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META-ANALYSIS

Cardiovascular Effects and Tolerability of GLP-1 Receptor Agonists

A Systematic Review and Meta-Analysis of 99,599 Patients

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ABSTRACT

BACKGROUND Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated significant cardiovascular (CV) benefits, particularly in patients with diabetes mellitus, but the safety and efficacy of different GLP-1 RAs across diverse populations remain insufficiently defined.

OBJECTIVES Previous meta-analyses of GLP-1 RAs have been limited by restricted populations, omission of recent trials, or incomplete safety synthesis; this study integrates the latest evidence across 21 randomized controlled trials and diverse populations using advanced meta-analytic methods.

METHODS Randomized controlled trials comparing GLP-1 RAs vs controls or placebo were included. Analyses were conducted in prespecified subgroups based on the GLP-1 RA used. Prespecified subgroups according to diabetes mellitus, kidney function, obesity, or heart failure were also performed. Main outcomes comprised mortality (all-cause and CV), trial-defined major adverse cardiovascular events (MACE) and serious adverse events. GRADE (Grading of Recommendations Assessment, Development and Evaluation) and trial sequential analyses were performed to evaluate certainty and conclusiveness of findings, respectively.

RESULTS A total of 21 trials encompassing 99,599 patients were included. Eight different GLP-1 RAs were used (lixisenatide, liraglutide, exenatide, semaglutide, efpeglenatide, dulaglutide, albiglutide, and tirzepatide), each administered at therapeutic doses and compared vs placebo or controls. Mean follow-up duration was 2.4 years. We found conclusive, high-certainty evidence that GLP-1 RAs reduced all-cause death (incidence rate ratio [IRR]: 0.88; 95% CI: 0.84-0.92; needed to treat [NNT] = 121), CV death (IRR: 0.87; 95% CI: 0.81-0.92; NNT = 170), and MACE (IRR: 0.87; 95% CI: 0.83-0.91; NNT = 66), compared with controls. GLP-1 RAs reduced serious adverse events (−9%), myocardial infarction (−15%), acute kidney failure (−9%), heart failure (−15%), and infections (−10%), but increased gastrointestinal (+63%) and gallbladder (+26%) disorders. There were no differences in stroke, pancreatitis, or neoplasm between groups. Results were mostly consistent across subgroups. Analysis by GLP-1 RA type revealed potential differences in efficacy and safety profiles.

CONCLUSIONS GLP-1 RAs reduce mortality and MACE in high-risk populations, highlighting benefits beyond glycemic control. These come at increased gastrointestinal and gallbladder risks. Variation in efficacy and tolerability supports tailoring GLP-1 RA therapy to individual patient characteristics and treatment goals. (PROSPERO [GLP-1 RAs Reduce Mortality and Cardiovascular Events Across the Spectrum of Treated Patients: A Systematic Review and Meta-Analysis]; CRD420251032222) (JACC. 2025;86:1805-1819) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

CV = cardiovascular

DM = diabetes mellitus

EF = ejection fraction

GI = gastrointestinal

GLP-1 = glucagon-like peptide-1

GLP-1 RA = glucagon-like peptide-1 receptor agonist

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IRR = incidence rate ratio

MACE = major adverse cardiovascular events

MI = myocardial infarction

NNH = number needed to harm

NNT = number needed to treat

RCT = randomized controlled trial

SAE = serious adverse event

Obesity and type 2 diabetes mellitus (DM) are among the most prevalent and rapidly increasing diseases worldwide.[1] Both are major drivers of cardiovascular (CV) disease, which remains the leading cause of morbidity and mortality worldwide, despite substantial advances in treatment and prevention.[2] In this context, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a novel and impactful therapeutic approach to address the intersecting epidemics of metabolic and CV disease.[3]

GLP-1 RAs exert multifaceted effects, including glucose-dependent insulin secretion, suppression of glucagon, delayed gastric emptying, enhanced insulin sensitivity, and appetite regulation via central nervous system pathways.[4,5] Since their approval in 2005, GLP-1 RAs have transformed the treatment of DM and obesity, now being endorsed as first-line therapies in light of their demonstrated CV and renal benefits in randomized controlled trials (RCTs).[6,7] Furthermore, emerging data support their efficacy in reducing CV events even in patients at elevated CV risk even without DM.[8,9] Notably, the CV benefits of GLP-1 RAs appear to manifest early after initiation, suggesting mechanisms beyond weight loss or glycemic control.[8,9] Proposed mechanisms include improvements in endothelial function, modulation of atherosclerotic plaque stability, reductions in blood pressure, and decreases in epicardial fat volume.[3,10,11]

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However, further investigation is needed to delineate the specific efficacy and safety profiles of GLP-1 RAs in patient populations with comorbid DM, chronic kidney disease (CKD), obesity, or heart failure (HF). Additionally, interdrug variability may exist among different GLP-1 RAs in both efficacy and safety profiles, which remains to be clarified, also in light of the growing number of published clinical trials testing the efficacy of different molecules belonging to the GLP-1 RA class. Concerns related to gastrointestinal (GI) tolerability and the potential for rare, but serious, adverse events (SAEs) also remain to be fully addressed with specific powered analyses.[12-14] These considerations underscore the need for granular subgroup analyses that may allow better individual treatments for CV risk reduction. Although several meta-analyses of GLP-1 RAs have been published, most focus exclusively on patients with DM, omit recently reported large-scale trials, or do not integrate efficacy and safety outcomes across diverse populations.[15,16] This study synthesizes 21 RCTs—including the latest CV and renal outcome studies—involving nearly 100,000 patients, applies incidence rate ratios (IRRs) to account for variable follow-up, incorporates trial sequential analysis, and provides the most comprehensive pooled evaluation to date of both efficacy and safety in DM and non-DM populations.

METHODS

This meta-analysis was reported following the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for pairwise and network meta-analyses[17,18] (Supplemental Table 1). The study protocol is registered in Prospective Register of Systematic Reviews (CRD420251032222). As the present research was a meta-analysis of published studies, the requirement for ethics committee approval was waived.

ELIGIBILITY CRITERIA. RCTs were considered eligible if they fulfilled the following criteria: 1) random allocation to treatment with a GLP-1 RA at therapeutic doses vs placebo or controls; and 2) investigating CV effectiveness and reporting at least 1 main outcome of interest. Studies involving investigational GLP-1 RAs not yet approved for clinical use were excluded. No language restrictions were applied.

SEARCH, DATA EXTRACTION, AND QUALITATIVE ASSESSMENT. Information sources included MEDLINE via PubMed, EMBase, Cochrane Library, Scopus,

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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and Central Register of Controlled Trials (CENTRAL) from data set inception to April 1, 2025. Detailed search strategy for each database is provided in Supplemental Table 2. Websites from leading cardiology societies, news outlets, and reference lists of eligible studies were also reviewed. References of the included articles were inspected with a snowball approach. Three investigators (M.B., L.S., and G.S.) independently screened records for eligibility. Study-level data were extracted independently and inserted into dedicated electronic spreadsheets. The same 3 investigators independently performed data extraction. There were no restrictions with respect to the language used or publication status. Disagreements were solved by discussion with the senior author (M.G.). Before analysis, the Cochrane's Risk of Bias (RoB) 2 tool risk was used to assess the quality/risk of bias for each study. RoB 2 was assessed independently by 2 investigators (C.L. and G.S.).[19] Disagreements were resolved through arbitration by a third reviewer (M.G.). Publication bias was assessed through visual assessment of contrast-adjusted and contour-enhanced funnel plots, and Egger's regression test. In case of significant publication bias, results were corrected using the trim and fill method.[20] For each endpoint of interest, the robustness of results per each individual outcome was rated as high, moderate, low, or very low according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, based on criteria including risk of bias, inconsistency, indirectness, imprecision, and potential publication bias.

ENDPOINTS. Main outcomes comprised mortality (all-cause and CV), trial-defined major adverse cardiovascular events (MACE), and SAEs. For trials reporting multiple definitions of MACE, the one more aligned with the definition "all-cause or CV death, myocardial infarction, or stroke" was prioritized.[21] This approach was used to prioritize hard ischemic endpoints over softer ones within the composite MACE endpoint to enhance the clinical relevance of the analysis. Secondary outcomes included myocardial infarction (MI), stroke, HF hospitalization, GI disorders, gallbladder disorders, acute kidney failure, infections, pancreatitis, and neoplasms.

STATISTICAL ANALYSIS. To account for different follow-up and biological variability, pairwise meta-analyses through random-effects models were conducted to estimate IRRs and 95% CIs based on recalculated patient-year for each outcome of interest. Patient-year were calculated on the reported mean or median time, when available, while using the prespecified intended follow-up period in other instances. Heterogeneity was assessed by means of τ^2 and I^2 statistic, and graded as low, moderate, or high for I^2 values of <25%, 25%-50% or >50%, respectively.[22] All analyses included a prespecified subgroup interaction test for the specific GLP-1 RA used.

Prespecified subgroup analyses to assess the robustness of findings across key patient subgroups included: 1) DM; 2) CKD; 3) obesity; or 4) reduced ejection fraction (EF). A sensitivity analysis using a leave-one-out approach was conducted to evaluate the impact of individual trials on the effect sizes. Sensitivity analyses excluding: 1) tirzepatide; 2) lixisenatide; 3) albiglutide; and 4) exenatide from the main analysis were also included. Finally, a sensitivity analysis using risk ratios (RRs), as well as a meta-regression based on follow-up duration, were run to assess the impact of effect measure selection (IRR vs RR) and varying follow-up times on the outcomes, respectively.

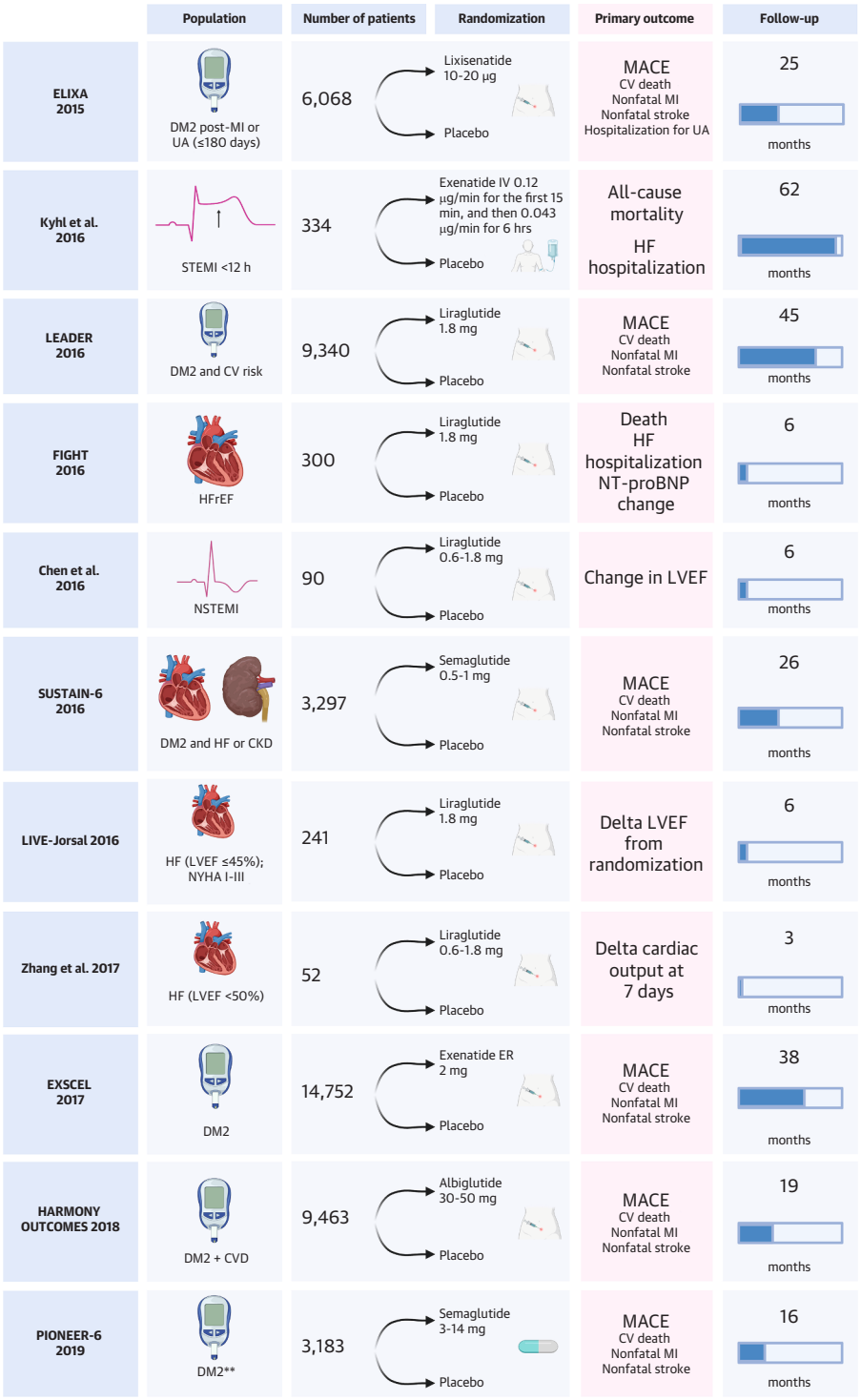
Number needed to treat (NNT) or number needed to harm (NNH) to prevent or cause an adverse event was calculated according to the absolute risk differences for the main outcomes. In addition, event rates and risk difference, alongside their CIs, were estimated across the outcomes to clarify the impact of GLP-1 RA treatment on absolute risks of events. All analyses were performed using R 4.3.1 software (R Foundation for Statistical Computing), packages "meta" and "netmeta."

RESULTS

STUDY SELECTION AND BASELINE CHARACTERISTICS. The systematic review process is summarized in Supplemental Table 3. After screening, 21 RCTs were included in the meta-analysis, encompassing 99,599 patients and 321,003 patient-years.[10,12,23-39] Mean follow-up duration was 2.4 years. The publication years of the studies spanned from 2015 to 2025, covering a diverse range of populations, including patients with established CV disease (eg, history of heart failure or prior cardiovascular events), those at high risk (eg, diabetes, obesity, or chronic kidney disease), or both. A total of 8 different GLP-1 RAs were used (lixisenatide, liraglutide, exenatide, semaglutide, efpeglenatide, dulaglutide, albiglutide, and tirzepatide), each administered at therapeutic doses and compared vs placebo or controls. **Figure 1** and Supplemental Tables 4 and 5 summarize the key characteristics of the included trials.

Mean age of enrolled patients was 66.9 years, with 32.7% being female. Across the included trials, the baseline body mass index ranged from 24.8 kg/m^2 to 37.2 kg/m^2, with mean values of 32.2 kg/m^2. Of the 21 trials included, 12 included patients with DM, 4 with

FIGURE 1 Adapted Graphical Overview for Evidence Reviews



*Age ≥50 years with cardiovascular disease (CVD), chronic heart failure (HF) (NYHA functional class II-III), or chronic kidney disease (CKD) stage ≥3; or ≥60 years with at least 1 cardiovascular (CV) risk factor; **type 2 diabetes mellitus (DM2) with CVD/CKD if ≥50 years or CV risk if ≥60 years; ***DM2 with CV event or CV risk; ****DM2 and either a history of CVD or current CKD plus at least one other CV risk factor. ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated hemoglobin; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-clinical summary score; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; SC = subcutaneous; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

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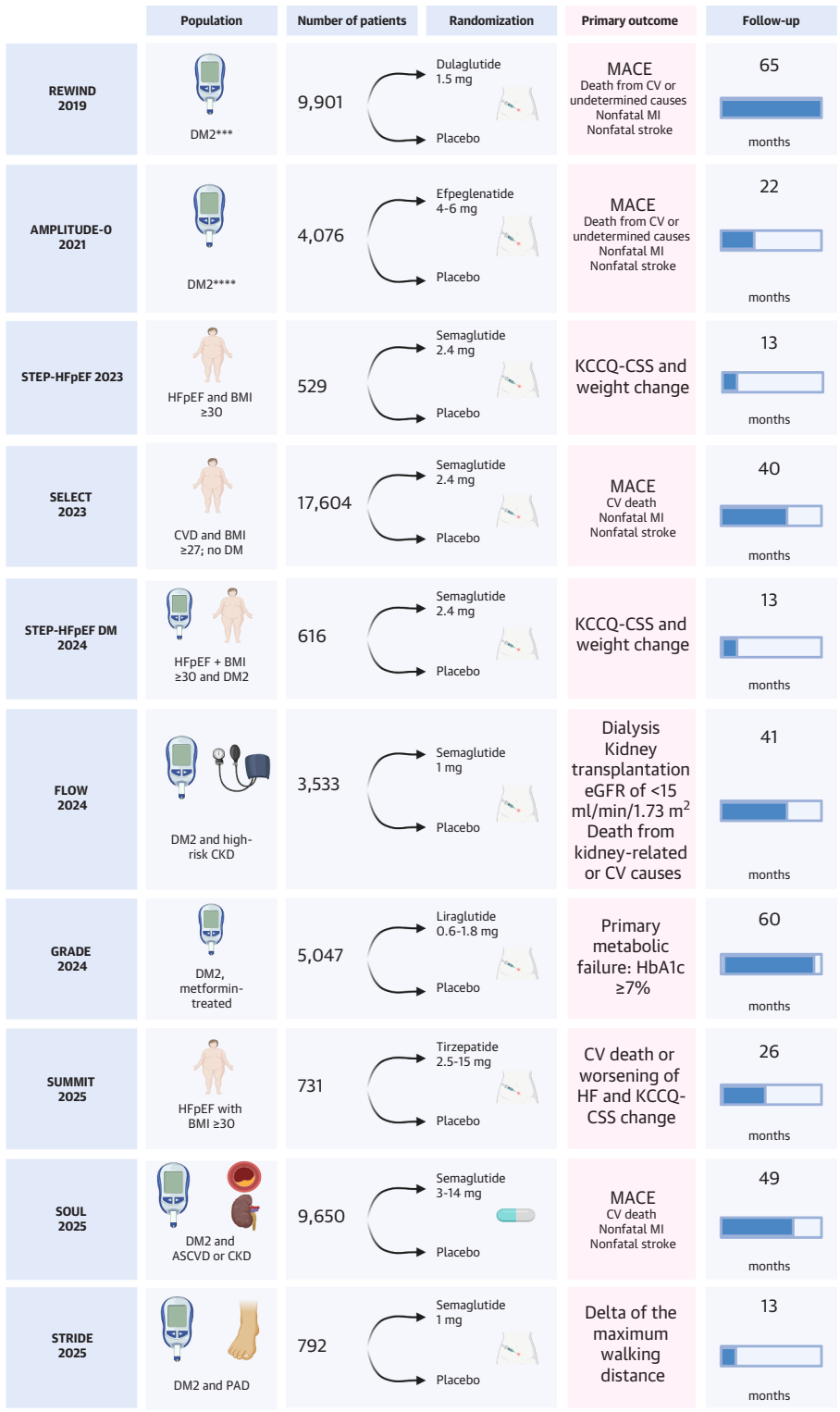
FIGURE 1 Continued



obesity, 7 with HF, 5 with CKD, and 3 with ACS (**Figure 1**). Supplemental Table 6 shows the endpoints available across included trials, with specific endpoint definitions detailed in Supplemental Table 7.

Overall, 6 studies raised some concern for bias (Supplemental Figure 1). Publication bias was detected for HF hospitalization and infections (Supplemental Figure 2). Trim-and-fill correction for outcomes with significant publication bias is shown in Supplemental Figure 3.

RESULTS IN THE OVERALL POPULATION STRATIFIED BY THE GLP-1 RA USED. Main outcomes. GLP-1 RAs were associated with a significant reduction in all-cause mortality compared with controls (IRR: 0.88; 95% CI: 0.84-0.92; $P < 0.01$, NNT = 121, GRADE = high-certainty evidence) (**Figure 2**, Supplemental Table 8). Statistical heterogeneity was low ($I^2 = 0\%$, $\tau^2 = 0$). Trial sequential analysis showed conclusive evidence for this endpoint (Supplemental Figure 4). There were no significant subgroup differences across different GLP-1 RAs used ($P_{int} = 0.77$). Results were consistent with the leave-one-out sensitivity analysis (Supplemental Figure 5).

CV mortality followed a similar trend to all-cause mortality, with GLP-1 RAs associated with a significant reduction in CV death (IRR: 0.87; 95% CI: 0.81-0.92; $P < 0.01$, NNT = 170, GRADE = high-certainty evidence) (**Figure 3**, Supplemental Table 8). Statistical heterogeneity was low ($I^2 = 0\%$, $\tau^2 = 0$). Trial sequential analysis showed conclusive evidence for this endpoint (Supplemental Figure 4). There were no significant subgroup differences across different GLP-1 RAs used ($P_{int} = 0.57$). Tirzepatide showed a numerical increased risk (IRR: 1.61; 95% CI: 0.53-4.93) in CV mortality vs controls. Results were consistent with the leave-one-out sensitivity analysis (Supplemental Figure 6).

GLP-1 RAs significantly reduced trial-defined MACE compared with controls (IRR: 0.87; 95% CI: 0.83-0.91; $P < 0.01$, NNT = 66, GRADE = high-certainty evidence) (**Figure 4**, Supplemental Table 8). Statistical heterogeneity was low ($I^2 = 9\%$, $\tau^2 = 0.0006$). Trial sequential analysis showed conclusive evidence for this endpoint (Supplemental Figure 4). There was a borderline nonsignificant subgroup difference across different GLP-1 RAs used ($P_{int} = 0.052$). Results were consistent with the leave-one-out sensitivity analysis (Supplemental Figure 7).

GLP-1 RAs were associated with a significant reduction in SAEs compared with controls (IRR: 0.91; 95% CI: 0.87-0.96; $P < 0.01$, NNH = 92, GRADE = moderate-certainty evidence) (**Figure 5**, Supplemental Table 8). Statistical heterogeneity was high ($I^2 = 74\%$, $\tau^2 = 0.005$). Trial sequential analysis showed conclusive evidence for this endpoint (Supplemental Figure 4). There were no significant subgroup differences across different GLP-1 RAs used ($P_{int} = 0.21$). Results were consistent with the leave-one-out sensitivity analysis (Supplemental Figure 8). Sensitivity analyses excluding: 1) tirzepatide; 2) lixisenatide; 3) albiglutide; and 4) exenatide (Supplemental Table 9), and sensitivity analysis using RR as well as meta-regression analysis for time of follow-up (Supplemental Table 10) found results to be consistent with the main analysis. Event rates and risk difference for the main outcomes are reported in **Table 1**.

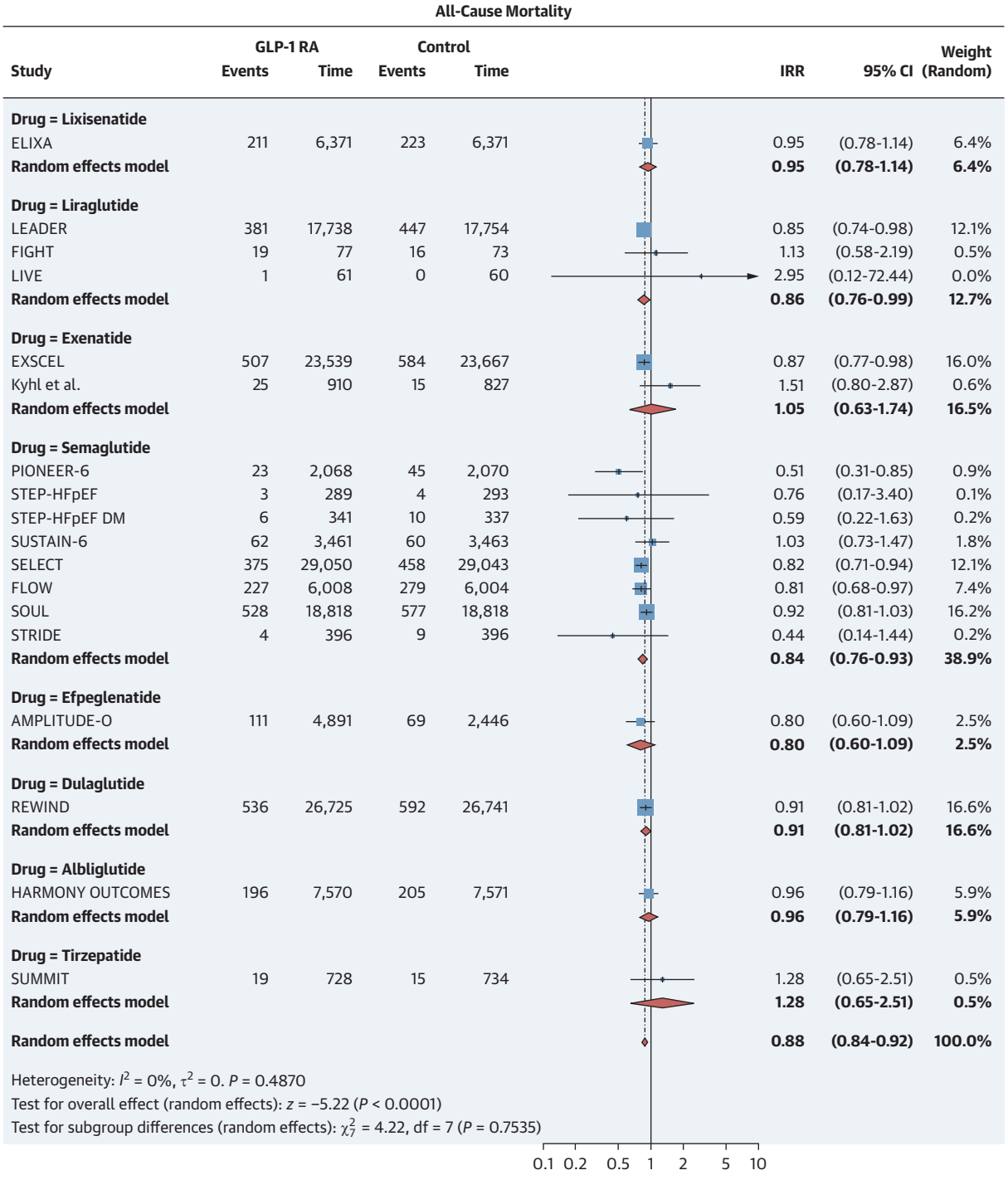
Secondary endpoints. GLP-1 RAs were associated with a significant reduction in MI (IRR: 0.85; 95% CI: 0.78-0.94; $P < 0.01$), hospitalization for HF (IRR: 0.85; 95% CI: 0.75-0.97; $P = 0.01$), and infections (IRR: 0.90; 95% CI: 0.85-0.96; $P < 0.01$) vs controls (Supplemental Figures 9 to 17). There was a numerical reduction in acute kidney failure (IRR: 0.91; 95% CI: 0.83-1.00; $P = 0.053$) with GLP-1 RAs compared with controls (Supplemental Figure 12). However, GLP-1 RAs were associated with a significant increase in GI disorders (IRR: 1.63; 95% CI: 1.36-1.97; $P < 0.01$), and gallbladder disorders (IRR: 1.26; 95% CI: 1.12-1.41; $P < 0.01$) vs controls (Supplemental Figures 13 and 14).

There were no differences between groups in the rate of stroke (IRR: 0.93; 95% CI: 0.81-1.06; $P = 0.27$), pancreatitis (IRR: 0.96; 95% CI: 0.76-1.22; $P = 0.74$), or neoplasms (IRR: 1.04; 95% CI: 0.98-1.10; $P = 0.20$) (Supplemental Figures 15 to 17).

There were significant subgroup differences across different GLP-1 RAs used for the outcomes of MI ($P_{int} < 0.01$) and GI disorders ($P_{int} < 0.01$) (Supplemental Figures 9 and 13). Leave-one-out sensitivity analysis found consistent results with the main analysis, except for the outcome of acute kidney failure in which there was a significant reduction with GLP-1 RA vs controls after the exclusion of the AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes) trial (Supplemental Figures 18 to 26).

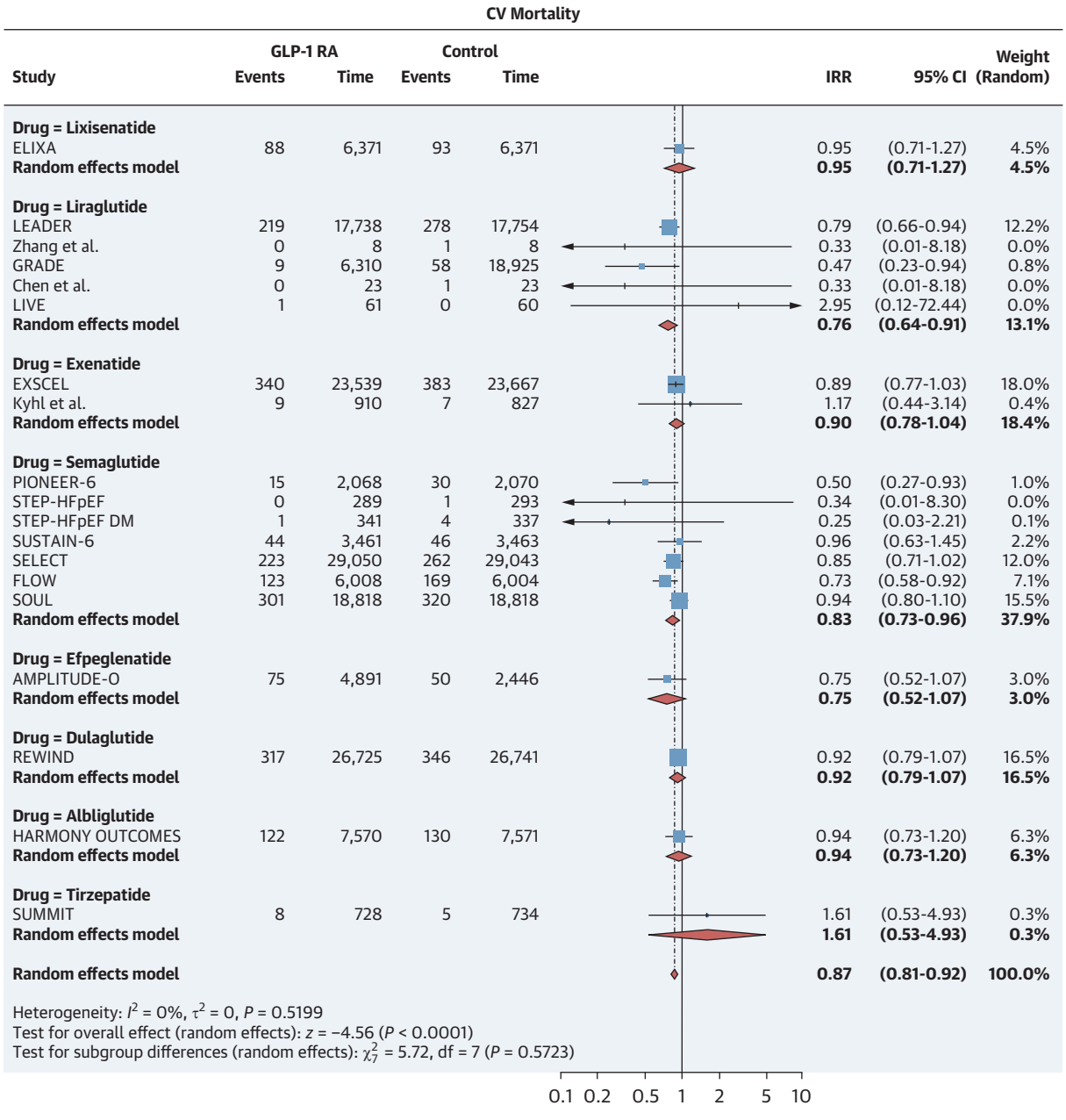
Certainty of evidence was deemed moderate for stroke, HF hospitalization, GI adverse events, infections and neoplasm, whereas it was deemed high for other secondary outcomes (Supplemental Table 8). Trim-and-fill correction were in the same direction of the main analysis (Supplemental Figure 3). Sensitivity analyses excluding: 1) tirzepatide; 2) lixisenatide; 3) albiglutide; and 4) exenatide

FIGURE 2 Forest Plot for the Analysis of All-Cause Mortality



Analyses were conducted according to prespecified subgroups for each individual glucagon-like peptide-1 receptor agonists (GLP-1 RAs), with results presented as both cumulative and agent-specific incidence rate ratios (IRRs) along with their corresponding 95% CIs. Weights of each individual trial on the analysis, the random-effects model for each GLP-1 RA class, and a test for subgroup differences are also reported.

FIGURE 3 Forest Plot for the Analysis of CV Mortality

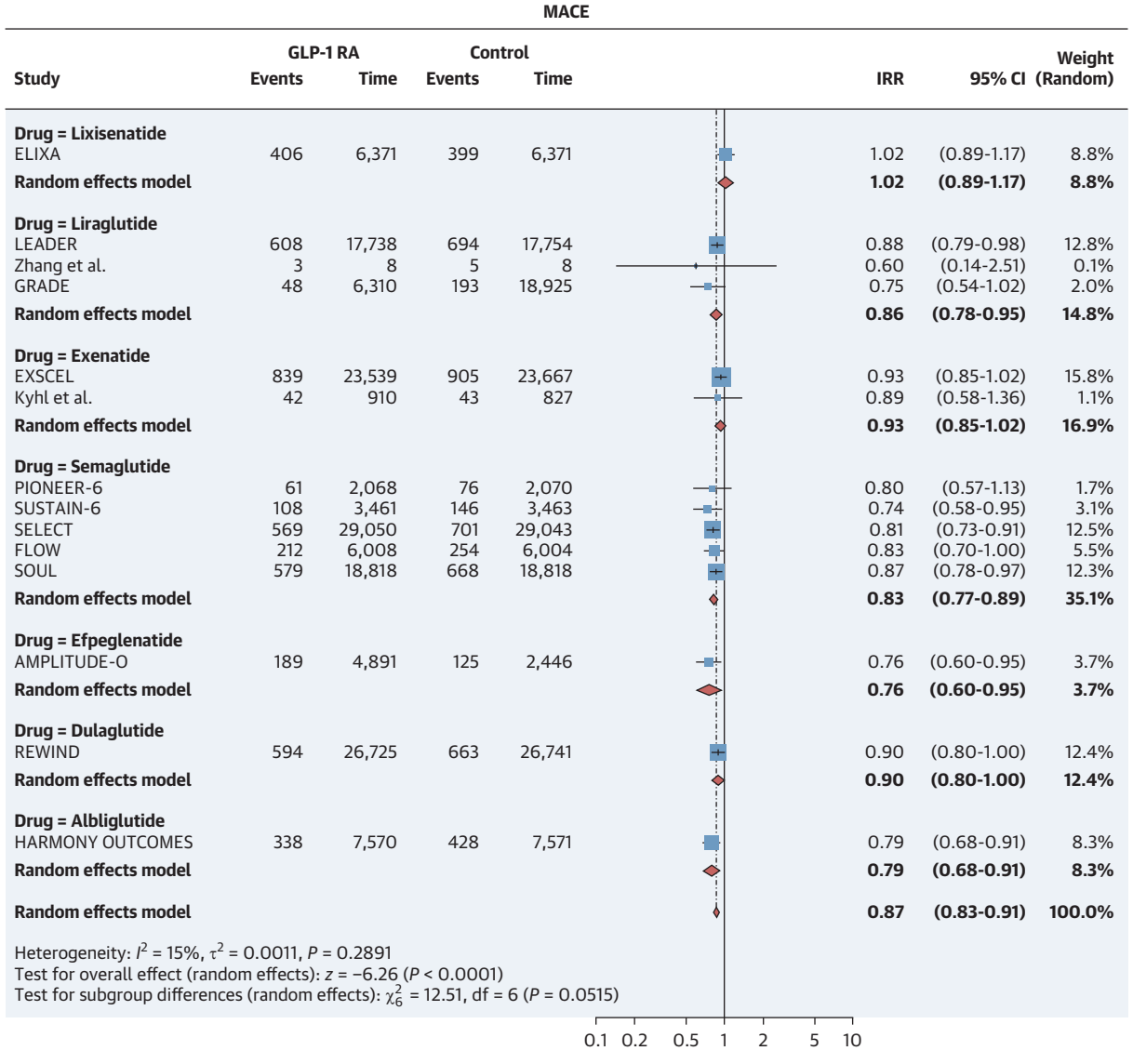


Analyses were conducted according to prespecified subgroups for each individual GLP-1 RA, with results presented as both cumulative and agent-specific IRRs along with their corresponding 95% CIs. Weights of each individual trial on the analysis, the random-effects model for each GLP-1 RA class, and a test for subgroup differences are also reported. Abbreviations as in Figures 1 and 2.

(Supplemental Table 9) and sensitivity analysis using RR as well as meta-regression analysis for time of follow-up (Supplemental Table 10) found results to be consistent with the main analysis. Event rates and risk difference for secondary outcomes are reported in Table 1.

RESULTS ACROSS PRESPECIFIED SUBGROUPS. Results were consistent across patients with and without DM (Supplemental Figure 27). Results were consistent across obese and nonobese patients, except for a significant subgroup interaction for hospitalization for HF (P_{int} = 0.04), with obese patients deriving

FIGURE 4 Forest Plot for the Analysis of MACE



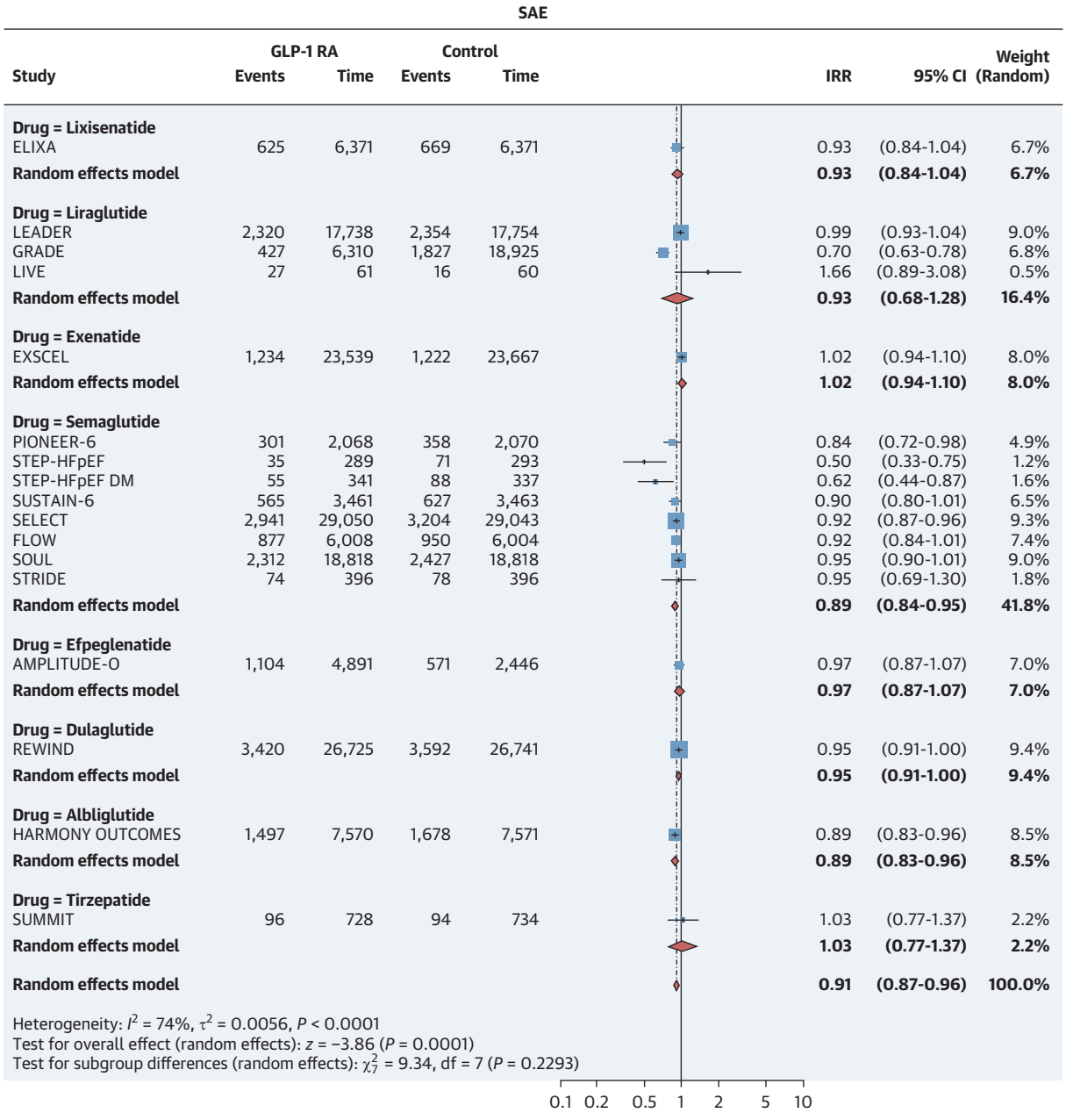
Analyses were conducted according to prespecified subgroups for each individual GLP-1 RA, with results presented as both cumulative and agent-specific IRRs along with their corresponding 95% CIs. Weights of each individual trial on the analysis, the random-effects model for each GLP-1 RA class, and a test for subgroup differences are also reported. Abbreviations as in Figures 1 and 2.

greater benefit from GLP-1 RA therapy than nonobese patients (Supplemental Figure 28). In the subgroup analysis by CKD status, results were generally consistent with the main analysis except for a significant subgroup interaction for GI disorders (P_{int} < 0.01), where GLP-1 RAs were not associated with an increased risk of GI events in CKD patients, unlike in those without CKD (Supplemental Figure 29). Finally, subgroup analysis by HF status showed results consistent with the main analysis (Supplemental Figure 30).

DISCUSSION

The main findings of this meta-analysis of RCTs evaluating GLP-1 RAs vs controls may be summarized as follows: 1) compared with controls, GLP-1 RAs were associated with reductions in all-cause mortality, CV mortality, and MACE; these findings were deemed conclusive by trial sequential analyses, with supporting evidence rated as high; 2) the benefits in all-cause and CV mortality and MACE with GLP-1 RAs, compared with controls, was consistent across

FIGURE 5 Forest Plot for the Analysis of SAEs



Analyses were conducted according to prespecified subgroups for each individual GLP-1 RA, with results presented as both cumulative and agent-specific IRRs along with their corresponding 95% CIs. Weights of each individual trial on the analysis, the random-effects model for each GLP-1 RA class, and a test for subgroup differences are also reported. Abbreviations as in Figures 1 and 2.

patient subgroups, including those with or without DM, obesity, CKD, or HF; 3) GLP-1 RAs were associated with an increase in GI and gallbladder disorders but with a reduction in SAEs compared with controls, that were consistent across patient subgroups, underscoring their overall favorable safety profile; 4) GLP-1 RAs were associated with reduced MI, HF hospitalizations, and infections compared with controls; 5) the observed reduction in HF hospitalizations associated with GLP-1 RAs may vary by obesity

TABLE 1 Absolute Event Rates and Risk Reduction

	Event Count GLP-1 RA	Patients GLP-1 RA	Absolute Risk, % GLP-1 RA	Event Count Control	Patients Control	Absolute Risk, % Control	RD (95% CI)	Trials Contributing to the Analysis, n
All-cause death	3,234	47,873	6.8	3,608	46,537	7.8	−0.008 (−0.011 to −0.005)	18
CV death	1,895	48,656	3.9	2,184	49,851	4.4	−0.006 (−0.008 to −0.003)	19
MACE	4,596	47,552	9.7	5,300	48,748	10.9	−0.015 (−0.018 to −0.011)	15
SAE	17,910	48,806	36.7	19,826	50,017	39.6	−0.035 (−0.051 to −0.018)	18
HF hospitalizations	1,067	34,603	3.1	1,257	37,151	3.4	−0.006 (−0.010 to −0.001)	14
Nonfatal MI	2,043	47,786	4.3	2,374	49,001	4.8	−0.006 (−0.009 to −0.003)	13
Nonfatal stroke	1,054	47,396	2.2	1,164	48,608	2.4	−0.002 (−0.004 to 0.000)	12
Neoplasms	2,310	46,784	4.9	2,191	45,469	4.8	0.001 (−0.002 to 0.004)	14
Infections	4,758	42,116	11.3	5,118	40,797	12.5	−0.011 (−0.017 to −0.005)	14
GI disorders	5,801	47,615	12.2	3,583	46,303	7.7	0.064 (0.043-0.085)	18
AKF	842	31,968	2.6	879	30,615	2.9	−0.002 (−0.005 to 0.000)	10
Pancreatitis	145	46,707	0.3	144	45,395	0.3	0 (−0.001 to 0.001)	13
Gallbladder disorders	683	27,015	2.5	543	27,017	2.0	0.005 (0.002-0.008)	8

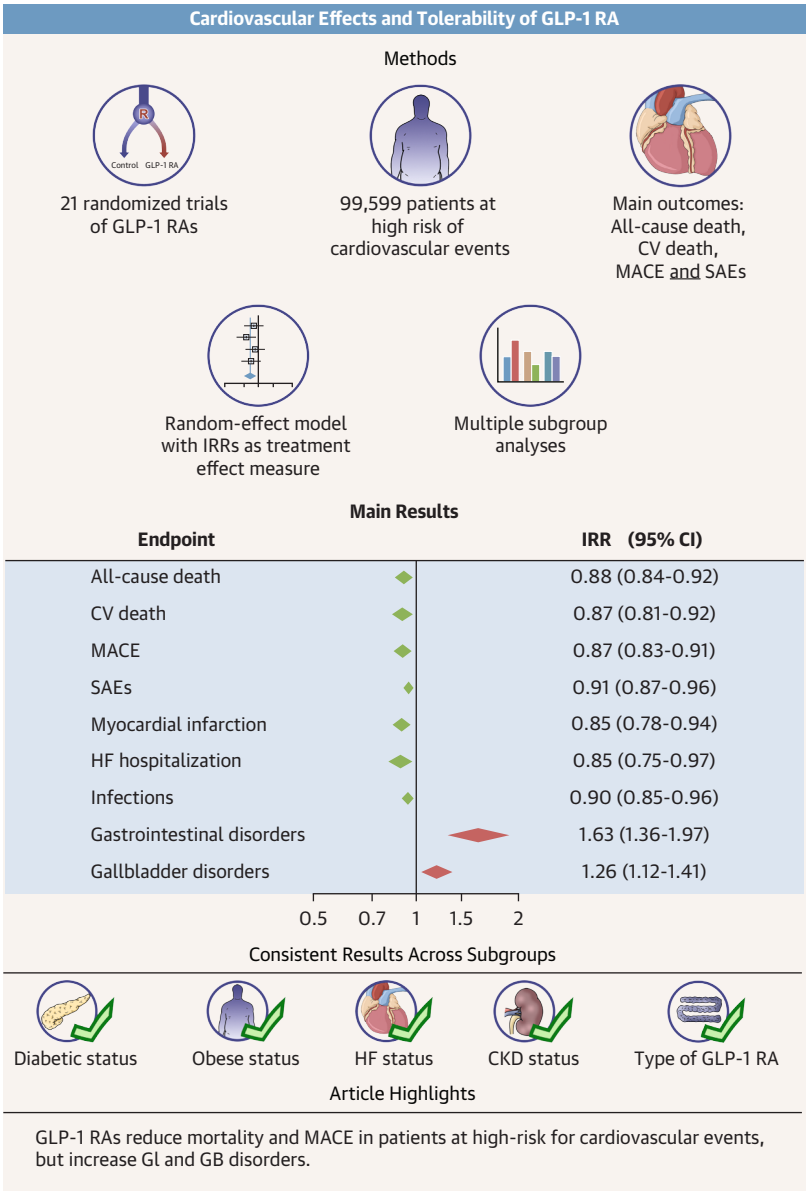
AKF = acute kidney failure; CV = cardiovascular; GI = gastrointestinal; HF = heart failure; MACE = major adverse cardiovascular events; MI = myocardial infarction; RD = risk difference; SAE = serious adverse events.

status, with a more marked effect seen in obese patients; and 6) variability in the efficacy and safety profiles of GLP-1 RAs may exist, suggesting the use of a specific GLP-1 RA should be tailored to individual risk profiles and clinical goals (**Central Illustration**). Overall, these findings highlight the significant prognostic benefits of GLP-1 RAs across diverse populations and support a tailored, agent-specific approach based on efficacy and safety profiles.

Originally developed as antihyperglycemic agents for diabetes management, GLP-1 RAs have progressively evolved into cornerstone therapies for cardiometabolic risk reduction. This transition was driven by landmark trials, including ELIXIA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 [Lixisenatide]),[23] LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results),[24] EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial),[30] HARMONY OUTCOMES (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus),[38] and REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes),[37] which demonstrated significant reductions in MACE among patients with DM at high CV risk. Subsequent trials broadened the evidence for the CV benefits of GLP-1 RAs to populations beyond those with DM. To this extent, SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity)[8] was the first large-scale trial to demonstrate that semaglutide reduced CV events in overweight or obese patients with high CV risk but without DM. Similarly, FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease)[35] confirmed both renal protective effects and CV benefits of GLP-1 RAs in patients with CKD, whereas SUMMIT (A Study of Tirzepatide [LY3298176] in Participants With Heart Failure With Preserved Ejection Fraction [HFpEF] and Obesity)[39] included patients with HF.

Our meta-analysis integrates the most up-to-date CV outcome trials and systematically compares all available GLP-1 RAs, including newer agents such as efpeglenatide[36] and the dual GIP/GLP-1 RA tirzepatide.[39] The consistent reduction in both all-cause and CV mortality as well as of MACE among key subgroups—including patients with or without DM, obesity, CKD, or HF—support the growing recognition that GLP-1 RAs exert pleiotropic effects beyond glycemic modulation. Notably, results were consistent after excluding from the main analysis tirzepatide, the only agent with a dual action on GIP and GLP-1 receptors. Our analysis is the first to emphasize that the underlying evidence meets a high level of certainty and is considered conclusive, suggesting limited value in conducting additional trials. The fact that these benefits extend beyond glycemic control is further supported by the significant subgroup interaction observed for MI, suggesting that nondiabetic and

CENTRAL ILLUSTRATION **Methods, Subgroup Analyses, and Main Results**



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Gastrointestinal disorders included nausea, vomiting, diarrhea, increased lipase level, abdominal pain, decreased appetite, or abdominal discomfort; gallbladder disorders included cholelithiasis, acute cholecystitis, or hepatobiliary disorders. CKD = chronic kidney disease; CV = cardiovascular; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; IRR = incidence rate ratios; MACE = major adverse cardiovascular events; SAEs = serious adverse events.

obese patients may derive greater benefit from GLP-1 RA therapy compared with their diabetic or non-obese counterparts. The cardioprotective mechanisms of GLP-1 RAs are likely multifactorial and incompletely understood, potentially involving anti-inflammatory actions, improved endothelial function, reductions in blood pressure and body weight, and modulation of atherothrombotic pathways.[40] Although demonstrating consistent prognostic and ischemic benefits of GLP-1 RAs across patient

subgroups, our analysis also highlighted that the magnitude of these effects may differ according to the specific agent used. These findings are consistent with recent network meta-analyses that also highlighted variability in CV and renal outcomes among different GLP-1 RAs.[16,41,42] However, these findings should be considered hypothesis-generating and warrant confirmation through dedicated head-to-head RCTs comparing the safety and efficacy profiles of different GLP-1 RAs.

In the subgroup of patients with HF, our findings are consistent with those from the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) and STEP-HFpEF DM (Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes) trials,[10,33] as well as a recent meta-analysis,[43] which demonstrated reductions in CV death or HF worsening among GLP-1 RA–treated patients with HFpEF. Notably, the majority of HF patients in our analysis had HFpEF, which limits the generalizability of our findings to those with HF with reduced EF, and we observed a more pronounced reduction in HF hospitalizations among obese compared with nonobese individuals and that HF patients experienced a greater reduction in infection risk with GLP-1 RAs compared with those without HF. These findings warrant further investigations and call for dedicated RCTs across the full spectrum of HF phenotypes, including preserved, mildly reduced, and reduced EF.

From a safety perspective, GLP-1 RAs were generally well tolerated, though associated with a moderate increase in GI and gallbladder-related events. Notably, they were linked to a reduction in SAEs and showed no increased risk of severe complications such as pancreatitis or neoplasms. These findings provide important reassurance regarding the safety and overall risk-benefit profile of this drug class in broad populations. However, a recent large observational study has suggested that GLP-1 RAs may be linked to adverse effects not captured in RCTs, such as sleep disturbances and arthritis.[44] Further RCTs are needed to clarify these potential associations. Furthermore, safety outcomes appeared to vary by agent, with a significant interaction observed between the specific GLP-1 RA used and the occurrence of GI disorders, suggesting that careful agent selection may further enhance tolerability.

To the best of our knowledge, this is the first meta-analysis to synthesize evidence from 21 RCTs—including the most recent CV and renal outcome studies—encompassing nearly 100,000 participants. It provides the most comprehensive pooled evaluation to date of both the efficacy and safety of different GLP-1 RAs in populations with and without diabetes. Notably, the use of IRRs to account for variable follow-up durations, the incorporation of trial sequential analysis to assess the certainty of results, the evaluation of evidence quality, and the calculation of risk difference, NNT, and NNH represent distinctive methodological strengths that enhance the clinical applicability of our findings. Finally, the unprecedented breadth of secondary analyses supporting the main results further reinforces the robustness of this study. The implications of these findings are relevant for daily practice. Current international guidelines from the American Diabetes Association[45] and European Society of Cardiology[6] already recommend GLP-1 RAs for patients with type 2 diabetes and established atherosclerotic CV disease. Our findings reinforce current recommendations and might support extending the use of GLP-1 RAs to patients with obesity or multiple CV risk factors, irrespective of diabetic status. Furthermore, this analysis helps identifying the most effective and safest agents for specific subgroups, potentially optimizing individualized GLP-1 RA therapy.

STUDY LIMITATIONS. First, the absence of patient-level data precluded a more detailed investigation of covariates potentially influencing treatment effects and introduce some heterogeneity in patient population and endpoint definitions across trials. Nevertheless, the robustness of our findings was supported by multiple sensitivity and subgroup analyses, which consistently yielded results aligned with the main analysis. Second, the included trials varied in terms of GLP-1 RA type, dosing schedules, study populations, and outcome definitions, introducing potential clinical heterogeneity. Although this variability may have introduced an unquantifiable risk of bias, we conducted multiple secondary analyses—most of them prespecified—with the aim of mitigating this heterogeneity and improving the clinical applicability of our findings. Notably, the vast majority of these analyses yielded results consistent with those of the main analysis. Third, significant statistical heterogeneity and risk of publication bias were observed for certain endpoints. To partially address these limitations we used a random-effects model and adjusted results with the trim and fill method as recommended. Fourth, patient-years were calculated based on available mean follow-up

durations, which may not account for events occurring in the early period, but only between-trial follow-up. Although this limitation could be properly addressed only by analyzing individual patient data, sensitivity analysis using other measures of effect and meta-regressions for the follow-up duration mitigate these concerns. Fifth, the lack of direct head-to-head comparisons among GLP-1 RAs restricts the strength of inferences regarding the superiority of specific agents. It should be acknowledged that, for some agents, multiple studies contributed to the analysis, thereby enhancing the robustness of the efficacy and safety estimates, whereas for others, data were limited to a single study. Furthermore, the generalizability of our results to certain high-risk populations, such as individuals with advanced CKD or those with HF with reduced EF, remains uncertain due to underrepresentation of these subgroups in the included trials. Finally, the benefits of GLP-1 RAs we observed in our analysis are limited to the treatment duration reported in each trial, typically around 1 year, with the optimal treatment length yet to be defined. Whether these effects persist after discontinuation, and the cost-effectiveness of prolonged use, remain areas for future investigation.

CONCLUSIONS

GLP-1 RAs offer substantial cardiovascular protection, including reductions in mortality and major adverse events across a broad spectrum of high-risk populations. Although their use is associated with an increased incidence of GI and gallbladder-related disorders, these findings underscore the therapeutic value of GLP-1 RAs beyond glycemic control. Given that some heterogeneity in efficacy and tolerability was observed across different agents, selection of a specific GLP-1 RA should be tailored to individual risk profiles and clinical goals.

DATA AVAILABILITY STATEMENT. All data are available upon reasonable request to the corresponding author.

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KEY WORDS cardiovascular effects, efficacy, GLP-1 receptor agonists, mortality, safety

APPENDIX For a list of the included studies and supplemental figures and tables, please see the online version of this paper.