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Arshad, Adam; Sarween, Nadia; Sharif, Adnan

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Systematic Review of Cardiovascular Outcome Trials Using New Antidiabetic Agents in CKD Stratified by Estimated GFR

Adam Arshad[1], Nadia Sarween[2] and Adnan Sharif[2,3]

[1]University College Hospitals, London, UK; [2]Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK; and [3]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

Introduction: Cardiovascular benefits observed with new antidiabetic agents may not extend to chronic kidney disease (CKD) patients. This study performed a systematic review and meta-analysis of cardiovascular outcome trials (CVOTs) using new antidiabetic agents stratified by kidney function.

Methods: MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials were searched for eligible studies up to November 16, 2020. Data were stratified by the trial entry estimated glomerular filtration rate (eGFR) and albuminuria. Primary major cardiovascular event (MACE) outcomes were extracted, and a meta-analysis with a random effects model was performed to estimate overall risk ratios (RRs).

Results: Our search identified 16 studies for inclusion (glucagon-like peptide-1 [GLP-1] analogues, $n = 6$; dipeptidyl-peptidase 4 [DPP-4] inhibitors, $n = 4$; and sodium-glucose cotransporter-2 [SGLT-2] inhibitors, $n = 6$) with a combined total of 150,816 participants (28.2% with eGFR <60 ml/min per 1.73 m^2, $n = 42,534$). The RR for MACE with GLP-1 analogues with an eGFR ≥60 ml/min per 1.73 m^2 was 0.87 (95% confidence interval [CI], 0.77–0.98; $P = 0.02$) and 0.90 (95% CI, 0.78–1.04; $P = 0.14$) with an eGFR <60 ml/min per 1.73 m^2. The RR for MACE with DPP-4 inhibitors with eGFR ≥60 ml/min per 1.73 m^2 was 0.99 (95% CI, 0.92–1.07; $P = 0.86$) and 0.99 (95% CI, 0.91–1.08; $P = 0.86$) with an eGFR <60 ml/min per 1.73 m^2. The RR for MACE with SGLT-2 inhibitors with an eGFR ≥60 ml/min per 1.73 m^2 was 1.01 (95% CI, 0.92–1.10; $P = 0.87$) and 0.85 (95% CI, 0.75–0.95; $P = 0.005$) with an eGFR <60 ml/min per 1.73 m^2. Most analyses had significant heterogeneity. Sufficient albuminuria data were unavailable to analyze empirically.

Conclusion: Clear evidence for MACE prevention in diabetes patients with an eGFR <60 ml/min per 1.73 m^2 currently exists for SGLT-2 inhibitors only. However, similar GLP-1 analogue effect sizes suggest a lack of sufficient power rather than a lack of effect.

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KEYWORDS: cardiovascular outcomes; chronic kidney disease; clinical trials; diabetes; meta-analysis; systematic review

The global estimate for the prevalence of people living with diabetes mellitus in 2017 is 451 million, with a projected increase to 693 million people by 2045.[1] Although glycemic control is associated with a reduction in the risk of microvascular complications, the cardiovascular benefits of antidiabetic agents vary between benefit versus harm.[2] In the context of advanced CKD, the evidence base for cardiovascular protection from antidiabetic agents is less clear.

This is an important issue because the prevalence of CKD among people with diabetes has been reported to range from 27.1% to 83.6%,[3] whether the underlying etiology is diabetic or nondiabetic kidney disease.[4] In the latest consensus report by the American Diabetes Association and the European Association for the Study of Diabetes, after first-line metformin and lifestyle intervention, the guidelines recommend the use of SGLT-2 inhibitors if the eGFR is 30 to <90 ml/min per 1.73 m^2 or GLP-1 analogues if the eGFR is <30 ml/min per 1.73m^2 (or SGLT-2 inhibitors are not tolerated).[5] The latest Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease from Kidney Disease: Improving Global Outcomes (KDIGO) recommend metformin and SGLT-2 inhibitors as first-line therapy for individuals with diabetes and an eGFR

Correspondence: Adnan Sharif, Department of Nephrology and Transplantation, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2WB, UK. E-mail: adnan.sharif@uhb.nhs.uk

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≥30 ml/min per 1.73 m^2, with GLP-1 analogues cited as preferred second-line additions[6] before the consideration of DPP-4 inhibitors. More recently, published clinical practice guidelines provide only a weak recommendation for starting SGLT-2 inhibitors or GLP-1 analogues in the context of CKD.[7]

The evidence base from the available data with regard to cardiovascular benefits among these new antidiabetic agents for people with concomitant diabetes and CKD is not well established. Only the SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) trial has specifically been designed to target individuals with both diabetes and CKD using a new antidiabetic agent with MACEs as the primary outcome.[8] Additional published CVOTs using new antidiabetic agents have included study recruits with CKD but with smaller numbers that preclude any conclusive judgment regarding efficacy.

Therefore, the aim of this study was to undertake a systematic review of all published CVOTs using new antidiabetic agents and to perform a meta-analysis of combined empirical data to determine if any significant class effect is observed on cardiovascular outcome in patients with type 2 diabetes and CKD stratified by entry eGFR or albuminuria.

METHODS

Search Strategy and Selection Criteria

Our inclusion criteria included any randomized, placebo-controlled trials testing GLP-1 analogues (both injectable and oral agents), DPP-4 inhibitors, or SGLT-2 inhibitors in patients with type 2 diabetes. Only studies with major adverse cardiovascular end points as the primary outcome and available data to allow CKD stratification were eligible for inclusion. We stratified data by an eGFR of 60 ml/min per 1.73 m^2 (threshold for CKD stage 3) and analyzed the data for cohorts with an eGFR above or below this level. There were limited data available for cohorts stratified at an eGFR of 45 ml/min per 1.73 m^2 or 30 ml/min per 1.73 m^2 to perform any pooled analyses. Studies without any stratified eGFR data were excluded. Because of the absence of sufficient data with regard to albuminuria, data were not analyzed stratified by urinary albumin excretion rates. The study was registered on the International Prospective Register of Systematic Reviews database (registration ID: CRD42020212499) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols checklist (Supplementary Figure S1).

Eight databases were searched to identify appropriate published and gray literature from January 1, 1975, to February 13, 2021. Our search strategy used for Ovid MEDLINE is described later and summarized in Supplementary Figure S2. These terms were appropriately adapted for alternative databases. We improved our search strategy by using snowballing techniques, such as checking references for all full-text articles and hand searching nonindexed journals. The following search terms were used for MEDLINE: "Cardiovascular.mp" OR "exp myocardial infarction/" OR "exp stroke/" OR "exp heart failure/" OR "exp Acute Coronary syndrome/" OR "ACS.mp" OR "Angina.mp or exp Angina Pectoris/" OR "Major Adverse Cardiac Event.mp" OR "exp Coronary Artery Disease/" OR "MACE.mp." These terms were used against the following search terms for each individual antidiabetic agent drug class:

- "exp Glucagon-like peptide 1" OR "GLP-1.mp" OR "lixisenatide.mp" OR "exp exenatide/" OR "exp liraglutide/" OR "semaglutide.mp" OR "albiglutide.mp" OR "dulaglutide.mp"
- "exp Dipeptidyl peptidase-4/" OR "exp Dipeptidyl-Peptidase IV inhibitors/" OR "DPP-4 inhibitors.mp" OR "DPP-IV inhibitors.mp" OR "Sitagliptin.mp or exp Sitagliptin Phosphate/" OR "exp Vildagliptin/" OR "Saxagliptin.mp" OR "Alogliptin.mp" OR "exp Linagliptin/"
- "exp Sodium-Glucose Transporter 2 Inhibitors/ or exp Sodium-Glucose Transporter 2/" OR "SGLT-2.mp" OR "Dapaglifozin.mp" OR "exp Canagliflozin" OR Empagliflozin.mp" OR "Sotagliflozin.mp"

References identified across the 11 databases were exported to Endnote X9.1 (Clarivate Analytics, Philadelphia, PA). Duplicates were removed using the deduplicate tool and manually searching the compiled list. The final articles were then exported to Rayan QCRI, a free web and mobile app for systematic reviews.

Two reviewers (AA and NS) screened the titles and abstracts independently and blinded from one another for relevance. Disagreements were resolved by AS. If, from the title and abstract, articles were deemed potentially relevant for inclusion, full texts were assessed. Full texts were then reviewed by each reviewer to determine their inclusion in the systematic review. There were no restrictions on language for the published literature.

Bias Assessment

The risk of bias in the selected articles was assessed using the Cochrane tool for assessing risk of bias in randomized trials.[9] Two reviewers assessed each article,

with a third reviewer being involved in cases of disagreement.

Data Analysis

The cardiovascular outcome of interest was MACE (a composite outcome composed of cardiovascular death, myocardial infarction, and stroke) as defined by each study for their primary outcome. The treatment effect was compared for the primary MACE outcome in baseline eGFR <60 versus ≥60 ml/min per 1.73 m^2 cohorts. Summary statistics were used from the individual trials because we did not have access to individual-level data. If raw event data were not available, we calculated these by transformation of relevant hazard ratios and 95% CIs from primary and/or secondary trial reports and their associated supplementary appendix files. Raw data were also extrapolated from studies that reported the number of participants per 1000 patient-year (e.g., CANVAS [Canagliflozin Cardiovascular Assessment Study]). The corresponding authors were contacted if the required data were not available from the published sources (either the main manuscript or the supplementary index), but we did not attain any additional data to allow ineligible studies to be included.

RR estimates were calculated in a random effects analytical model. Interstudy heterogeneity was assessed with the I^2 index and Cochran's Q test. We considered I^2 values lower than 25% to indicate low heterogeneity, values of 26% to 50% to indicate moderate heterogeneity, and values greater than 50% to indicate high heterogeneity. Cochran's Q statistic P values below 0.05 were considered indicators for significant heterogeneity. All analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) using the *meta* and *metafor* packages.

Finally, we calculated the fragility index of the primary MACE outcomes as described by Walsh *et al.*[10] to complement the published P values and test for robustness of statistically significant results. It is defined as the minimum number of patients from 1 or more trials included in the meta-analysis for which a modification on the event status (i.e., changing events to nonevents or nonevents to events) would change the statistical significance of the pooled treatment effect.[11] After specific event-status modifications, a statistically significant pooled treatment effect could be turned nonsignificant, and a statistically nonsignificant treatment effect could be turned significant. The method used to evaluate the fragility index of meta-analyses is based on a re-evaluation of the statistical significance of the pooled treatment effect of modified meta-analyses iteratively derived from the original meta-analysis by performing single event-status modifications in each arm of each trial in turn. These were calculated using the following online tool: http://clinicalepidemio.fr/fragility_ma/.

Role of the Funding Source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study Inclusion

Our systematic review identified 16 eligible randomized controlled trials for meta-analysis of the pooled empirical data. Figure 1 outlines the study inclusion flow and confirms 16 eligible studies for our meta-analysis (GLP-1 analogues, $n = 6$; DPP-4 inhibitors, $n = 4$; and SGLT-2 inhibitors, $n = 6$). The extracted data related to 150,816 study participants, of whom 28.2% had a study entry eGFR <60 ml/min per 1.73 m^2 ($n = 42,534$). Risk of bias is shown in Figure 2. Risk of publication bias was low (Supplementary Figure S3), and all studies were ranked as high quality in accordance with Grading of Recommendations, Assessment, Development, and Evaluations recommendations.[12]

Study Characteristics of GLP-1 Analogue CVOTs

The 6 GLP-1 receptor analogue studies included were ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome),[13] LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results),[14] SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes),[15] EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial),[16] Harmony Outcomes,[17] and PIONEER 6 (Peptide Innovation for Early Diabetes Treatment 6).[18] The key features of these studies are summarized in Table 1. Across these 6 studies, data were available for a cohort of 46,024 patients, with 10,773 patients (23.4%) being documented as having an eGFR <60 ml/min per 1.73 m^2 at recruitment (from all studies).

Study Characteristics of DPP-4 Inhibitor CVOTs

The 4 DPP-4 inhibitor studies included were SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53),[19] EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care),[20] TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin),[21] and CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in

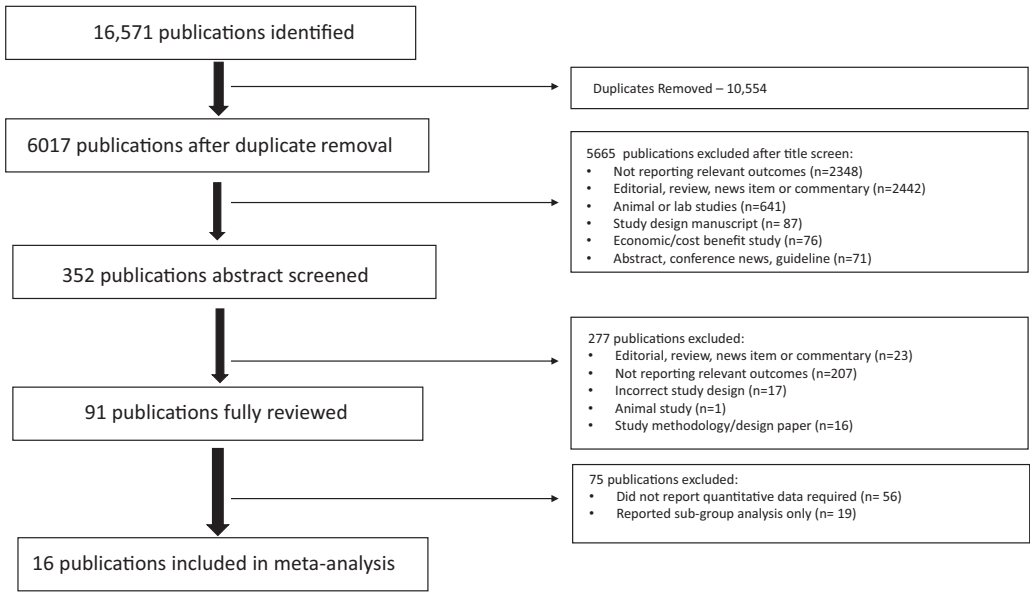

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart of studies included in the meta-analysis after systematic review and reasons for exclusion.

Patients With Type 2 Diabetes Mellitus).[22] The key features of these studies are summarized in Table 1. Across these 4 studies, we analyzed data for a cohort of 43,522 patients, with 9858 patients (22.7%) being documented as having an eGFR <60 ml/min per 1.73 m^2 at recruitment (from all studies).

Study Characteristics of SGLT-2 Inhibitor CVOTs

The 6 SGLT-2 inhibitor studies included were CANVAS,[23] DECLARE TIMI-58 (Dapagliflozin Effect on Cardiovascular Events),[24] EMPA-REG ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients),[25] VERTIS (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial),[26] EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction),[27] and SCORED.[8] The key features of these studies are summarized in Table 1. Across these 6 studies, we analyzed data for a cohort of 56,869 patients, with 19,311 patients (34.0%) being documented as having an eGFR <60 ml/min per 1.73 m^2 at recruitment (from all studies).

Primary Outcome Stratified by eGFR

In the overall pooled analysis of empirical data, treatment with a GLP-1 analogue led to a 13% RR reduction in primary outcome MACE in study participants with starting eGFR rates ≥60 ml/min per 1.73 m^2 (RR = 0.87; 95% CI, 0.77–0.98; $P = 0.02$). For study participants with an eGFR <60 ml/min per 1.73 m^2, treatment with a GLP-1 analogue led to a 10% RR reduction in the primary outcome MACE that was not statistically significant (RR = 0.90; 95% CI, 0.78–1.04; $P = 0.14$). Significant heterogeneity was only observed in the analysis involving the ≥60 ml/min per 1.73 m^2 cohort, with borderline significance in the <60 ml/min per 1.73 m^2 cohorts (Figure 3a and b, respectively).

Treatment with a DPP-4 inhibitor was not associated with a statistically significant reduction in the primary outcome MACE across the 4 assessed studies for patients with an eGFR ≥60 ml/min per 1.73 m^2 (RR = 0.99; 95% CI, 0.92–1.07; $P = 0.86$). A similar result was attained for patients with an eGFR <60 ml/min per 1.73 m^2 (RR = 0.99; 95% CI, 0.91–1.08; $P = 0.86$). Heterogeneity was not found to be significant in the analyses (Figure 3a and b).

Treatment with an SGLT-2 inhibitor was not associated with a significant reduction in MACE outcomes in participants with an eGFR ≥60 ml/min per 1.73 m^2

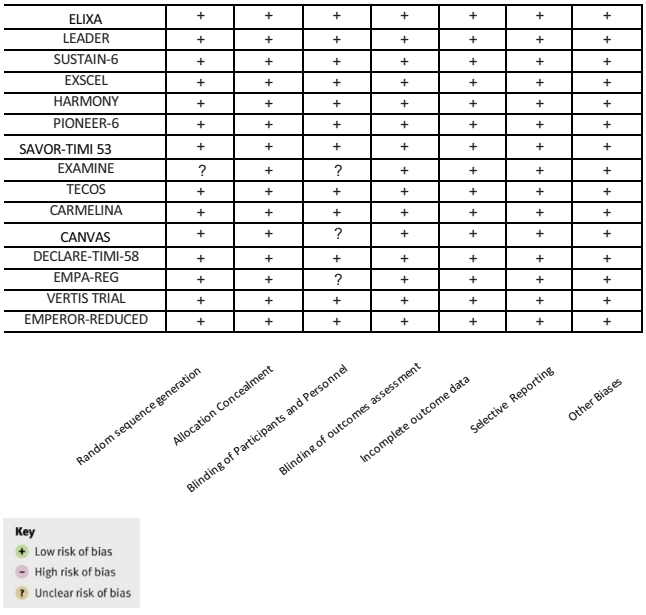

Figure 2. Risk of publication bias.

Table 1. Baseline characteristics as reported in the included studies for GLP-1 analogues, DPP-4 inhibitors, and SGLT-2 inhibitors

GLP-1 receptor analogues						
	ELIXA	**LEADER**	**SUSTAIN-6**	**EXSCEL**	**HARMONY**	**PIONEER 6**
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Semaglutide[a]
Trial size (*n*)	6068	9340	3297	14,752	9463	3183
Age (yr)	60	64	65	62	64	66
Male sex, *n* (%)	4207 (69)	6003 (64)	2002 (61)	9149 (62)	6569 (69)	2176 (68)
Non-White ethnicity, *n* (%)	1492 (25)	2102 (23)	561 (17)	3577 (24)	2880 (30)	883 (28)
Body mass index (kg/m^2)	32.0	32.5	32.8	31.8	32.3	32.3
Diabetes duration (yr)	13.5	12.9	13.9	12.0	14.1	14.9
Established cardiovascular disease, *n* (%)	6068 (100)	7598 (81.0)	2735 (83.3)	10,782 (73.1)	9463 (100)	2695 (84.7)
Estimated glomerular filtration rate (ml/min per 1.73 m^2), *n* (%)						
<30	11 (0.2)	224 (2.4)	214 (6.5)	14 (0.1)	Excluded from study	29 (0.9)
<60	1701 (28.0)	2158 (23.1)	1878 (57.0)	3191 (21.6)	2222 (23.5)	856 (26.9)
>60	5157 (71.8)	7182 (74.5)	4716 (36.5)	11,415 (78.3)	7241 (76.5)	2308 (72.2)

DPP-4 inhibitors				
	SAVOR-TIMI 53	**EXAMINE**	**TECOS**	**CARMELINA**
Drug	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin
Trial size (*n*)	16,492	5381	14,671	6979
Age (yr)	60	61	65.5	65.8
Male sex, *n* (%)	11,037 (66.9)	3651 (67.9)	10,374 (70.7)	4390 (62.9)
Non-White ethnicity, *n* (%)	4085 (24.8)	3909 (72.6)	4714 (32.1)	2589 (37.1)
Body mass index (kg/m^2)	31.1	28.7	30.2	31.3
Diabetes duration (yr)	10.3	7.2	11.6	14.7
Established cardiovascular disease, *n* (%)	Study does not strictly state CVD prevalence in each study arm	5381 (100)	14671 (100)	3978 (57)
Estimated glomerular filtration rate (ml/min per 1.73 m^2) , *n* (%)				
<30	336 (2.0)	157 (2.9)	Excluded from study	1062 (15.2)
<60	2918 (17.7)	1408 (26.2)	1907 (13.0)	3286 (47.1)
>60	14,814 (80.3)	3815 (70.9)	14,431 (87.0)	3359 (37.7)

SGLT-2 inhibitors						
	CANVAS	**DECLARE TIMI 58**	**EMPA-REG**	**VERTIS**	**EMPEROR REDUCED**	**SCORED**
Drug	Canagliflozin	Dapaglifozin	Empagliflozin	Ertugliflozin	Empagliflozin	Sotagliflozin
Trial size (*n*)	10,142	17,160	7020	8246	3730	10,584
Age (yr)	63.3	64.0	63.1	64.4	66.9	69.0
Male sex, *n* (%)	6509 (64.2)	10,738 (62.6)	5016 (71.5)	5769 (70.0)	2873 (76.1)	5830 (55.1)
Non-White ethnicity	2198 (21.7)	3507 (20.4)	2125 (30.2)	1006 (12.2)	1101 (29.5)	1835 (17.3)
Body mass index (kg/m^2)	32.0	32.0	30.6	32.0	27.9	31.8
Diabetes duration (yr)	13.5	10.5	> 10 years (exact time not provided)	13.0	Not documented	Not documented
Established cardiovascular disease, *n* (%)	6656 (65.6)	6974 (40.6)	6964 (99.2)	8246 (100)	3730 (100)	Study does not strictly state CVD prevalence in each study arm
Estimated glomerular filtration rate (in ml/min per 1.73 m^2), *n* (%)						
<30	Excluded from study	Excluded from study	Excluded from study	Excluded from study	2 (0.1)	813 (7.7)
<60	2300 (22.7)	1265 (7.3)	1819 (25.9)	1807 (21.9)	1799 (48.2)	9771 (92.3)
>60	8851 (77.3)	15,894 (92.5)	5199 (74.1)	6438 (78.1)	1929 (51.7)	0

CVD, cardiovascular disease; DDP-4, dipeptidyl-peptidase 4; EMPA-REG, (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; VERTIS, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.
[a]Oral administration (rest of GLP-1 receptor analogues all subcutaneous).

(hazard ratio = 1.01; 95% CI, 0.92–1.10; P = .87). However, among patients with an eGFR <60 ml/min per 1.73 m^2, treatment with SGLT-2 inhibitors was associated with a 15% reduction in the risk of the primary outcome MACE (RR = 0.85; 95% CI, 0.75–0.95; P = 0.005). Heterogeneity was not observed in the analysis involving the ≥60 ml/min per 1.73 m^2 cohort, with borderline significance in the <60 ml/min per 1.73 m^2 cohort (Figure 3a and b, respectively).

Primary Outcome Stratified by Albuminuria

A formal meta-analysis was not undertaken because of the limited studies providing data for primary cardiovascular outcomes stratified by albuminuria.

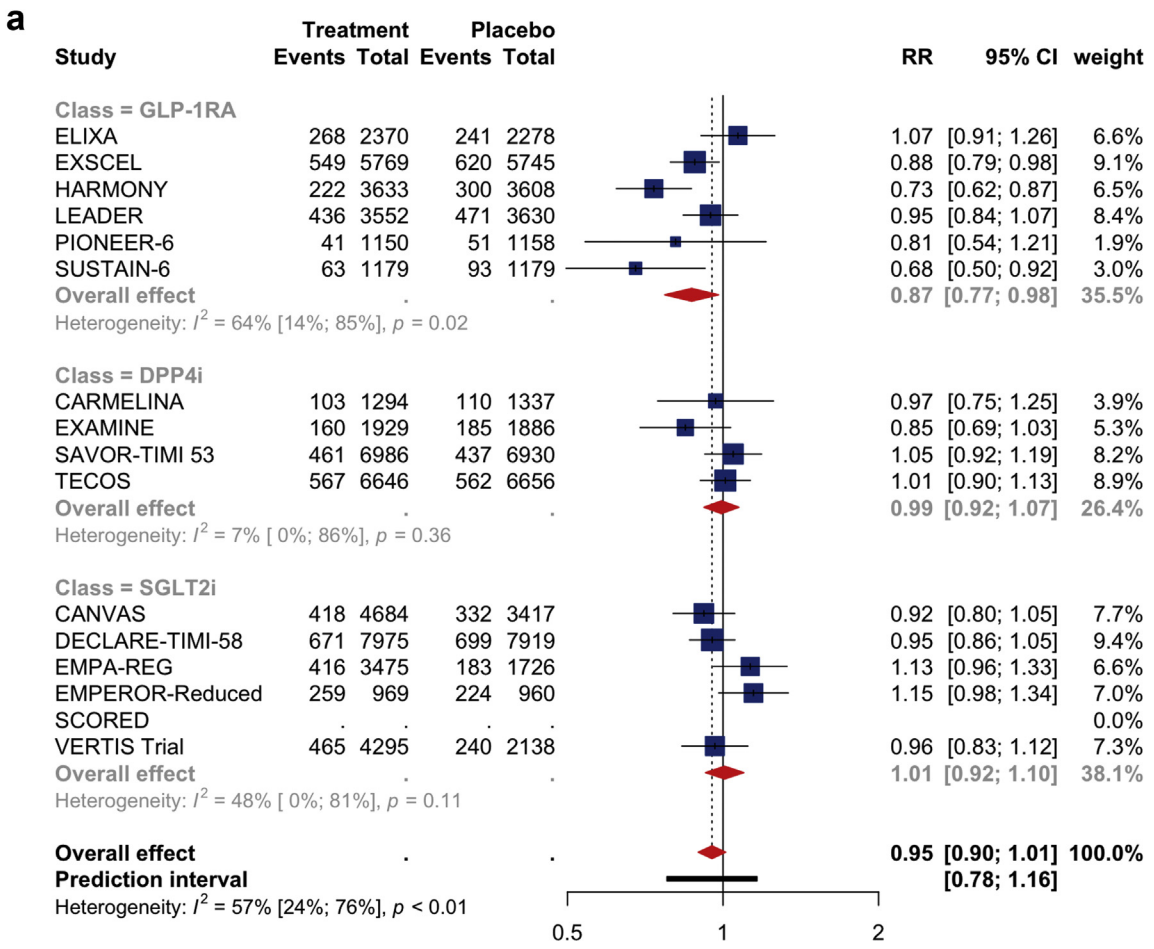

Figure 3. The primary outcome after meta-analysis of pooled empirical data for glucagon-like peptide-1 receptor analogues (GLP-1RA), dipeptidyl-peptidase 4 inhibitors (DPP4i), and sodium-glucose cotransporter-2 inhibitors (SGLT2i) stratified by (a) estimated glomerular filtration rate ≥60 ml/min per 1.73 m^2 or (b) estimated glomerular filtration rate <60 ml/min per 1.73 m^2. CI, confidence interval; RR, relative risk. (Continued)

Fragility Index Calculations

The results of our fragility index calculations are shown in Supplementary Figure S4 for study cohorts with an eGFR above or below 60 ml/min per 1.73 m^2 and ranged from 12 to 89. The fragility index is the minimum number of patients whose status would have to change from a nonevent to an event (or vice versa) that is required to turn a statistically significant result to a nonsignificant result; the smaller the fragility index, the more fragile the trial's outcome. Therefore, with our lowest fragility index score obtained of 12 (SGLT-2 inhibitor effect on the primary cardiovascular outcome in study participants with an eGFR <60 ml/min per 1.73 m^2), 12 single-event status modifications would be sufficient to change a statistically significant effect to a statistically nonsignificant effect (Supplemental Figure S4C).

DISCUSSION

Despite the emerging clinical evidence from large CVOT studies across different classes of antidiabetic agents, the evidence for improved cardiovascular outcomes for patients with both diabetes and CKD is limited. In this systematic review and meta-analysis, we extracted data from published CVOT studies using GLP-1 analogues, DPP-4 inhibitors, or SGLT-2 inhibitors and stratified primary MACE outcomes above and below an entry threshold eGFR of 60 ml/min per 1.73 m^2. For patients with concomitant diabetes and CKD (based on eGFR <60 ml/min per 1.73 m^2), our results conclude SGLT-2 inhibitors afford protection from MACEs, although fragility index studies suggest this statistically significant outcome can be altered with event reclassification of only 12 study participants. No statistically significant benefit is observed with the use of GLP-1 analogues in patients with an eGFR <60 ml/min per 1.73 m^2, although the observed effect size is similar to the statistically significant benefit seen in patients with a preserved eGFR (suggesting a lack of adequate statistical power for the CKD cohort). No benefit was observed for DPP-4 inhibitors in any cohort. These analyses support the recent guidance supporting the use of SGLT-2

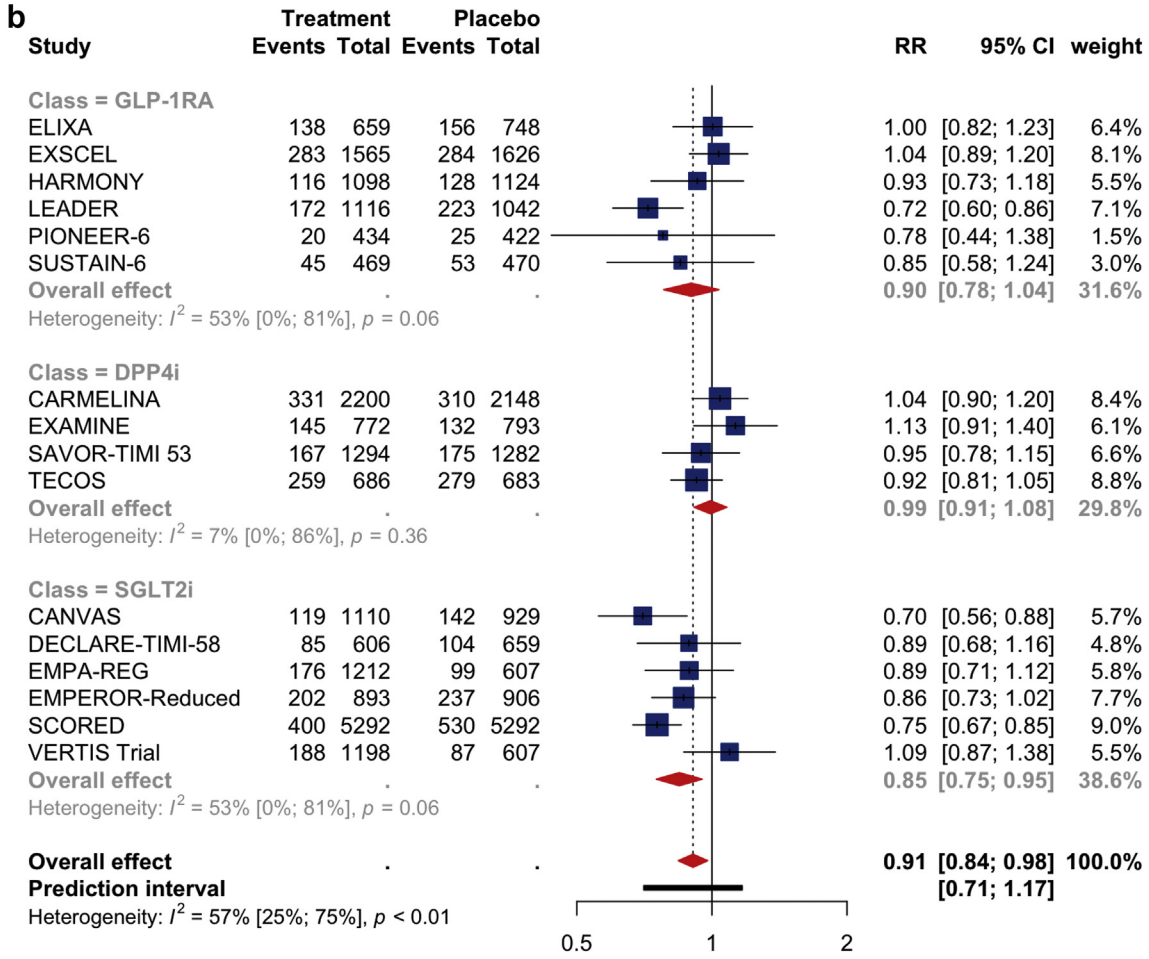

Figure 3. Continued

inhibitors over other new antidiabetic agents by providing targeted information for a high-risk cohort of individuals with both diabetes and renal impairment.

CVOT studies using new antidiabetic agents provide an evidence base for the improvement of cardiovascular and renal outcomes selectively for patients with diabetes.[28] However, they fail to specifically establish whether an important subgroup of patients with concomitant diabetes and CKD share these cardiovascular benefits, which is important because these patients are at increased risk for cardiovascular events due to a complex interplay of underlying pathophysiological deficits.[29] For example, in a retrospective cohort study using primary care data from the UK Clinical Practice Research Datalink and linked inpatient data from the Hospital Episode Statistics, Currie *et al.*[30] concluded both reduced eGFR and proteinuria were independently associated with an increased risk of MACE regardless of diabetes status. However, the risk of MACE in the same eGFR state was 4.6 to 2.4 times higher in patients with type 2 diabetes compared with those without diabetes.[30] Even after adjustment for known cardiovascular risk factors (e.g., diabetes and hypertension), mortality risk progressively increases with worsening eGFR. Data from the Atherosclerosis Risk in Communities study demonstrate patients with an eGFR between 15 and 60 ml/min per 1.73 m^2 have approximately double to triple the cardiovascular mortality risk relative to patients with an eGFR greater than 60 ml/min per 1.73 m^2.[31] Therefore, establishing a clear evidence base for pharmacologic therapy with newer antidiabetic agents for patients with diabetes and CKD is important.

Recently, the American Diabetes Association recommended in their 2019 Standards of Medical Care that an SGLT-2 inhibitor (or GLP-1 analogue) should be considered in patients with type 2 diabetes and CKD not meeting individualized glycemic goals with metformin and lifestyle interventions.[32,33] The recent KDIGO guidance went a step further and placed SGLT-2 inhibitor use on par with metformin for first-line therapy consideration. Our data support the use of SGLT-2 inhibitors for cardiovascular protection in patients with eGFR <60 ml/min per 1.73 m^2. The mechanisms for SGLT-2 inhibitors providing cardiovascular protection have already been reviewed and remain a

matter of speculation.[34] Importantly, baseline and time-dependent changes in cardiometabolic risk factors such as blood pressure, lipid profile, or glycemia do not fully explain SGLT-2 inhibitor effects. Indeed, the glucose-lowering effect of SGLT-2 inhibitors declines with lower eGFR thresholds. One hypothesis is that the cardiovascular protection is primarily driven by the attenuation of adverse outcomes related to heart failure.[35] Clinical support for this comes from pooled treatment effects of 2 studies, EMPEROR-reduced and DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure), that showed a similar reduction in the composite outcome of first hospitalization for heart failure or cardiovascular death using SGLT-2 inhibitors regardless of the eGFR threshold.[36] Heart failure and CKD have a bidirectional relationship, with the prevalence of heart failure increasing as eGFR declines,[37] and justifies the recommendation of SGLT-2 inhibition as a first-line therapy for eligible CKD patients. However, data from the SCORED trial would reinforce the need for added vigilance because of the increased risk for adverse events in a CKD cohort including diarrhea, volume depletion, genital mycotic infections, and diabetic ketoacidosis.[8]

In our pooled analysis, neither GLP-1 analogues or DPP-4 inhibitors demonstrate any cardiovascular protection for people with reduced eGFR, although GLP-1 analogue use in patients with preserved renal excretory function was beneficial. Cardiovascular protection from GLP-1 analogues putatively relates to both direct (modulation of sodium and water homeostasis, anti-inflammatory properties, and decreased oxidative stress) and indirect (weight loss, improved blood pressure and glycaemia, and improved ventricular modeling) effects.[38] Our data confirm the cardiovascular safety, but no cardiovascular benefit, of DPP-4 inhibitors in people with reduced eGFR and support guidance placing them behind other new antidiabetic agents for priority in treatment algorithms for CKD patients. Indeed, recent *post hoc* analyses of the EXAMINE study have even suggested detrimental effects of the DPP-4 inhibitor alogliptin in study participants with an eGFR <60 ml/min per 1.73 m^2 (significantly increased hazard ratio for nonfatal myocardial infarction), but this speculative hypothesis-generating work requires further validation.[39]

The main limitation of this study was the inability to analyze the pooled data stratified by albuminuria because of limited studies providing this information in either the main manuscript or supplementary information. Both eGFR and albuminuria are important independent risk factors for MACE, but the latter has more discriminatory power in the determination of adverse cardiovascular outcomes (especially cardiovascular-related death). This observation is based on individual-level data from 637,315 individuals without a history of cardiovascular disease from 24 cohorts (median follow-up of 4.2–19.0 years) included in the Chronic Kidney Disease Prognosis Consortium.[40] Although not eligible for inclusion in our empirical data because of its composite end point including renal outcomes, CREDENCE (Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical Evaluation) further supports the use of SGLT-2 inhibitors for cardiovascular protection among CKD patients with albuminuria.[41] In this randomized controlled trial, SGLT-2 inhibition with canagliflozin versus placebo was associated with a reduction in secondary outcomes including death from renal/cardiovascular causes and a reduction in death from cardiovascular causes.

Our results should be interpreted in the context of several other limitations. The methods used to evaluate creatinine and/or albuminuria varied across cohorts, and the definition of primary cardiovascular outcomes was not consistent between studies. Study recruitment was also based on single assessments of creatinine-based eGFR and/or albuminuria, which may be susceptible to a degree of variability, and varied between studies for eligibility. The absence of individual patient-level data prohibit more focused probing of granular raw data and does not allow a meta-regression to explore confounding effects to explain significant heterogeneity. Although our pooled analysis has explored new antidiabetic agents broadly by class, it is clear that some outcomes are drug specific rather than a generic class effect among the SGLT-2 inhibitors,[42] GLP-1 receptor analogues,[43] and DPP-4 inhibitors.[44] Therefore, these factors should all be taken into account in the interpretation of our data. The fragility index is a useful metric for demonstrating how easily statistical significance or nonsignificance based on a threshold P value may be overturned and highlights the fragility of some reported effect sizes of antidiabetic agents and cardiovascular outcomes. Finally, our study was not able to ascertain differences in adverse events for patients with a reduced GFR. A recent network meta-analysis from Palmer *et al.*[45] demonstrated improvements in cardiovascular and renal outcomes for people on SGLT-2 inhibitors and GLP-1 analogues, but notable differences in benefit versus harm were seen stratified by individualized patient profiles.[45] We can speculate that adverse events may be more prominent in the context of reduced GFR, and this should be the topic of further research.

In conclusion, our data suggest only SGLT-2 inhibitors have a clinical evidence base for the prevention of major adverse cardiovascular outcomes for individuals with an eGFR <60 ml/min per 1.73 m^2

among the new antidiabetic agents, although caution should be exercised due to the fragility of the data. From our analysis, we suggest SGLT-2 inhibitors should be considered the first-line therapeutic choice followed by GLP-1 analogues and finally DPP-4 inhibitors. These data support the recent KDIGO guidance for diabetes management in the setting of CKD[6] and provide clarity on treatment algorithms in the setting of renal impairment. Further work is required to determine if these recommendations can be translated to diabetes management in the setting of CKD with albuminuria. Because of the growing epidemiologic burden of concomitant diabetes and CKD, we believe targeted pharmacologic interventions are warranted in this high-risk cohort, and inclusion criteria for novel drugs should ensure broad inclusion criteria to be translatable to the real world.

DISCLOSURE

AS reports advisory board fees with Boeringher Ingelheim/Lilly Alliance and speaker fees from Napp Pharmaceuticals. All the other authors declared no competing interests.

AUTHOR CONTRIBUTIONS

AA and AS designed the study, AA and NS undertook systematic review, AA and AS analyzed the data, AA and AS made the figures, AS drafted the paper, and AA and AS revised the paper. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist.

Figure S2. Databases used for literature search.

Figure S3. Funnel plot of publication bias.

Figure S4. Fragility index in study cohorts with all new antidiabetic agents.

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