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ORIGINAL ARTICLE

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Larger effect size in composite kidney outcomes than in major cardiovascular events associated with sodium-glucose cotransporter-2 (SGLT2) inhibitors compared with glucagon-like peptide-1 receptor agonists (GLP-1RAs): A pooled analysis of type 2 diabetes trials

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Abstract

Aim: To compare treatment effect sizes between a composite kidney outcome (CKO) and three-point major adverse cardiovascular event (MACE-3) outcomes with use of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), and to investigate the relationship between treatment effects on CKO and MACE-3 in patients with type 2 diabetes (T2D).

Materials and Methods: We performed a MEDLINE database search up to December 31, 2021 to identify all placebo-controlled Phase 3 trials which investigated the efficacy of glucose-lowering interventions, and selected those reporting results for CKO and MACE-3. Hazard ratios (HRs) with 95% confidence intervals (CIs) for both outcomes were extracted for each trial, and we evaluated differences in treatment effect sizes by using a ratio of HRs (rHR): the HR for CKO to the HR for MACE-3. A random-effects meta-analysis was used to obtain the overall rHR across trials and according to subgroup. We investigated the relationship between treatment effects on CKO and MACE-3 using the coefficient of determination (R^2) with weighted meta-regression. The study protocol was registered on PROSPERO (CRD42022299690).

Results: A total of 12 studies fulfilled the prespecified criteria, and comprised a total of 104 987 patients with T2D. On average, treatment effect sizes were 17% greater for CKO than for MACE-3 (rHR 0.83, 95% CI 0.74 to 0.92; $I^2 = 50\%$; $P = 0.03$; $\tau^2 = 0.0161$), especially for trials of SGLT2 inhibitors compared with GLP-1RAs. For secondary outcomes, treatment effect size was 22%, 21%, 16% and 9% greater for CKO than for myocardial infarction, stroke, death from cardiovascular causes, and hospitalization for heart disease, respectively. MACE-3 and CKO were moderately

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correlated (ρ = 0.40; $P = 0.21$), and only 11% (95% CI 1% to 54%) of the variability in the MACE-3 effect could be explained by the variability in the CKO effect.

Conclusion: In T2D patients, treatment effect sizes were greater for kidney than for macrovascular (MACE-3) outcomes, with important differences according to the drugs considered. CKO and MACE-3 are independent. Caution must be taken when interpreting CKO in the absence of MACE-3 data.

KEYWORDS

CKD-DT2, composite kidney outcome, MACE-3, meta-analysis

1 | INTRODUCTION

Patients with coexisting type 2 diabetes (T2D) and chronic kidney disease (CKD) are at high risk for both cardiovascular events and premature death.[1-3] With the requirement of the US authorities to assess cardiovascular safety for all new blood glucose-lowering drugs in 2008, many randomized trials evaluating sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) against placebo have been conducted.[4]

Results from these randomized trials as well as large-scale systematic review and network meta-analysis of 764 trials suggest that, compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors and GLP-1RAs are more effective in reducing cardiovascular disease (CVD), kidney failure, hospital admission for heart failure, and all-cause mortality. Nevertheless, some differences in cardiorenal protection exist between SGLT2 inhibitors and GLP-1RAs. For example, SGLT2 inhibitors reduce admissions to hospital for heart failure, and cause genital infection to a greater extent than GLP-1RAs, whereas GLP-1RAs reduce nonfatal stroke and increase severe gastrointestinal events to a greater extent than SGLT2 inhibitors.[5] This evidence was confirmed by findings from several recent meta-analyses, which suggested that the cardiorenal benefits of SGLT2 inhibitors and GLP-1RAs may be partially mediated by improvements in intermediate outcomes such as reductions in blood pressure, body weight, glycated haemoglobin (HbA1c), or albumin-to-creatinine ratio with no increase in the risk of hypoglycaemia.[6-9]

Based on the above evidence, SGLT2 inhibitors and GLP-1RAs are now recommended for diabetic patients in secondary prevention, with the choice of molecule guided by safety and type of micro- or macrovascular complications. At present, there are no randomized clinical trials to support these recommendations with regard to the choice between gliflozin and GLP-1RAs in cases of renal failure or CVD. Estimation of the differences in treatment effect size between major adverse cardiovascular events (MACE-3) and a composite kidney outcome (CKO) may help to overcome this issue and guide health authorities and clinicians to choose the most appropriate drug in these contexts. In addition, whether the magnitude of treatment effects differs according to MACE-3 or CKO remains uncertain. To the best of our knowledge, the difference between CKO and MACE-3 with regard to treatment effect size has not yet been formally investigated.

The aim of this study therefore was, first, to investigate whether there is a difference in treatment effect sizes between the two major cardiorenal outcomes (MACE-3 and CKO) in patients with T2D, and between CKO and each component of the MACE-3 outcome. Second, we aimed to investigate the relationship between treatment effects on kidney composite outcome and major cardiovascular events.

2 | METHODS

2.1 | Search strategy and selection criteria

In this meta-analysis study, we searched MEDLINE (via PubMed), up to December 31, 2021 for published randomized placebo-controlled trials (RCTs) which evaluated the efficacy of new glucose-lowering drugs, mainly SGLT2 inhibitors and GLP-1RAs, on both cardiovascular and renal outcomes in patients with T2D. Observational studies (cohort, case-control), cases series or cases reports were excluded. This pooled analysis was aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The study protocol was registered on PROSPERO (CRD42022299690).

2.2 | Data extraction and risk of bias assessment

Data extraction and trial bias assessment were performed independently by two reviewers (A.D. and M.C.B.), with disagreement resolved by consensus. For each study that met the eligibility criteria, the following information was extracted: the name of the first author, year of publication, study design (superiority or noninferiority), follow-up, sample size, presence of a run-in period, outcome status (MACE-3 as primary outcome vs. MACE-3 as secondary outcome), patients' clinicopathological characteristics (sex, age, body mass index [BMI], estimated glomerular filtration rate [eGFR], HbA1c, systolic blood pressure, history of heart failure or CVD, and T2D duration), treatment (SGLT2 inhibitors and GLP-1RAs), and clinical outcomes (number of event for each primary and secondary outcome and adjusted hazard ratio [HR] and 95% confidence interval [CI] associated with outcomes). Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias Tool (Rob2) for RCTs.[10] In Rob2, the following characteristics were considered: randomization sequence generation and

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allocation concealment (selection bias); the blinding of participants and personnel (performance bias); the blinding of outcome (detection bias); incomplete outcome data (attrition bias); and selective reporting (reporting bias).

2.3 | Data synthesis and analysis

The primary outcome was analysis of the two major cardiorenal outcomes: three-point MACE-3 for cardiovascular outcomes (MACE-3), a composite of death from cardiovascular causes, fatal or nonfatal stroke, and fatal or nonfatal myocardial infarction, and CKO, consisting of end-stage renal disease (except for the ELIXA trial,[11] which used new-onset macroalbuminuria), decline in kidney function defined as a decrease in eGFR above a certain threshold (≥30%, ≥40%, and ≥50%), and death from renal causes. The secondary outcomes were all-cause mortality, hospitalization for heart failure, and each component of the MACE-3 outcome: death from cardiovascular causes, myocardial infarction and stroke. To evaluate the differences in effect size between the two major cardiorenal outcomes, we applied a meta-epidemiological approach using a two-step process.[12] In Step 1, the differences in treatment effect size between the two major cardiorenal outcomes were quantified within each study by using the ratio of HRs (rHR): HR for CKO to the HR for MACE-3 (rHR = HR_{CKO}/$HR_{MACE\text{-}3}$). An HR <1 indicated a large treatment effect, and an rHR <1.0 indicated a greater effect size for CKO relative to MACE-3 in the same study. The standard error (SE) of the log rHR was computed by applying the method used by Tan et al, as follows:[13]

$$SE\,(logrHR) = \sqrt{Var(logHR_{CKO}) + Var(logHR_{MACE-3}) - \rho \times 2 \times SE(logHR_{CKO}) \times SE(logHR_{MACE-3})}.$$

In Step 2, a combined difference (rHR) and 95% CI between CKO and MACE-3 across studies was estimated using a random-effects model. Heterogeneity across trials were investigated using the I^2 statistic, the Cochrane Q test, and between-study variance τ^2. We performed sensitivity analyses to evaluate the robustness of results by testing different levels of correlation ($\rho = 0$ to 0.95) in treatment effect estimates between CKO and MACE-3. We applied the same methodology to assess the difference in treatment effect size between CKO and the secondary endpoints (each component of the MACE-3 outcome, hospitalization for heart failure, and all-cause mortality). Furthermore, we estimated the ratio of the absolute difference (rAD) between CKO and MACE-3, hospitalization for heart failure, and all-cause mortality using the same methodology that was described for the rHR. An absolute difference (AD) <0 indicated a great effect of treatment, and rAD <0 indicated a great effect size for CKO relative to the MACE-3 in the same study. Subgroup analyses using a meta-regression model were based on study design (superiority or noninferiority), use of a run-in period (yes vs. no), outcome status (MACE-3 as primary outcome vs. MACE-3 as secondary outcome), type of treatment (SGLT2 inhibitors and GLP-1RAs), baseline eGFR (<60 mL/min per 1.73 m^2 vs. ≥60 mL/min per 1.73 m^2), presence of baseline CVD (all patients with CVD vs. none) or the presence of baseline heart failure (≥20% vs. <20%), and the median values for age, BMI, HbA1c level, duration of diabetes, duration of follow-up, and sample size to ensure balance between the comparison groups.

Finally, we investigated the relationship between treatment effects on CKO and MACE-3 by using a meta-regression of log $HR_{MACE\text{-}3}$ on log HR_{CKO} weighted by within-study variance. To analyse the proportion of variance in treatment effect on MACE-3 that is predictable from the treatment effect on CKO (R^2 at trial-level), the Spearman correlation ρ values between log $HR_{MACE\text{-}3}$ and log HR_{CKO} were calculated. The 95% CI for R^2 was estimated using a 1000-bootstrap procedure. All analyses were performed using the "*meta*" *R* package, and *P* values < 0.05 were taken to indicate statistical significance.

3 | RESULTS

3.1 | Individual trials characteristics

Of 1026 trials retrieved from MEDLINE, we excluded 997 trials that did not meet the inclusion criteria. By assessing the 29 full-text trials, we excluded 12 that measured major cardiovascular events without kidney outcomes, and five that assessed the effects of other treatment on kidney and cardiovascular outcomes (three for selective mineralocorticoid receptor antagonists and two for DPP-4 inhibitors). Therefore, a total of 12 trials fulfilled the prespecified criteria (Figure S1), with low risk of bias (Figure S2), comprising a total of 104 987 patients with T2D.[11,14-25] Eight studies used a noninferiority design with switching to superiority, two exclusively evaluated noninferiority, and two exclusively evaluated superiority. All trials, except CREDENCE[23] and LEADER (secondary analysis),[15] used a three-point composite cardiovascular event as the primary outcome. The CKO comprised end-stage renal disease in all trials, except for the ELIXA trial,[11] which used new-onset macroalbuminuria, death from renal causes in seven trials, decline in kidney function defined as a decrease in eGFR above a certain threshold (≥ 30% in one trial, ≥ 40% in four trials, and ≥ 50% in one trial). The glucose-lowering drugs that were evaluated against placebo comprised six SGLT2 inhibitors and six GLP-1RAs.

Patient characteristics at baseline were: age 60 to 69 years; HbA1c 7.2% to 8.9%, eGFR 44.4 to 85.3 mL/min per 1.73 m^2 and history of heart failure 10.1% to 31.5%, and all patients included in the VERTIS CV, ELIXA and EMPA-REG OUTCOME trials had baseline CVD (Table 1). During a median follow-up of 3 years, 7614 patients died, of whom 63% died from cardiovascular causes; 11 712 patients experienced a MACE-3 outcome, the CKO occurred in 4768 patients, hospital admission for heart failure in 3823 patients, fatal or nonfatal myocardial infarctions in 5493 patients, and fatal or non-fatal stroke in 2962 patients. In the SCORED trial, a benefit with regard to MACE-3 was observed without any CKO benefit, while a benefit was observed with regard to CKO without any MACE-3 benefit in the DECLARE-TMI 58 trial.[21]

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TABLE 1 Baseline characteristics and use of glucose-lowering drugs across trials

Trials (participant; inclusion period; sites)	Key inclusion criteria	Drugs (dose, administration route)	Age, years[a]	Sex (male)	BMI, kg/m^2[a]	Diabetes duration, years[a]	HbA1c, %[a]	History of HF	SBP, mm Hg[a]	eGFR, mL/min per 1.73 m^2[a]	Follow-up, years, median (IQR)	Event rates in placebo group	Cardiovascular composite outcome	Kidney composite outcome
REWIND (n = 9901; Aug 18, 2011 to Aug 14, 2014; 371 sites in 24 countries)	Age ≥ 50/55/60 years with CVD or high-risk CV factors; ≤ 2 antidiabetic drugs ± insulin, BMI ≥23 kg/m^2, and HbA1c ≤ 9%	Dulaglutide, 1.5 mg/week, subcutaneous	66.2 (6.5)	5312 (54%)	32.3 (5.7)	10.5 (7.2)	7.3 (1.1)	853 (9%)	137.2 (16.8)	77 (23)	5.4 (5.1 – 5.9)	2.7 per 100 person-years	MACE-3 (nonfatal stroke, nonfatal myocardial infarction, and death from CV causes or unknown causes)	ACR >33.9 mg/mmol relative to baseline, a sustained 30% reduction or greater decline in eGFR or renal replacement therapy
ELIXA (n = 6068; July 9, 2010 to Aug 2, 2013 from 49 countries)	Age ≥ 30 years; eGFR >30 mL/min/1.73 m^2 with ASCVD within 180 days, and HbA1c 5.5-11.0%	Lixisenatide, 10 μg/day or 20 μg/day, subcutaneous	60 (10)	4207 (69%)	30.1 (5.6)	9.2 (8.2)	7.7 (1.3)	1358 (22%)	129 (17)	76.7 (21.3)	2.1 (NR)	6.3 per 100 person-years	MACE-3 (CV death, nonfatal myocardial infarction, nonfatal stroke)	New-onset macroalbuminuria
LEADER (n = 9340; September 2010 to April 2012; 410 sites in 32 countries)	Age ≥ 50 years with CVD/HF/CKD or age ≥ 60 years with ≥1 CV risk factor, and HbA1c ≥ 7%	Liraglutide, 1.8 mg/day, subcutaneous	64 (7)	6003 (64%)	32.5 (6.3)	12.8 (8.0)	8.7 (1.6)	1667 (18%)	136 (18)	80 (NR)	3.8 (NR)	3.9 per 100 person-years	MACE-3 (nonfatal stroke, nonfatal myocardial infarction, and death from CV causes)	Doubling creatinine level or new-onset of macroalbuminuria, an eGFR ≤45 mL/min/1.73 m^2 or need for continuous renal replacement therapy or death from renal cause
SUSTAIN-6 (n = 3297; February 2013 to December 2013; 230 sites in 20 countries)	Age ≥ 50 years with CVD/HF/CKD ≥ stage 3 or age ≥ 60 years with ≥1 CV risk factor, and HbA1c ≥ 7%	Semaglutide, 0.5 mg/week or 1.0 mg/week, subcutaneous	64.6 (7.4)	2002 (61%)	32.8 (6.2)	13.9 (8.1)	8.7 (1.5)	777 (24%)	135.6 (17.2)	80 (61 – 92)	2.1 (NR)	4.4 per 100 person-years	MACE-3 (nonfatal stroke, nonfatal myocardial infarction including silent, and death from CV causes)	New or worsening nephropathy (macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance ≤45 mL/min/1.73 m^2 or the need for continuous renal replacement therapy
EXSCEL (n = 14 752; June 18, 2010 to September 16, 2015; 687 sites in 35 countries)	Age ≥ 18 years with primary prevention of CVD (30% of sample) or established CVD (70% of sample), and HbA1c 6.5-10%	Exenatide, 2 mg/week, subcutaneous	62 (9)	9149 (62%)	32.7 (6.4)	12 (7 – 18)	8.0 (7.3 – 8.9)	2389 (16%)	135 (17)	77 (61 – 92)	3.2 (2.2 – 4.4)	4.0 per 100 person-years	MACE-3 (nonfatal stroke, nonfatal myocardial infarction, and death from CV causes)	New-onset persistent macroalbuminuria, ≥40% worsening eGFR, kidney replacement therapy, or death due to kidney disease
AMPLITUDE-O (n = 4076; May 11, 2018 to April 25, 2019;	Age ≥ 18 years with prior CVD or age ≥ 50 years (if male) or age ≥ 55 years (if female) with ≥1 CV	Efpeglenatide, 4 mg/week or 6 mg/week, subcutaneous	64.5 (8.2)	2732 (67%)	32.7 (6.2)	15.4 (8.8)	8.9 (1.5)	737 (18%)	134.9 (15.5)	72.4 (22.4)	1.81 (1.69 – 1.98	5.3 per 100 person-years	MACE-3 (nonfatal stroke, nonfatal myocardial infarction, and death from CV	Incident macroalbuminuria plus ACR ≥30% from baseline, a sustained decrease

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TABLE 1 (Continued)

Trials (participant; inclusion period; sites)	Key inclusion criteria	Drugs (dose, administration route)	Age, years[a]	Sex (male)	BMI, kg/m^2[a]	Diabetes duration, years[a]	HbA1c, %[a]	History of HF	SBP, mm Hg[a]	eGFR, mL/min per 1.73 m^2[a]	Follow-up, years, median (IQR)	Event rates in placebo group	Cardiovascular composite outcome	Kidney composite outcome
344 sites in 28 countries)	risk factor and eGFR 25.0 to 59.9 mL/min/1.73 m^2, and HbA1c ≥ 7%												causes or undetermined causes)	eGFR (≥40% or <15 mL/min/1.73 m^2 for ≥30 days) or kidney replacement therapy for ≥90 days
DECLARE-TIMI 58 (n = 17 160; 882 sites in 33 countries)	Age ≥ 40 years with eGFR ≥60 mL/min/1.73 m^2 and with ≥1 ASCVD risk factor or established ASCVD, and HbA1c 6.5-12%	Dapagliflozin 10 mg/day, oral	63.9 (6.8)	10 738 (63%)	32.1 (6.0)	11.0 (6.0 – 16.0)	8.3 (1.2)	1724 (10%)	135.1 (15.3)	85.2 (15.4)	4.2 (3.9 – 4.4)	5.8 per 1000 person-years	MACE-3 (ischaemic stroke, myocardial infarction, and death from CV causes)	≥40% decrease in eGFR to <60 mL/min/1.73 m^2, new end-stage renal disease, or death from renal causes
SCORED (n = 10 584; December 8, 2017 to January 20, 2020; in 44 countries)	Age ≥ 18 years with CKD (eGFR 25 to 60 mL/min/1.73 m^2) and with ≥1 CV risk factor, and HbA1c ≥ 7%	Sotagliflozin, 200 mg/day or 400 mg/day (if no unacceptable side effects), oral	69 (63-74)	5830 (55%)	31.8 (28.1 – 36.2)	NR	8.3 (7.6 – 9.3)	3283 (31%)	138 (127 – 149)	44.5 (37.0 – 51.4)	1.3 (1.0 – 1.69)	7.5 per 100 person-years	MACE-3 (ischaemic stroke, myocardial infarction, and death from CV causes)	Sustained decrease of ≥50% in eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR <15 mL/min/1.73 m^2 for ≥30 days
VERTIS CV (n = 8246 with 4023 patients from cohort 1: December 2013 to July 2015; and 4223 patients from cohort 2: June 2016 to April 2017; 567 sites in 34 countries)	Age ≥ 40 years with established ASCVD, and HbA1c 7.0-10.5%	Ertugliflozin, 5 mg/day or 15 mg/day, oral	64.4 (8.1)	5769 (70%)	32.0 (5.5)	13.0 (8.4)	8.2 (1.0)	1958 (24%)	133.3 (13.8)	75.8 (20.9)	3.5 (4.3 in cohort 1 and 2.7 in cohort 2	4.0 per 100 person-years	MACE-3 (nonfatal stroke, non-fatal myocardial infarction, and death from CV causes)	Death from renal cause, or renal replacement therapy, or doubling of the serum creatinine level
CANVAS program (n = 10 142) including CANVAS (n = 4330) and CANVAS-R (n = 5812); 667 sites in 30 countries)	Age ≥ 30 years with history of symptomatic ASCVD or age ≥ 50 years ≥2 CV risk factor, and HbA1c ≥ 7 to ≤10.5%	Canagliflozin 100 mg/day or 300 mg/day, oral	63.3 (8.3)	6509 (64%)	32.0 (5.9)	13.5 (7.8)	8.2 (0.9)	1461 (14%)	136.6 (15.8)	76.5 (20.5)	2.4 (NR)	31.5 per 1000 person-years	MACE-3 (nonfatal stroke, non-fatal myocardial infarction, and death from CV causes)	Sustained decrease of ≥40% in eGFR, need for renal transplantation, or death from renal causes

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TABLE 1 (Continued)

Trials (participant; inclusion period; sites)	Key inclusion criteria	Drugs (dose, administration route)	Age, years[a]	Sex (male)	BMI, kg/m^2[a]	Diabetes duration, years[a]	HbA1c, %[a]	History of HF	SBP, mm Hg[a]	eGFR, mL/min per 1.73 m^2[a]	Follow-up, years, median (IQR)	Event rates in placebo group	Cardiovascular composite outcome	Kidney composite outcome
CREDENCE (n = 4401; March 2014 to May 2017; 690 sites in 34 countries)	Age ≥ 30 years; eGFR >30 and <90 mL/min/1.73 m^2 with albuminuria (ACR >300 to 5000 mg/g), treated with RASB, and HbA_{1C} 6.5-12.0%	Canagliflozin 100 mg/day, oral	63.0 (9.2)	2907 (66%)	31.3 (6.2)	15.8 (8.6)	8.3 (1.3)	652 (15%)	140.0 (15.6)	56.2 (18.2)	2.62 (0.02 to 4.53)	61.2 per 1000 person-years	MACE-3 (nonfatal stroke, nonfatal myocardial infarction, and death from CV causes)	End-stage kidney disease (dialysis, transplantation, or sustained eGFR <15 mL/min/1.73 m^2), doubling of the serum creatinine level, or death from renal causes
EMPA-REG OUTCOME (n = 7020; September 2010 to April 2013, 590 sites in 42 countries)	Age ≥ 18 years with BMI ≤45 kg/m^2 and eGFR ≥30 mL/min/1.73 m^2 with no antidiabetic's drugs within 12 weeks and HbA1c ≥ 7.0 to ≤9.0% or stable antidiabetic drugs within 12 weeks and HbA1c ≥ 7.0 to ≤10.0%	Empagliflozin, 10 mg/day or 25 mg/day, oral	63.1 (8.6)	5016 (71%)	30.6 (5.3)	NR	8.1 (0.9)	706 (10%)	135.3 (16.9)	74.2 (21.6)	3.1 (NR)	43.9 per 1000 person-years	MACE-3 (nonfatal stroke, nonfatal myocardial infarction, and death from CV causes)	Doubling creatinine, end-stage kidney disease, or renal death

[a]Data are mean and standard deviation.

Abbreviations: ACR, albumin-to-creatinine ratio; ASCVD, atherosclerosis cardiovascular disease; BMI, body mass index; CV, cardiovascular; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, hospitalization for heart failure; IQR, interquartile range; MACE-3, major adverse cardiovascular events; NR, not reported; SBP, systolic blood pressure.

Trials: REWIND: Researching Cardiovascular Event with a Weekly Incretin in Diabetes; ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL: Exenatide Study of Cardiovascular Event Lowering; EMPLITUDE-O: Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk; DECLARE-TIMI 58: Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; SCORED: Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; VERTIS CV: Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial; CANVAS: Canagliflozin Cardiovascular Assessment Study; CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients.

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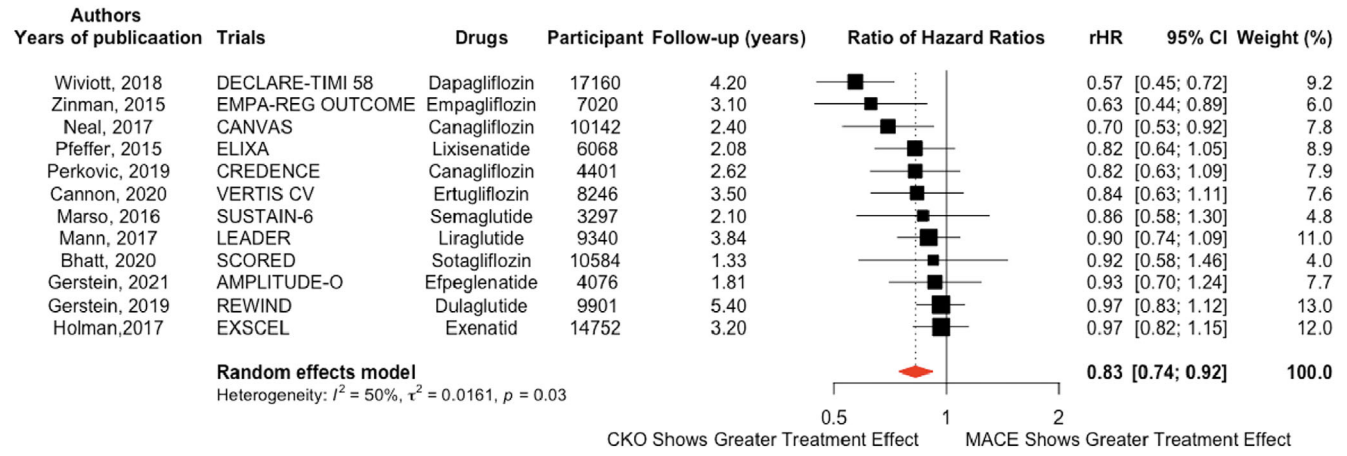


FIGURE 1 Ratios of hazard ratios (rHRs) for the composite kidney outcome (CKO) and major adverse cardiovascular events (MACE-3) for 12 trials. An rHR <1.0 indicates greater treatment effect size for CKO than for MACE-3. REWIND, Researching Cardiovascular Event with a Weekly Incretin in Diabetes; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; EMPLITUDE-O, Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

3.2 | Differences in treatment effect size between MACE-3 and CKO

Under the assumption of no dependency between the two cardiac and renal outcomes (ρ = 0), treatment effect sizes, on average, were 17% greater for the CKO than for MACE-3 (pooled rHR 0.83, 95% CI 0.74 to 0.92), with moderate heterogeneity across trials (I^2 = 50%; P = 0.03; τ^2 = 0.0161; Figure 1). In sensitivity analyses, we found consistent results testing different levels of correlation (ρ = 0.05 to 0.95) in treatment effect estimates between CKO and MACE-3 (Figure S3). For secondary outcomes, on average, treatment effect sizes were 22% (rHR 0.78; 95% CI 0.69 to 0.87) greater with CKO than with myocardial infarction, with low heterogeneity across trials (I^2 = 16%; P = .30; τ^2 = 0.0088). The corresponding treatment effect sizes were 21% (rHR 0.79, 95% CI 0.65 to 0.97; I^2 = 69%; P = 0.04; τ^2 = 0.0636), 16% (rHR 0.84, 95% CI 0.75 to 0.95; I^2 = 42%; P = 0.06; τ^2 = 0.0179), and 9% (rHR 0.91, 95% CI 0.83 to 0.99; I^2 = 0%; P = 0.54; τ^2 < 0.0001) greater with CKO than with strokes, death from cardiovascular cause, and hospitalization for heart disease, respectively (Figure S4). In addition, we found that treatment effect sizes were 17% (rHR 0.83, 95% CI 0.74 to 0.93) greater with CKO than with all-cause mortality, with moderate heterogeneity across trials (I^2 = 47%; P = 0.03; τ^2 = 0.0174). For the rAD, we found that death from cardiovascular cause was 5.5 times greater than CKO (rAD 5.53, 95% CI 0.70 to 10.37) with a higher heterogeneity across trials (I^2 = 100%; P < 0.001; τ^2 = 72.96), while the ADs were similar between CKO and the remaining cardiovascular events, hospitalization for heart failure and all-cause mortality (Figure S5).

3.3 | Subgroup analyses

In subgroup analyses stratified by study characteristics, there were large differences in treatment effect estimates between CKO and MACE-3 for trials of SGLT2 inhibitors (rHR 0.72, 95% CI 0.62 to 0.84; I^2 = 33%) compared with GLP-1RAs (rHR 0.93, 95% CI 0.85 to 1.01; I^2 = 0%), with a statistically significant interaction test (P < 0.01; Figure 2). Stratified by specific SGLT2 inhibitors, differences were greater for trials of dapagliflozin (rHR 0.57, 95% CI 0.45 to 0.72), empagliflozin (rHR 0.63, 95% CI 0.44 to 0.89) and canagliflozin (rHR 0.79, 95% CI 0.63 to 0.98) than for sotagliflozin (rHR 0.96, 95% CI 0.61 to 1.52). In addition, differences seemed greater for trials that included a run-in period (rHR 0.78, 95% CI 0.68 to 0.90) than those which did not (rHR 0.93, 95% CI 0.82 to 1.05), with a trend towards significance in the interaction test (P = 0.07). No clear differences by follow-up duration were found: the rHR was 0.81 (95% CI 0.68 to 0.97) for trials with a median length of follow-up of more than 3 years and 0.83 (95% CI, 0.73 to 0.93) for follow-up duration of less than 3 years (interaction test P = 0.87). We did not find any significant differences by sample size, outcome status or trial design (Figure 2).

On stratification by specific patient baseline characteristics, despite the absence of a significant interaction test, differences in treatment effect estimates between CKO and MACE-3 seemed greater for patients with a higher CVD (rHR 0.78, 95% CI 0.66 to 0.92; I^2 = 0%), those with a lower frequency of history of heart failure (rHR 0.79, 95% CI 0.67 to 0.92; I^2 = 66%), and those with moderate kidney function (eGFR > 60 mL/min

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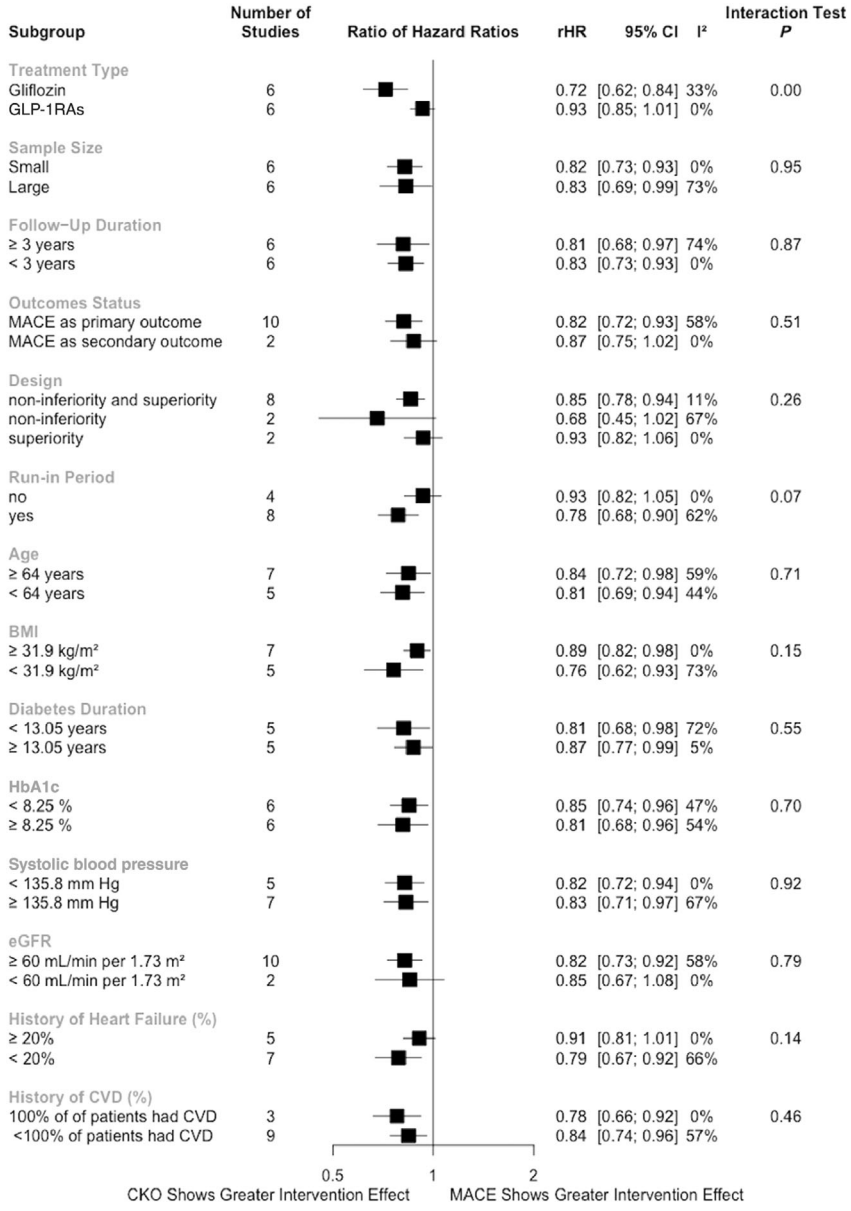


FIGURE 2 Subgroup analyses comparing treatment effect sizes between composite kidney outcome (CKO) and major adverse cardiovascular events (MACE-3) by trials and patients' characteristics. Ratio of hazard ratio (rHR) <1.0 indicates greater treatment effect size for CKO than for MACE-3. For age, body mass index (BMI), glycated haemoglobin (HbA1c), duration of diabetes, duration of follow-up, and sample size, cutoff values are median. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2

per 1.73 m^2; rHR 0.82, 95% CI 0.73 to 0.92; I^2 = 58%). For each of these subgroups of very-high-risk patients, we also assessed the differences in treatment effect with regard to cardiorenal protection (Figure S6). Among patients with moderate kidney function (eGFR > 60 mL/min per 1.73 m^2), difference were greater great for trials of SGLT2 inhibitors (rHR 0.67, 95% CI 0.57 to 0.80; I^2 = 30%) compared with GLP-1RAs (rHR 0.93, 95% CI 0.85 to 1.01; I^2 = 0%), with a statistically significant interaction test (P = 0.010). In trials in which all patients had established CVD at inclusion, the difference seemed to be in favour of SGLT2 inhibitors (rHR 0.74, 95% CI 0.56 to 0.97; I^2 = 36%), while for trials in which more than 20% of patients had established heart failure, the differences were similar between SGLT2 inhibitors (rHR 0.86, 95% CI 0.67 to 1.09; I^2 = 0%) and GLP-1RAs (rHR 0.92; 95% CI 0.82 to 1.04; I^2 = 0%). In analyses by weight, systolic blood pressure and HbA1c, no additional clear differences were found (Figure 2).

3.4 | Meta-regression: Association between CKO and MACE-3

Figure S7 shows the correlation of treatment effect between MACE-3 and CKO. Overall, we found a nonsignificant moderate correlation between MACE-3 and CKO estimated by the Spearman correlation coefficient (n = 12; ρ = 0.40; P = 0.21). According to the coefficient of determination (R^2) at trial level in the weighted meta-regression model, only 11% (95% CI 1% to 54%) of the variability in the MACE-3 effect could be explained by the variability in the CKO effect. The slope of the regression line was positive at 0.20 (P = 0.295).

4 | DISCUSSION

In patients with T2D at highest risk of CVD or with established CVD, we found that treatment effect size was 17% greater for the

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composite renal outcome than for major cardiovascular outcomes, with a greater difference for SGLT2 inhibitors than for GLP-1RAs, and a trend for trials that used run-in period design. This difference was largely driven by gliflozin whose effect on renal events was 28% greater than its effect on major cardiovascular events, whereas GLP-1RAs had a similar effect on major renal and cardiovascular events.

The greater effect benefits of glucose-lowering drugs on composite renal compared with major cardiovascular outcomes was consistent for each of the MACE-3 components as well as for hospital admission for heart failure, and all-cause mortality.

Cardiovascular outcome trials and meta-analyses of these have demonstrated that SGLT2 inhibitors and GLP-1RAs are protective against cardiorenal events and mortality.[6,8] More importantly, evidence from large observational real-world studies confirmed these cardiorenal benefits.[26-29] The PRECARE study confirms the beneficial effects of dapagliflozin 10 mg per day for 24 weeks on cardiorenal events in 1402 patients with T2D.[26] Moreover, data from routine clinical practice evaluating the effectiveness and safety of 1.5 mg dulaglutide once weekly for 12 months also confirms the beneficial effects on both clinical and laboratory outcomes in 626 patients with uncontrolled T2D.[27] In addition to this existing evidence, our study provides three important messages. First, we provide the evidence that in cardiovascular outcome trials, the protection against composite renal events afforded by the newer antiglycaemic drugs was significantly greater than that against major cardiovascular events. For example, in patients with T2D, regardless of their history of cardiovascular or renal diseases, the addition of SGLT2 inhibitors or GLP-1RAs to the standard care provides 17 times greater protection against composite renal outcomes than for major cardiovascular events. Second, protection against composite renal events was 28 times greater with SGLT2 inhibitors than with GLP-1RAs. These findings have relevant impact on the clinical practice management of T2D patients with established CVD or severe kidney impairment, or patients with heart failure with or without preserved systolic ejection fraction, as to date, no head-to-head comparison of RCTs has been conducted to evaluate the superiority of gliflozin compared with GLP-1RAs. Third, among SGLT2 inhibitors, when compared with sotagliflozin, the amount of protection against renal events was 43 times greater with dapagliflozin, 37 times greater with canagliflozin, and 21 times greater with empagliflozin.

Quantifying the magnitude of the treatment effect in a particular clinical setting such as in T2D patients with established CVD could help refine recommendations regarding the appropriate therapeutic strategy to adopt especially in the absence of clear evidence. This rHR can be seen as a metric to quantify this treatment effect size and may be used to guide treatment strategy. In our study, the rHR quantifies this importance for SGLT2 inhibitors with regard to renal outcomes compared to major cardiovascular events and could help clinicians in their current practice to better choose the type of molecule according to its impact on the type of cardiac or renal protection targeted. However, the rAD was similar between composite renal outcome and cardiovascular outcome except for death from cardiovascular causes. The relatively short follow-up in these studies ranging from 1.33 to 5.4 years could explain this lack of difference for the absolute risk ratio. Nevertheless, correlation between treatment effect for CKO and MACE-3 was moderate and nonsignificant, with only 11% of the variability in the MACE-3 effect explained by the variability in the CKO effect, suggesting independence between cardiorenal outcomes. This variability in the proportion of variance explained between MACE-3 and CKO supports the complexity of mechanisms involved in cardiorenal protection of SGLT2 inhibitors and GLP-1RAs.

The present study has some strengths. First, to the best of our knowledge, this is the first study to quantify the magnitude of treatment effects in patients with T2D at highest risk of cardiovascular or established CVD. Second, these new results show that the treatment effects on CKO and MACE-3 outcomes are independent, with only 11% of the variability in one being explained by the other, suggesting the need for further investigation to explore the mechanism involved in cardiorenal protection.

The study also has some limitations. First, high heterogeneity was observed for differences in treatment effect between MACE-3 or stroke and CKO. Participant characteristics, study design, and presence of advanced CKD stage and history of CVD at inclusion could explain this heterogeneity, with caution required in the interpretation of these findings. Second, the absence of patient-level data limits the possibility to explore the possible source of heterogeneity and to enable a rigorous surrogacy investigation. Third, the definitions of renal outcomes were not consistent across studies, and there was an absence of adjudication of renal outcomes which contributes to this heterogeneity. Finally, because of our limited sample, we were unable to stratify analyses by precise categories of baseline blood pressure, history of established CVD or heart failure, HbA1c level and duration of follow-up.

This study has several implications for further trials. First, we have identified patterns of patients who will obtain greater renal benefits than reduction of MACE-3 when SGLT2 inhibitors or GLP-1RAs are added to the standard of care, namely, patients with history of established CVD, or history of heart failure as well as those with impaired renal function. In addition, in trials in which patients had moderate kidney function or in which patients had established CVD at inclusion, the difference in treatment effect was in favour of SGLT2 inhibitors over GLP-1RAs, while for trials in which more than 20% of patients had established heart failure, the difference was similar between SGLT2 inhibitors and GLP-1RAs, supporting the January 2022 (Standards of medical care in diabetes - 2022; American Diabetes Association; Volume 45, Supplement 1) American Diabetes Association recommendation. However, head-to-head comparisons of data from RCTs are needed to drive clear evidence. Second, the benefit of treatment with regard to cardiorenal outcomes appears to differ according to study design, especially studies that used a run-in period to select more adherent patients. This run-in period contributes to a decrease in external validity by reducing the generalizability of the results to the entire target population. Third, we found that MACE-3 and CKO are independent, thereafter, further trials should include and report results of both endpoints.

In conclusion, this study shows that, in patients with T2D at high cardiovascular risk or established CVD, treatment effect sizes were

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greater for CKO than for MACE-3 outcomes, with important differences with regard to trial design and some drugs. CKO and MACE-3 were independent, and relationships varied according to the drug considered. To optimize the design of future clinical trials, caution must be taken when interpreting MACE-3 in the absence of CKO data. Furthermore, pooled individual patient data are needed to support our conclusions.

CONFLICT OF INTERESTS

Alhassane Diallo, Miguel Carlos-Bolumbu, Eric Renard and Florence Galtier declare no competing interests.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14859.

DATA AVAILABILITY STATEMENT

Data available on request from the authors: the data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTORS

Alhassane Diallo conceived the study design, analysed the data, and drafted the first version of the manuscript, Miguel Carlos-Bolumbu supervised data collection, and critically revised the manuscript, and Eric Renard and Florence Galtier interpreted and substantially revised the manuscript. All authors approved the final version of the manuscript.

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