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Cardiovascular and Kidney Outcomes of Glucagon-Like Peptide 1 Receptor Agonist Therapy in Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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Keywords
Diabetes · Chronic kidney disease · Glucagon-like peptide 1 receptor agonists · Renal insufficiency

Abstract

Introduction: The effects of glucagon-like peptide 1 receptor agonists (GLP-1 RA) in patients with diabetes and established chronic kidney disease (CKD) remain unclear. ***Methods:*** We systematically searched PubMed, Embase, and Cochrane Library from inception to May 2024 for randomized controlled trials (RCTs) and respective post hoc studies comparing GLP-1 RAs versus placebo in patients with type 2 diabetes mellitus (T2DM) and established CKD (as per study definition or otherwise defined as having an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 and/or urine albumin-to-creatinine ratio more than 30 mg/g). We applied a random-effects model to pool risk ratios (RRs), hazard ratios (HRs), and 95% confidence intervals (CIs). ***Results:*** We included 10 RCTs and post hoc analyses comprising 18,042 patients, of whom 9,164 (50.8%) were treated with GLP-1 RAs. There were significantly lower rates of major adverse kidney events (RR 0.82; 95% CI: 0.74–0.90; $p < 0.001$; high certainty) and a slightly lower incidence of all-cause mortality (HR 0.84; 95% CI: 0.71–1.00; $p = 0.046$; moderate

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certainty) with the use of GLP-1 RAs relative to placebo. This kidney protection remained consistent in patients with stage 3b CKD (RR 0.78; 95% CI: 0.65–0.94; p = 0.009; high certainty). No significant differences were observed in major adverse cardiovascular events (HR 0.89; 95% CI: 0.78–1.02; p = 0.090; low certainty) or cardiovascular mortality (HR 0.80; 95% CI: 0.60–1.09; p = 0.155; very low certainty), possibly due to a lack of statistical power. ***Conclusion:*** GLP-1 RAs were tied to a lower incidence of all-cause mortality and major adverse kidney events in patients with T2DM and established CKD.

Introduction

Type 2 diabetes mellitus (T2DM) is the most common cause of chronic kidney disease (CKD) in the developed world, leading to end-stage kidney disease and need for kidney replacement therapy [1, 2]. Up to 40% of these patients will develop CKD in their lifetime [3]. Despite the substantial burden this condition places on healthcare systems, cardiovascular disease, rather than end-stage kidney disease, is the primary cause of mortality in patients with T2DM and CKD [4].

To mitigate the cardiovascular and kidney complications associated with T2DM, the standard of care of antidiabetic drugs for diabetic kidney disease – sodium-glucose cotransporter 2 inhibitors, renin-angiotensin system blockers, and finerenone – has been increasingly prescribed [5]. Even so, patients on optimized medical therapy for T2DM still face an excess risk of mortality, kidney events, and cardiovascular events. Therefore, reducing the effects of multi-morbidity in this population remains an unmet need [5, 6].

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have shown promising results in reducing major adverse cardiovascular events (MACEs) in patients with T2DM, regardless of baseline cardiovascular disease [7, 8]. Nonetheless, their effects may depend on kidney function [9]. As a result, the cardiovascular and kidney efficacy of GLP-1 RA therapy in patients with established CKD should not be extrapolated from a population with normal baseline kidney function without proper assessment.

Previous evidence on the cardiovascular and kidney protective effects of GLP-1 RA therapy in patients with T2DM and CKD has been mixed, with randomized controlled trials (RCTs) and post hoc analyses showing both protective and neutral results in this regard [6, 8, 10, 11]. In addition, previous meta-analyses have been unable to adequately assess kidney outcomes in this setting [12, 13]. Herein, we aimed to conduct a systematic review and meta-analysis of RCTs and respective post hoc analysis to elucidate the role of GLP-1 RA therapy in patients with T2DM and CKD.

Material and Methods

This systematic review with meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions recommendations [14, 15]. As such, it was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD42024554712.

Search Strategy and Data Extraction

N.F. and V.B. systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials from inception to May 2024 with the following search terms: "GLP-1," "glucagon-like peptide-1," "dulaglutide," "albiglutide," "liraglutide," "semaglutide," "exenatide," "lixisenatide," "T2DM," "DM2," "diabetes mellitus," "type 2 diabetes," "MACE," "major adverse cardiovascular events," "cardiovascular mortality," "death," "myocardial infarction," "stroke," "major adverse kidney events," "major kidney disease events," "kidney failure," "dialysis," along with the Cochrane sensitive search for randomized studies. The search strategy applied to each database is available in the online supplementary Material (for all online suppl. material, see https://doi.org/10.1159/000543149). We applied no language or date restrictions, nor used any filters for the search in any database. The references from all included studies, previous systematic reviews, and meta-analyses were also searched manually for any additional studies. Two authors (N.F. and M.M.G.) independently extracted the data following predefined search criteria and quality assessment.

Eligibility Criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: (1) RCTs or post hoc analyses of RCTs; (2) comparing a GLP-1 RAs with placebo; (3) enrolling patients with T2DM and CKD; (4) with a primary outcome of MACE or major adverse kidney events (MAKEs), as per study definition; and (5) reporting cardiovascular or kidney outcomes of interest. We excluded studies without a placebo arm or including

patients with other types of diabetes mellitus. CKD was defined as per study definition or otherwise defined as having an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 and/or urine albumin-to-creatinine ratio more than 30 mg/g.

Endpoints and Subanalyses

Our outcomes of interest included all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, hospitalization for heart failure, MACE (as per study definition as three or four-point MACE, depending on the addition of death for unknown cause or hospitalization for unstable angina to the three-point composite of cardiovascular mortality, nonfatal stroke, and nonfatal myocardial infarction), and MAKE (as per study definition). Definitions of MACE and MAKE varied slightly across included studies and were reported in online supplementary Table 1. We conducted a prespecified subanalysis of patients with stage 3b CKD defined as having an eGFR between 30 and 45 mL/min/1.73 m^2. Additionally, we performed a leave-one-out sensitivity analysis for the MACE and MAKE outcomes given that study dominance may have been a concern.

Quality Assessment

Quality assessment of RCTs and their post-hoc analyses was performed by two independent reviewers (N.F. and T.A.C.) using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, in which studies are scored as high, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting biases [16]. Small study effect was investigated by funnel plot analysis of point estimates according to study weights. Egger's regression test could not be performed due to the limited number of included studies in the main outcomes ($n < 10$). Further, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was employed by two independent authors (N.F. and A.N.) using the GRADEpro Guideline Development Tool, which allows categorizing the level of certainty of the evidence in this meta-analysis as high, moderate, low, or very low. Any disagreements were discussed and resolved through a consensus [15, 17].

Statistical Analysis

We preferred to analyze hazard ratios (HRs) with 95% confidence intervals (CIs) to preserve time-to-event data when available in the included studies. Otherwise, we pooled risk ratios (RRs) with 95% CI in binary outcomes. p values <0.05 were deemed significant for treatment effects. Cochran Q test and I^2 statistics were used to assess for heterogeneity; p values inferior to 0.10 and I^2>25% were considered significant for heterogeneity. We applied a restricted maximum likelihood random-effects model for all outcomes to account for methodological and demographic heterogeneity across included studies, as per Cochrane recommendations [15]. R software version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses, using the *meta* package.

Results

Study Selection and Characteristics

As detailed in Figure 1, the initial search yielded 3,578 results. After removal of duplicate records and ineligible studies, 37 remained and were fully reviewed based on inclusion and exclusion criteria. Of these, a total of 10 studies were included, comprising 18,042 patients [6–8, 10, 11, 18–22]. Baseline studies characteristics are displayed in Table 1. A total of 9,164 (50.8%) patients received GLP-1 RAs. The prevalence of hypertension varied from 86 to 95.8%, while the average duration of T2DM varied from 10.5 to 15.6 years. The average follow-up ranged from 1.3 to 5.4 years across included studies. Up to 63.3% of patients were on insulin therapy, while the maximal proportion of users of sodium-glucose cotransporter-2 inhibitors at enrollment was 15.7.

Pooled Analysis of all Studies

Kidney Outcomes and All-Cause Mortality

GLP-1 RA therapy was significantly associated with a lower incidence of MAKE as compared with placebo (RR 0.82; 95% CI: 0.74–0.90; $p < 0.001$; $I^2 = 7\%$; Fig. 2a). In patients at CKD stage 3b, results remained consistent (RR 0.78; 95% CI: 0.65–0.94; $I^2 = 0\%$; $p = 0.009$; Fig. 2b).

Only three studies reported the outcome of all-cause mortality. In the pooled analysis, GLP-1 RA therapy was associated with a marginal lower all-cause mortality rate relative to placebo (HR 0.840; 95% CI: 0.708–0.997; $I^2 = 57\%$; $p = 0.046$; Fig. 3).

Cardiovascular Outcomes

There was no significant difference between GLP-1 RAs and placebo in terms of MACE (HR 0.89; 95% CI: 0.78–1.02; $p = 0.090$; $I^2 = 56\%$; Fig. 4), cardiovascular mortality (HR 0.80; 95% CI: 0.60–1.09; $p = 0.155$; $I^2 =$

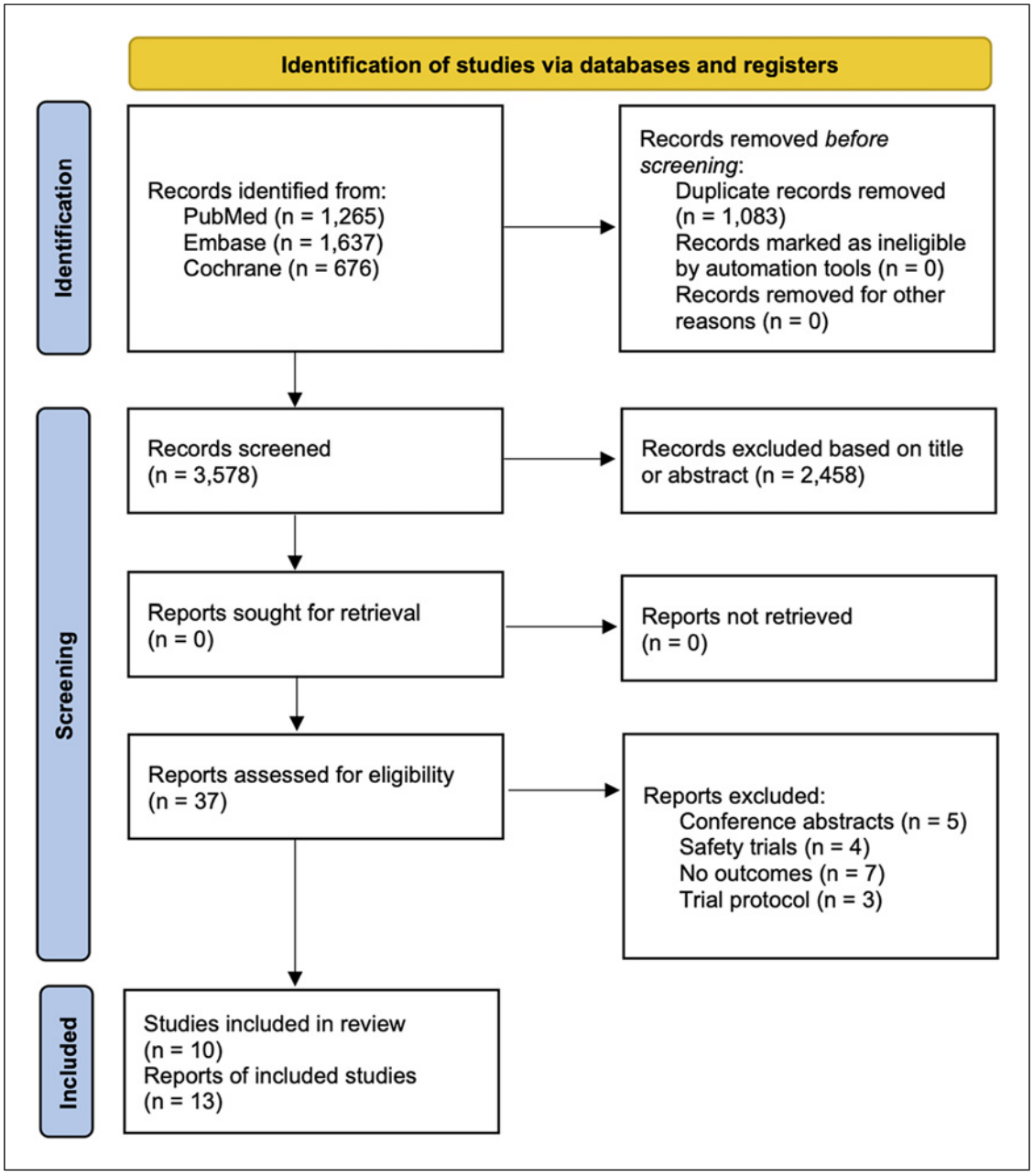

Fig. 1. PRISMA flowchart diagram of study screening and selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

76%; Fig. 5a), myocardial infarction (HR 0.88; 95% CI: 0.75–1.03; $p = 0.103$; $I^2 = 0\%$; Fig. 5b), stroke (HR 0.91; 95% CI: 0.55–1.53; $I^2 = 81\%$; $p = 0.734$; Fig. 5c), or hospitalizations for heart failure (HR 0.88; 95% CI: 0.59–1.31; $p = 0.535$; $I^2 = 74\%$; online suppl. Fig. S1). Nonetheless, one should note that this was possibly due to a lack of statistical power, given the inclusion of studies with small sample sizes.

Leave-One-Out Sensitivity Analysis

We performed a leave-one-out sensitivity analysis for outcomes in which study dominance was a concern – MACE and MAKE (overall analysis). In the outcome of MACE, no study showed a major contribution to heterogeneity (online suppl. Fig. S2a). Although the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial [6] accounted for over 45% of the weight of the

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Table 1. Study characteristics at baseline

characteristics	AMPLITUDE-O, 2023[a]		ELIXA, 2018[b]		EXSCEL, 2017[a]		FLOW, 2024		FREEDOM, 2022[a]		HARMONY, 2018[a]		LEADER, 2016		PIONEER-6, 2019[a]		REWIND, 2019[a]		SUSTAIN-6, 2016	
	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB	GLP-1 RA	PB
Sample size, *n*	841	425	596	552	1,565	1,626	1,767	1,766	196	212	1,098	1,124	1,116	1,042	434	422	944	988	469	470
Age, years[c]	64.6	64.4	61.2	61.2	62.0	62.0	66.6	66.7	63.0	63.0	64.1	64.2	67.3	67.3	66.0	66.0	66.2	66.2	64.6	64.6
Follow-up duration, years[c]	1.8		2.1		3.2		3.4		1.3		1.5		3.8		1.3		5.4		1.9	
Female, %	34.1	31.0	32.0	31.0	38.0	38.0	29.4	31.1	37.5	35.9	30.0	31.0	38.1	39.4	31.9	31.4	46.6	46.1	38.5	40.0
HbA1c, %[c]	NA	NA	8.0	8.0	8.0	8.0	7.8	7.8	8.0	8.0	8.7	8.7	8.7	8.6	8.2	8.2	7.3	7.4	8.7	8.7
Duration of T2DM, years[c]	15.6	15.0	11.2	11.7	12.0	12.0	NA	NA	10.4	10.2	14.1	14.2	15.4	14.9	14.7	15.1	10.5	10.6	14.2	13.6
BMI, kg/m^2	32.8	32.4	30.2	30.5	31.8	31.7	31.9	32.0	32.4	31.9	32.3	32.3	32.6	32.7	32.3	32.3	32.3	32.3	32.8	32.8
Hypertension, %	91.5	91.1	NA	NA	NA	NA	NA	NA	NA	NA	86.0	87.0	95.6	95.8	NA	NA	93.0	93.3	93.6	91.9
Medication use, %																				
Any insulin	63.3	61.7	50.0	48.0	46.2	46.5	61.3	61.4	35.8	35.2	60.0	58.0	43.7[a]	45.6[a]	60.8	60.4	24.0	23.7	58.0[d]	58.1[d]
Metformin	73.6	72.8	NA	NA	76.4	76.8	NA	NA	84.8	84.9	73.0	74.0	75.8[a]	77.1[a]	76.7	78.0	81.3	81.1	72.3[d]	74.8[d]
SGLT2i	15.1	15.0	0.0	0.0	1.2	0.7	15.7	15.5	NA	NA	7.0	6.0	NA	NA	10.4	8.8	NA	NA	0.1[d]	0.2[d]
ACEi	NA	NA	59.0	61.0	48.1	49.3	35.4	34.8	NA	NA	48.0	50.0	51.8[a]	50.3[a]	NA	NA	NA	NA	49.8[d]	49.8[d]
ARB	NA	NA	27.0	26.0	31.7	30.7	60.3	60.1	NA	NA	34.0	32.0	31.9[a]	31.8[a]	NA	NA	NA	NA	33.3[d]	36.0[d]
ACEi/ARB	80.1	80.0	NA	NA	NA	NA	NA	NA	76.9	74.9	NA	NA	NA	NA	NA	NA	81.0	82.0	NA[d]	NA[d]
Betablocker	66.0	64.3	NA	NA	55.5	55.8	NA	NA	52.6	53.5	66.0	67.0	56.8[a]	54.1[a]	NA	NA	45.2	45.9	55.8[d]	58.8[d]
Statin	81.2	80.3	91.0	92.0	74.3	72.7	NA	NA	66.5	67.9	84.0	84.0	72.9[a]	71.4[a]	NA	NA	66.3	66.0	72.9[d]	73.9[d]
Aspirin	68.6	67.3	NA	NA	64.1	63.1	NA	NA	59.1	59.4	77.0	77.0	63.8[a]	62.1[a]	NA	NA	NA	NA	65.9[d]	64.8[d]
eGFR <30 mL/min/m^2, *n*	NA	NA	NA	NA	8	6	218	182	NA	NA	NA	NA	117	107	16	13	NA	NA	46	61
UACR, mg/mmol	3.1	3.2	NA	NA	NA	NA	582.3[e]	557.8[e]	NA	NA	NA	NA	47.3[e]	51.8[e]	NA	NA	1.80	1.88	NA	NA
Current smoker, %	15.8	15.3	13.0	14.0	11.8	11.6	12.6	11.7	NA	NA	16.0	16.0	8.2	8.4	11.6	10.4	14.0	14.4	NA	NA

Gerstein et al. [18], Pfeffer et al. [19], Holman et al. [20], Perkovic et al. [6], Ruff et al. [11], Hernandez et al. [7], Marso et al. [10], Husain et al. [21], Gerstein et al. [8], Marso et al. [22]. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonists; PB, placebo; SGLT2i, sodium-glucose cotransporter-2 inhibitors; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio. [a]Data refer to the overall population rather than the CKD subgroup, except for the sample size (patients with CKD). [b]Subgroup of patients with microalbuminuria (UACR 30–300 mg/g), except for the sample size (patients with micro or macroalbuminuria). [c]Mean or median. [d]Data refer to the subgroups of semaglutide 1.0 mg and placebo 1.0 mg. [e]Milligram/gram.

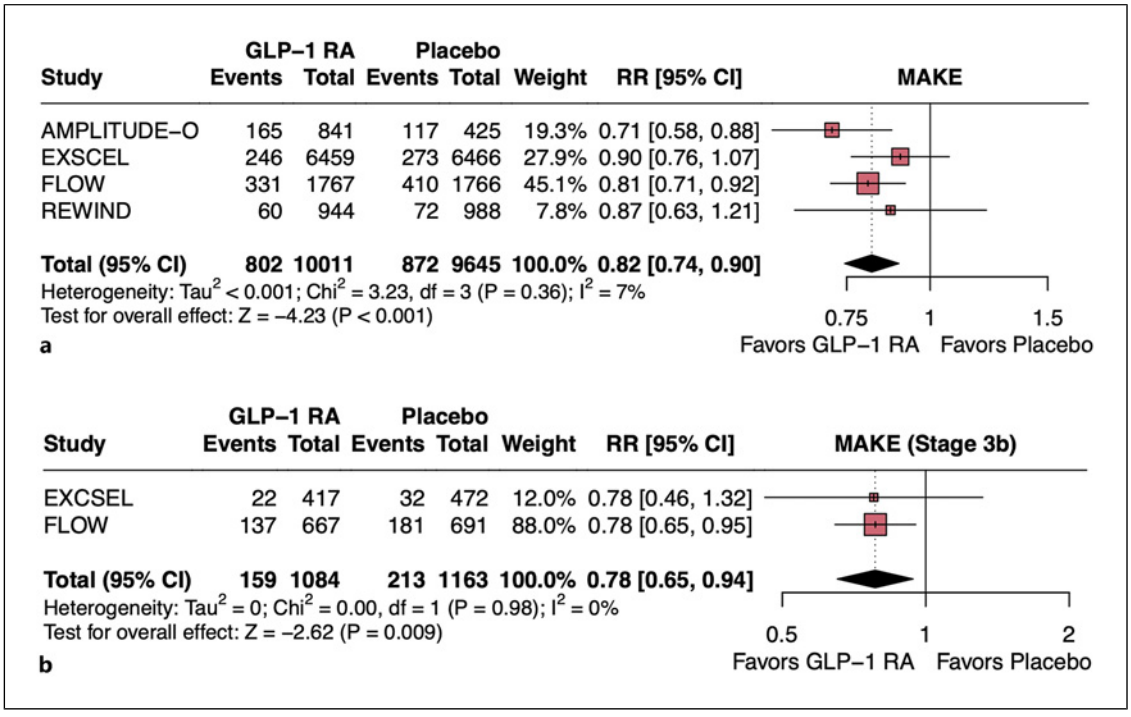

Fig. 2. GLP-1 RA therapy was associated with a lower incidence of MAKE in the overall population (**a**) and in patients with stage 3b CKD (**b**). CI, confidence interval; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MAKEs, major adverse kidney events; RR, risk ratio.

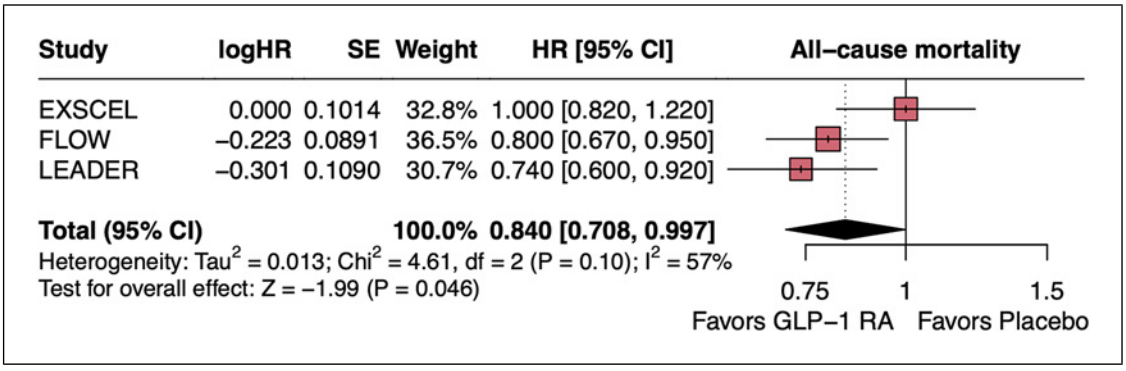

Fig. 3. GLP-1 RA therapy was associated with a slightly lower all-cause mortality rate. CI, confidence interval; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; SE, standard error.

overall analysis, results remained consistent after removal of this study. Results became nonsignificant favoring the GLP-1 RA group after removing any of most studies, except for the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) and FREEDOM Cardiovascular Outcomes studies [11, 19]. As for MAKE, results remained significant and favored the GLP-1 RAs group after removing any of the four studies (online suppl. Fig. S2b). However, between-study heterogeneity measured by I^2 was reduced to zero after removing the Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) or Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trials [18, 20]. These findings are most consistent with the interpretation that the findings of the overall analyses are a result of the pooling all studies together rather than a finding driven by a single large study, such as the FLOW trial.

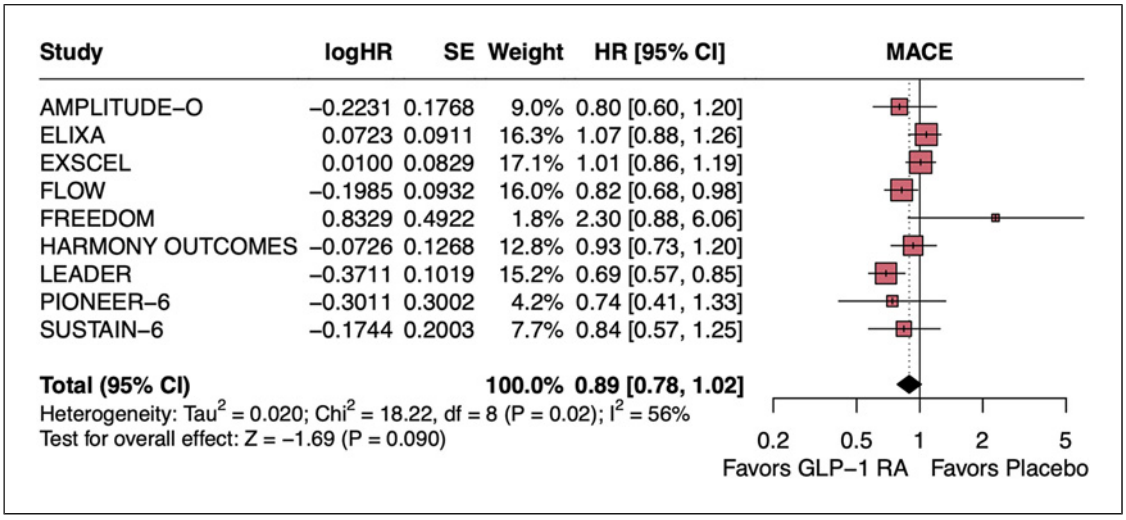

Fig. 4. GLP-1 RA therapy was associated with a lower incidence of MACE. CI, confidence interval; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MACEs, major adverse cardiovascular events; HR, hazard ratio; SE, standard error.

Quality Assessment

Individual RCT appraisal is reported in online supplementary Figure S3. The EXSCEL trial was deemed to have some concerns in the domain regarding the randomization process [20]. This was mainly driven by the fact that there was a statistically significant higher use of sodium-glucose cotransporter-2 inhibitors and lipid-lowering medications in the exenatide group relative to placebo.

Funnel plot analysis for the outcome of MACE showed a slight asymmetry of the distribution of studies' weights against their standard errors (online suppl. Fig. S4). However, a small study effect could not be confirmed because Egger's regression has not been performed due to the limited number of included studies ($n < 10$).

The GRADE assessment is displayed in online supplementary Table 2. There was high certainty of evidence for the outcomes of MAKE (both overall and subgroup analyses). There was moderate certainty of evidence for the outcomes of all-cause mortality and myocardial infarction due to a high between-study heterogeneity and imprecision due to a neutral result, respectively. Imprecision due to a neutral result refers to the difficulty determining the true direction of effect, that is, whether there was an increase or reduction, considering that the result crosses the null effect. In addition, there was low certainty of evidence for the outcome of MACE due to a high between-study heterogeneity. Finally, the outcomes of cardiovascular mortality and stroke had very low certainty of evidence due to a high between-study heterogeneity and imprecise CIs.

Discussion

In this meta-analysis of 10 studies (RCTs or their post hoc analyses) comprising 18,042 patients, we compared cardiovascular and kidney outcomes of GLP-1 RA therapy versus placebo in patients with T2DM and established CKD. We found that GLP-1 RAs were tied to a slightly lower incidence of all-cause mortality and a significantly lower incidence of MAKE, including in patients with stage 3b CKD. Nonetheless, there was no significant difference between groups in terms of MACE or its components – cardiovascular mortality, stroke, or myocardial infarction, which raises concerns over a lack of statistical power.

Patients with diabetic kidney disease still face an excess risk of mortality, MACE, and MAKE even if on optimized medical treatment with first-line options such as sodium-glucose cotransporter-2 inhibitors, finerenone, and renin-angiotensin system blockers [5, 23]. In this regard, GLP-1 RAs emerged with promising cardiovascular outcomes as an add-on therapy in cardiovascular outcome trials and post hoc analyses of RCTs involving a broader population of patients with T2DM, although with mixed findings in terms of kidney outcomes [24, 25]. Even so, primary analyses with patients with T2DM and established CKD had been lacking until the release of the FLOW trial in early 2024, which was stopped early for efficacy with evidence of kidney and cardiovascular protection [6].

In our analysis, GLP-1 RAs were linked to a 18% lower incidence of MAKE as compared with placebo in patients

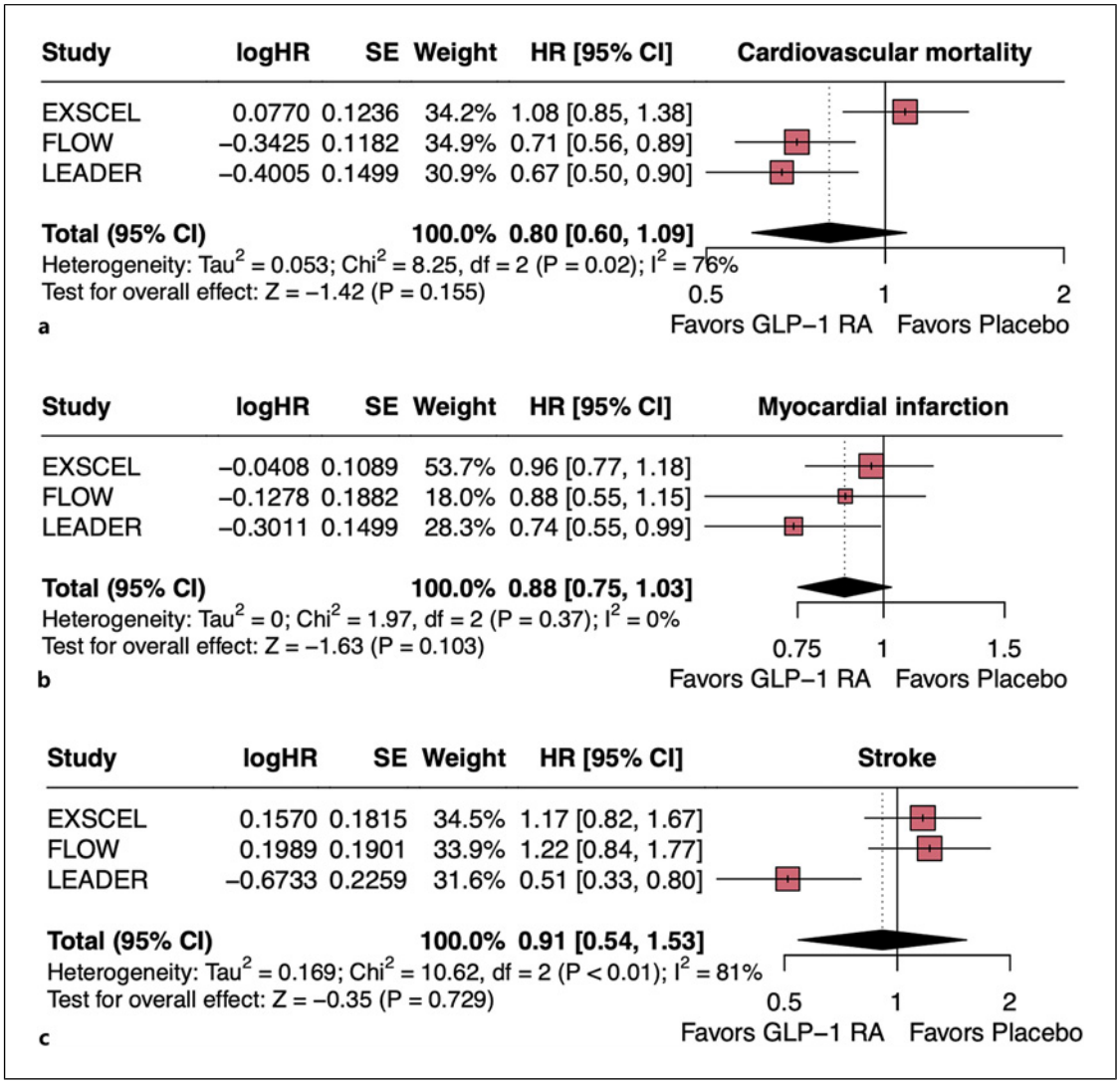

Fig. 5. There was no significant difference between GLP-1 RAs and placebo in terms of cardiovascular mortality (**a**), myocardial infarction (**b**), or stroke (**c**). CI, confidence interval; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; SE, standard error.

with T2DM and established CKD. These kidney benefits may be explained by several mechanisms, through direct and indirect effects. In patients with T2DM, the most pronounced mechanism would be glycemia regulation in a glucose-dependent fashion [26]. Moreover, additional mechanisms beyond that of glycemic control have been demonstrated by preclinical studies, in which the GLP-1 molecule has been associated with improvements in kidney hemodynamics, natriuresis, and fluid homeostasis [23]. In addition, GLP-1 RAs might directly reduce oxidative stress and inflammation in the kidneys, further attenuating the mechanisms behind kidney impairment progression [27].

In contrast, we found no significant benefit in Cardiovascular Outcomes for patients with T2DM and established CKD. At present, there is no clear rationale to explain why patients with T2DM and established CKD on GLP-1 RAs would not also benefit from cardiovascular protection, which has been demonstrated across the spectrum of cardiovascular risk in patients with and without T2DM [10, 28]. In fact, one would expect a larger magnitude of effect of cardiovascular protection in this population, considering that CKD is itself a nontraditional cardiovascular risk factor, leading over two-thirds of patients with CKD to develop cardiovascular disease [26]. In this sense, we hypothesize that this apparent absence of cardiovascular protection may

be a result of a lack of statistical power in the subgroup of patients with CKD, especially considering the small sample size in most of the included studies. However, one should note that we were able to increase the sample size in almost three-fold as compared with previous meta-analyses of patients with T2DM that evaluated the subgroup of patients with CKD at baseline [24, 25]. Therefore, we herein display the most powered analysis to date. Without a dedicated RCT to patients with CKD and T2DM to primarily evaluate cardiovascular outcomes in the near future, our results stand out as the most comprehensive and at least hypothesis-generating at present.

This study is not without limitations. First, the lack of access to individual patient data prevented more detailed subanalyses, such as subgroup analyses of patients with micro or macroalbuminuria, on sodium-glucose cotransporter-2 inhibitors, with previous cardiovascular events, or across the spectrum of residual kidney function. Second, the inclusion of post hoc analyses – which not necessarily reflect the baseline characteristics of the main trial – may have introduced confounding to our analyses, which could not be addressed in full by the present study. Third, given the non-inferiority design of most RCTs and respective post hoc analyses included, we cannot rule out the hypothesis that our cardiovascular outcomes may be underpowered to detect significant differences between groups. Nevertheless, our analysis stands as the most up-to-date at present. Finally, we were unable to conduct meta-regression analyses due to the limited number of studies for each outcome.

In conclusion, our meta-analysis of 10 RCTs and post hoc analyses of RCTs found a significant benefit in terms of kidney protection, but not cardiovascular protection, in patients with T2DM and CKD treated with GLP-1 RAs relative to placebo. Further dedicated RCTs to assess cardiovascular outcomes in this population are needed to confirm our findings.

Statement of Ethics

There was no requirement for informed consent or Institutional Review Board approval for this meta-analysis, given that the data are publicly available, and we did not have access to individual patient data. All patients provided written informed consent before enrollment in the individual studies.

Conflict of Interest Statement

All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Funding Sources

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Author Contributions

Conceptualization: N.F. and M.G.M.G. Data curation: N.F., M.M.G., and V.B. Formal analysis: N.F. and A.N. Funding acquisition: none. Investigation: N.F., M.M.G., V.B., A.N., and M.G.M.G. Methodology: N.F., A.N., and M.G.M.G. Project administration: N.F. and M.G.M.G. Software: N.F. and A.N. Resources: N.F., M.M.G., and V.B. Supervision: L.C.S.P., L.T., J.A.M.-N. and M.G.M.G. Validation: N.F. and M.M.G. Visualization: N.F. and A.N. Writing – original draft: N.F., M.M.G., V.B., A.N., T.A.C., A.G., L.A.L., and O.R.G. Writing – review and editing: all authors.

Data Availability Statement

The data that support the findings of this study are publicly available as previously published reports, as per references below. The dataset used for our analyses is available from the corresponding author (N.F.) upon reasonable request.

References

1 Perkovic V, Agarwal R, Fioretto P, Hemmelgarn BR, Levin A, Thomas MC, et al. Management of patients with diabetes and CKD: conclusions from a "kidney disease: improving global outcomes" (KDIGO) controversies conference. Kidney Int. 2016;90(6):1175–83. https://doi.org/10.1016/j.kint.2016.09.010

2 U.S. Renal Data System. USRDS 2013 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2013. Available from: http://www.usrds.org/2013/pdf/v2_ch12_13.pdf

3 Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA. 2016;316(6):602–10. https://doi.org/10.1001/jama.2016.10924

4 Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. 2024 heart disease and stroke statistics: a report of us and global data from the American heart association. Circulation. 2024;149(8):e347–913. https://doi.org/10.1161/CIR.0000000000001209

5 De Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the American diabetes association (ada) and kidney disease: improving global outcomes (kdigo). Diabetes Care. 2022;45(12):3075–90. https://doi.org/10.2337/dci22-0027

6 Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024:NEJMoa2403347.

7 Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519–29. https://doi.org/10.1016/S0140-6736(18)32261-X
8 Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121–30. https://doi.org/10.1016/S0140-6736(19)31149-3
9 Filippatos TD, Elisaf MS. Effects of glucagon-like peptide-1 receptor agonists on renal function. World J Diabetes. 2013;4(5):190–201. https://doi.org/10.4239/wjd.v4.i5.190
10 Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22. https://doi.org/10.1056/nejmoa1603827
11 Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. Nat Med. 2022;28(1):89–95. https://doi.org/10.1038/s41591-021-01584-3
12 Kelly M, Lewis J, Rao H, Carter J, Portillo I, Beuttler R. Effects of GLP -1 receptor agonists on cardiovascular outcomes in patients with type 2 diabetes and chronic kidney disease: a systematic review and meta-analysis. Pharmacotherapy. 2022;42(12):921–8. https://doi.org/10.1002/phar.2737
13 Krisanapan P, Sanpawithayakul K, Patthar-anitima P, Thongprayoon C, Miao J, Mao MA, et al. Safety and efficacy of GLP-1 receptor agonists in type 2 diabetes mellitus with advanced and end-stage kidney disease: a systematic review and meta-analysis. Diseases. 2024;12(1):14. https://doi.org/10.3390/diseases12010014
14 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
15 Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Handbook for Systematic Reviews of Interventions version 6.4. (updated August 2023). Available from: https://training.cochrane.org/handbook
16 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
17 McMaster University and Evidence Prime. GRADEpro GDT: GRADEpro guideline development tool. 2022. Available from: http://www.gradepro.org/
18 Gerstein HC, Mian R, Ramasundarahettige C, Branch KRH, Del Prato S, Lam CSP, et al. Cardiovascular and renal outcomes with varying degrees of kidney disease in high-risk people with type 2 diabetes: an epidemiological analysis of data from the AMPLITUDE-O trial. Diabetes Obes Metab. 2024;26(4):1216–23. https://doi.org/10.1111/dom.15417
19 Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and Acute coronary Syndrome. N Engl J Med. 2015;373(23):2247–57. https://doi.org/10.1056/NEJMoa1509225
20 Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–39. https://doi.org/10.1056/NEJMoa1612917
21 Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841–51. https://doi.org/10.1056/NEJMoa1901118
22 Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44. https://doi.org/10.1056/NEJMoa1607141
23 Muskiet MHA, Tonneijck L, Smits MM, Van Baar MJB, Kramer MHH, Hoorn EJ, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol. 2017;13(10):605–28. https://doi.org/10.1038/nrneph.2017.123
24 Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;7(10):776–85. https://doi.org/10.1016/S2213-8587(19)30249-9
25 Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653–62. https://doi.org/10.1016/S2213-8587(21)00203-5
26 Michos ED, Bakris GL, Rodbard HW, Tuttle KR. Glucagon-like peptide-1 receptor agonists in diabetic kidney disease: a review of their kidney and heart protection. Am J Prev Cardiol. 2023;14:100502. https://doi.org/10.1016/j.ajpc.2023.100502
27 Greco E, Russo G, Giandalia A, Viazzi F, Pontremoli R, De Cosmo S. GLP-1 receptor agonists and kidney protection. Medicina. 2019;55(6):233. https://doi.org/10.3390/medicina55060233
28 Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221–32. https://doi.org/10.1056/NEJMoa2307563