions for kidney disease progression across the subsets of trials.

Figure S3: Absolute risk reductions for heart failure events across the subsets of trials.

Figure S4: Absolute risk reductions for major cardiovascular events across the subsets of trials.

Figure S5: Absolute risk reductions for all-cause mortality across the subsets of trials.

Figure S6: Absolute risk reductions for cardiovascular mortality across the subsets of trials.

Figure S7: Absolute risk reductions for myocardial infarction across the subsets of trials.

Figure S8: Absolute risk reductions for stroke across the subsets of trials.

Figure S9: Relative risk reductions for kidney disease progression according to eGFR and albuminuria levels.

Figure S10: Relative risk reductions for heart failure events according to eGFR and albuminuria levels.

Figure S11: Relative risk reductions for major cardiovascular events according to eGFR and albuminuria levels.

Figure S12: Absolute risk reductions for kidney disease progression among the trials with no missing data for each eGFR or albuminuria subgroup.

Figure S13: Absolute risk reductions for heart failure events among the trials with no missing data for each eGFR or albuminuria subgroup.

Figure S14: Absolute risk reductions for major cardiovascular events among the trials with no missing data for each eGFR or albuminuria subgroup.

Item S1: Search algorithm.

Item S2: Calculation of incidence rate differences and standard errors for the meta-analysis of incidence rate difference.

Item S3: Calculation of incidence rates and standard errors for the meta-analysis of incidence rate in the control group.

Table S1: Trial inclusion criteria and definition of index disease and risk factors.

Table S2: Risk of bias assessment.

Table S3: Trial outcome definitions.

Table S4: IRDs between SGLT2 inhibitor and placebo for treatment-related adverse events.

Table S5: Absolute effects of SGLT2 inhibitors on adverse events according to eGFR or albuminuria levels.

Table S6: Absolute risk reductions for kidney and cardiovascular outcomes among the trials with no missing subgroup data.

ARTICLE INFORMATION

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Does SGLT2 inhibitor treatment improve outcomes in patients with CKD and albuminuria?

Kidney Medicine

Meta-analysis of RCTs

10 trials included through Nov 2020

N = 61,821

With a history of:

Type 2 diabetes

CKD

Heart Failure

Incidence rate difference between SGLT2 inhibitor and placebo (per 1000 patient-years)

GFR (mL/min/1.73m²)	Heart failure events	uACR (mg/g)	Heart failure events	Kidney disease events
<45	-16.0	>300	-14.8	-17.3
45 – 60	-9.5	30 – 300	-8.7	-1.4
≥60	-1.9	<30	-2.1	-2.2
	P=0.001		P=0.006	P=0.001

The pooled incidence rate difference for major cardiovascular events was greater in lower eGFR and overt albuminuria subgroup

Conclusion: SGLT2 inhibitor treatment resulted in greater reductions of cardiovascular events in individuals with lower eGFR and in individuals with higher albuminuria levels. Individuals with higher albuminuria also had fewer kidney events when treated with SGLT2 inhibitors.

Reference: Chun KJ and Jung HH. SGLT2 inhibitors and kidney and cardiac outcomes according to eGFR and albuminuria levels: A meta-analysis of randomized controlled trials. *Kidney Medicine*, 2021.

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