

Systematic review/Meta-analysis

GLP-1 receptor agonists in cardiometabolic disease: a meta-analysis of 102,486 patients

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may provide cardiovascular benefits beyond glycaemic control. This meta-analysis evaluated their effects on cardiovascular and related clinical outcomes. PubMed, Cochrane Library, and Google Scholar were searched up to March 20, 2026, for randomized controlled trials comparing GLP-1 RAs with placebo in adults with or without type 2 diabetes. Outcomes included mortality, major adverse cardiovascular events (MACE), myocardial infarction, stroke, heart failure hospitalization (HHF), acute kidney injury (AKI), pancreatitis, and infections. Random-effects meta-analyses were conducted using RevMan 5.4.1. Twenty-eight randomized controlled trials (RCTs) involving 52,527 GLP-1 RA recipients and 49,959 placebo recipients were included. GLP-1 RAs were associated with significant reductions in all-cause mortality (RR = 0.86), cardiovascular mortality (RR = 0.86), MACE (RR = 0.87), myocardial infarction (RR = 0.86), stroke (RR = 0.88), and infections (RR = 0.90). No significant effects were observed on AKI, pancreatitis, or HHF. GLP-1 RAs were associated with lower risks of cardiovascular outcomes and mortality.

Key words: GLP-1 receptor agonists, cardiovascular, diabetes, obesity, meta-analysis.

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, accounting for an estimated 18.6 million deaths annually, with age-standardized mortality rates remaining persistently elevated despite advances in preventive and therapeutic strategies [1, 2]. Metabolic disorders, particularly type 2 diabetes mellitus (T2DM) and obesity, contribute substantially to this burden, affecting more than 460 million individuals globally and highlighting the close interplay between metabolic dysfunction and cardiovascular pathology [3–5].

Following the U.S. Food and Drug Administration (FDA) mandate in 2008 requiring cardiovascular safety evaluation of new antidiabetic therapies, large cardiovascular outcome trials (CVOTs) have been conducted for all novel glucose-lowering agents [6, 7]. Among these, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated significant reductions in major adverse cardiovascular events (MACE), with particularly pronounced effects in reducing ischemic events related to atherosclerotic cardiovascular disease (ASCVD) [6–9]. GLP-1 receptor agonists, including liraglutide, semaglutide, dulaglutide, and the dual GLP-1/GIP receptor agonist tirzepatide, were initially developed for the treatment of T2DM and act by mimicking the endogenous incretin hormone GLP-1, thereby enhancing glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying [10, 11].

Given their dual role in improving glycaemic control and promoting weight reduction, GLP-1 RAs are currently recommended as second-line therapy following metformin, and as the preferred first injectable therapy in patients inadequately controlled with oral agents [12]. Several meta-analyses have previously synthesized the cardiovascular benefits of GLP-1 RAs; however, the publication of recent randomized controlled trials (RCTs) has expanded the available evidence base [13–17].

Therefore, we aimed to conduct an updated systematic review and meta-analysis to evaluate the cardiovascular outcomes associated with GLP-1 RA therapy in individuals both with and without T2DM, thereby informing clinical decision-making and guideline development.

Methods

This meta-analysis was conducted in accordance with the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. The protocol for this meta-analysis has been registered in PROSPERO (CRD420261383030). As this review did not involve

any direct patient data collection or investigation by the authors, ethical approval was not needed.

Literature search

We conducted a comprehensive search of the Cochrane Library, PubMed, and Google Scholar databases from their inception to March 20, 2026. The search strategy used a combination of targeted keywords and Medical Subject Headings (MeSH) terms, including “GLP-1 agonist”, “semaglutide”, “exenatide”, “albiglutide”, “dulaglutide”, “liraglutide”, “tirzepatide”, “type 2 diabetes”, “obesity” and “RCT”. Boolean operators (AND, OR) were applied to optimize the search and ensure the inclusion of all relevant studies. Further details regarding the search terms and strategy are provided in Supplementary Table S1.

Eligibility criteria

The inclusion criteria for this review were as follows: (1) study design: randomized controlled trials (RCTs); (2) population: patients aged 18 years and above with or without type 2 diabetes; (3) intervention: GLP-1 RA; (4) comparator: placebo; (5) outcome: reporting at least one relevant clinical outcome of interest.

No restriction was imposed on the type of GLP-1 RA. Studies were excluded if they were not RCTs, including case reports, case series, observational studies, or animal-based studies.

Study selection, data extraction and outcomes

Rayyan software was used to screen and remove duplicates from the studies identified in the online search. Following removal of duplicates, two authors (M.S. and M.F.) independently carried out title and abstract screening. Afterwards, a comprehensive full-text review was performed by the same authors. In instances of disagreement, a third author (G.V.) facilitated resolution.

Study characteristics, such as authors and study locations, inclusion criteria, total population, drug and dosage, sample size, age, sex, BMI, and comorbidities (diabetes, hypertension, smoking etc.) were extracted. The primary outcomes included MACE and all-cause mortality. The secondary outcomes included cardiovascular mortality, hospitalization due to HF (HHF), MI, stroke, acute kidney injury (AKI), risk of infections and pancreatitis.

Risk of bias and certainty of evidence assessment

For randomized controlled trials (RCTs), the Risk of Bias 2 (RoB 2) tool was used. Two reviewers (M.A. and R.A.) independently assessed six do-

mains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of outcomes, (5) selection of reported results, and (6) overall risk of bias [19]. Discrepancies were resolved through discussion or consultation with a third reviewer (G.V.).

Statistical analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4.1. Pooled effect estimates were calculated using the Mantel–Haenszel method, and a random-effects model based on the DerSimonian–Laird approach was applied to account for between-study variability. A p -value of < 0.05 was considered statistically significant [20].

Heterogeneity was assessed using the χ^2 test and quantified using the I^2 statistic in accordance with Cochrane recommendations [20]. I^2 values of 0–40% were considered low, 30–60% moderate, and 50–90% substantial heterogeneity. A χ^2 p -value of < 0.1 indicated statistically significant heterogeneity. In cases of significant heterogeneity, a leave-one-out sensitivity analysis was conducted to evaluate the robustness of the findings. Publication bias was assessed using a funnel plot for outcomes reported by ≥ 10 studies.

Results

Search results and study selection

A total of 1,398 records were identified through database searching, including PubMed, Google Scholar and the Cochrane Library. After removal

of duplicates ($n = 1,561$), 689 records remained for screening. During title and abstract screening, 447 records were excluded, leaving 242 reports for which full texts were sought. Of these, 14 reports could not be retrieved. Consequently, 228 full-text articles were assessed for eligibility. Following full-text review, 200 reports were excluded for the following reasons: wrong outcomes ($n = 35$), inappropriate study design ($n = 136$), and wrong publication type ($n = 29$). Ultimately, 28 studies met the inclusion criteria and were included in the qualitative and quantitative synthesis (meta-analysis) [10, 11, 21–46] (Figure 1).

Baseline characteristics of the included studies

A total of 28 RCTs involving 52,527 participants in the GLP-1 RA group and 49,959 participants in the placebo group were included. The mean age of participants ranged from 53 to 70 years, with females representing approximately 30% to 83% of the study populations. The majority of trials enrolled patients with type 2 diabetes mellitus (T2DM), established cardiovascular disease, obesity, heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). Baseline body mass index (BMI) ranged from 24.8 to 38.3 kg/m². The concomitant antiplatelet and anti-T2DM therapy mainly consisted of aspirin, clopidogrel, ADP receptor inhibitors, P2Y12 inhibitors, metformin, insulin sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, ACE inhibitors and α -glucosidase inhibitors. The duration of follow-up varied substantially across studies, ranging

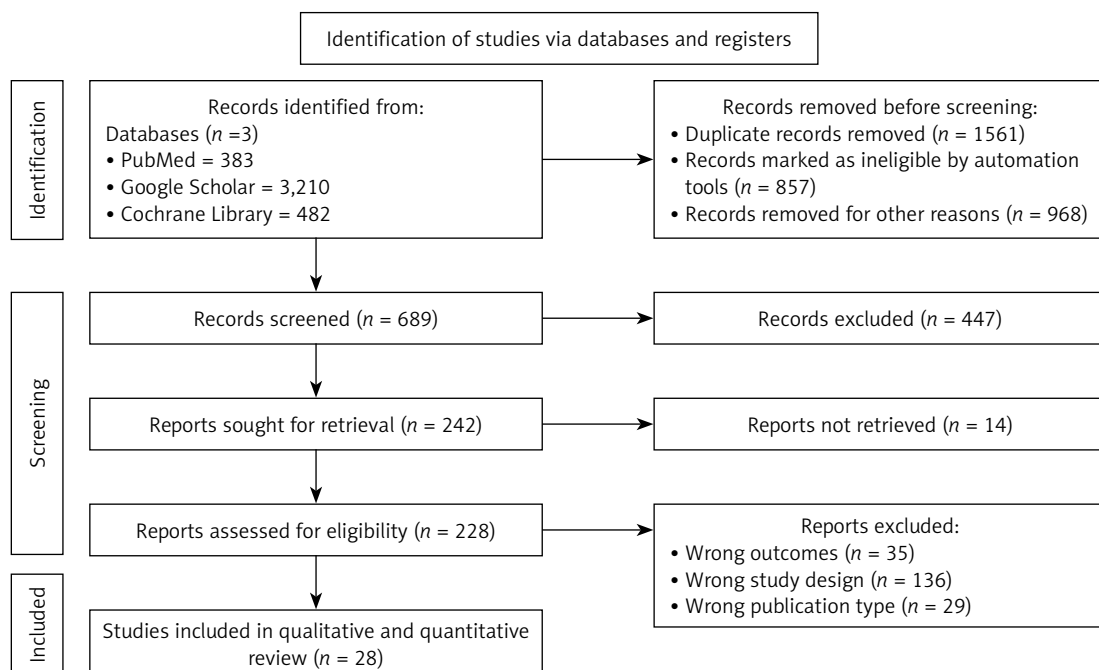


Figure 1. PRISMA flow diagram depicting the study selection process

from short-term trials of 52 weeks extending up to 5.4 years in long-term trials (Table I) [10, 11, 21–46].

Outcomes

All-cause mortality

A total of 27 randomized controlled trials including 50,380 participants in the GLP-1 RA group and 47,805 in the control group were analysed for all-cause mortality. GLP-1 receptor agonists were associated with a statistically significant reduction in all-cause mortality (RR = 0.86; 95% CI: 0.80–0.92; I^2 = 0%; p < 0.0001).

In subgroup analyses, liraglutide demonstrated a modest but statistically significant reduction in all-cause mortality across four trials (RR = 0.86; 95% CI: 0.76–0.98; I^2 = 0%; p = 0.03). Similarly, semaglutide, evaluated across ten trials, was associated with a significant reduction in mortality (RR = 0.86; 95% CI: 0.80–0.92; I^2 = 0%; p < 0.0001).

In contrast, albiglutide, assessed across five trials, showed no significant effect on all-cause mortality (RR = 0.94; 95% CI: 0.78–1.14; I^2 = 0%; p = 0.52). Likewise, exenatide, evaluated in two trials, did not demonstrate a significant effect (RR = 1.06; 95% CI: 0.63–1.77; I^2 = 68%; p = 0.83) (Figure 2). All of the included studies for this particular outcome were reported to have a low risk of publication bias (Supplementary Figure S2).

Cardiovascular mortality

A total of 20 randomized controlled trials including 43,704 participants in the GLP-1 RA group and 41,916 in the control group were analysed. GIP/GLP-1 receptor agonists were associated with a statistically significant reduction in cardiovascular mortality (RR = 0.86; 95% CI: 0.81–0.92; I^2 = 0%; p < 0.00001).

In subgroup analyses, liraglutide, evaluated across five trials, demonstrated a significant reduction in cardiovascular mortality (RR = 0.75; 95% CI: 0.63–0.89; I^2 = 0%; p = 0.001). Similarly, semaglutide, assessed in seven trials, was also associated with a significant reduction in cardiovascular mortality (RR = 0.83; 95% CI: 0.73–0.95; I^2 = 27%; p = 0.008).

In contrast, exenatide, evaluated in two trials, did not show a statistically significant association with cardiovascular mortality (RR = 0.89; 95% CI: 0.78–1.02; I^2 = 0%; p = 0.10) (Figure 3). All of the included studies for this particular outcome were reported to have a low risk of publication bias (Supplementary Figure S3).

Major adverse cardiovascular events

A total of 18 randomized controlled trials including 48,280 participants in the GLP-1 RA group

and 46,168 in the control group were analysed for MACE. GLP-1 receptor agonists were associated with a statistically significant reduction in MACE (RR = 0.87; 95% CI: 0.83–0.90; I^2 = 11%; p < 0.00001).

In subgroup analyses, semaglutide, evaluated across eight trials, demonstrated a significant reduction in MACE (RR = 0.83; 95% CI: 0.78–0.88; I^2 = 0%; p < 0.00001). Similarly, liraglutide, assessed in three trials, showed a significant association with lower MACE risk (RR = 0.87; 95% CI: 0.79–0.97; I^2 = 0%; p = 0.008).

In contrast, exenatide, evaluated in two trials, did not show a statistically significant association with MACE (RR = 0.93; 95% CI: 0.85–1.01; I^2 = 0%; p = 0.10). Likewise, albiglutide, assessed in two trials, showed a statistically significant reduction in MACE (RR = 0.74; 95% CI: 0.55–0.99; I^2 = 28%; p = 0.04) (Figure 4). No evidence of substantial publication bias was identified for the included studies reporting this outcome (Supplementary Figure S4).

Heart failure hospitalizations

A total of 15 randomized controlled trials including 34,519 participants in the GLP-1 RA group and 33,762 in the control group were analysed for HHF. GLP-1 receptor agonists were not associated with a statistically significant reduction in HHF (RR = 0.89; 95% CI: 0.78–1.00; I^2 = 38%; p = 0.05).

In subgroup analyses, semaglutide, evaluated across six trials, did not demonstrate a statistically significant association with HHF (RR = 0.77; 95% CI: 0.53–1.12; I^2 = 54%; p = 0.17). Similarly, liraglutide, assessed across four trials, showed no significant association with HHF (RR = 0.97; 95% CI: 0.80–1.18; I^2 = 12%; p = 0.76). Exenatide, evaluated in two trials, also did not demonstrate a significant association with HHF (RR = 0.80; 95% CI: 0.50–1.26; I^2 = 67%; p = 0.33) (Figure 5). All included studies reporting this outcome were reported to have a moderate risk of publication bias (Supplementary Figure S5).

Risk of stroke

A total of 13 randomized controlled trials including 39,956 participants in the GLP-1 RA group and 37,823 in the control group were analysed for risk of stroke. GIP/GLP-1 receptor agonists were associated with a statistically significant reduction in the risk of stroke (RR = 0.88; 95% CI: 0.81–0.97; I^2 = 0%; p = 0.008).

In subgroup analyses, liraglutide, evaluated across three trials, did not show a statistically significant association with stroke (RR = 0.90; 95% CI: 0.73–1.11; I^2 = 0%; p = 0.33). Similarly, semaglutide, assessed across six trials, did not show a significant association with stroke (RR = 0.91; 95% CI: 0.78–1.06; I^2 = 15%; p = 0.24) (Fig-

Table 1. Baseline characteristics of the included studies

Trial name	Year	Drug	Control	Patients, <i>n</i>	Population	Age [years]*			CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo	Female, %							
PIONEER 8	2019	Oral semaglutide 3 mg	Placebo	184	T2DM	61 ±10	60 ±10	52.9	57.1	NR	Yes	NR	NR	31.0 ±6.8	52 weeks
PIONEER 8	2019	Oral semaglutide 7 mg	Placebo	182	T2DM					NR	Yes	NR	NR	31.1 ±7.0	52 weeks
PIONEER 8	2019	Oral semaglutide 14 mg	Placebo	181	T2DM					NR	Yes	NR	NR	30.8 ±6.3	52 weeks
STEP 2	2021	Semaglutide 2.4 mg weekly	Placebo	404	Obesity and T2DM	55 ±11	55 ±11	52.9	47.1	NR	Yes	NR	NR	35.9 ±6.4	75 weeks
STEP 2	2021	Semaglutide 1.0 mg weekly	Placebo	403	Obesity and T2DM					NR	Yes	NR	NR	35.3 ±5.9	75 weeks
HARMONY 2	2016	Albiglutide 30 mg weekly	Placebo	101	T2DM	53.3 ±11.3	53.1 ±11.7	42.6	46	NR	Yes	NR	NR	33.7 ±5.1	52 weeks
HARMONY 2	2016	Albiglutide 50 mg weekly	Placebo	99	T2DM					NR	Yes	NR	NR	33.9 ±5.5	52 weeks
SCALE Diabetes	2015	Liraglutide 3.0 mg	Placebo	423	T2DM with overweight/obesity	55.0 ±10.7	54.7 ±9.8	48.2	54.2	Not reported	100%	Metformin 57.5%, metformin + sulfonylureas 20.9%, metformin + glitazone 5.3%, diet only 11.2%	NR	37.1 ±6.5	68 weeks
SCALE Diabetes	2015	Liraglutide 1.8 mg	Placebo	211	T2DM with overweight/obesity					Not reported	100%	Metformin 54.4%, metformin + sulfonylureas 21.6%, metformin + glitazone 6.4%, diet only 14.2%	NR	37.0 ±6.9	68 weeks

Table 1. Cont.

Trial name	Year	Drug	Control	Patients, <i>n</i>	Population	Age [years]*		Female, %		CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo	GLP-1 RA	Placebo							
HARMONY 1	2014	Albiglutide	Placebo	301	T2DM	55.2 ±9.98	54.9 ±9.40	38.7	41.7	Not reported	100%	Yes	Pioglitazone + metformin 81.3%, pioglitazone alone 18.7%	NR	33.6 ±5.9	52 weeks
HARMONY 5	2014	Albiglutide	Placebo	271	Type 2 diabetes	54.5 ±9.5	55.7 ±9.6	50.2	39.1	NR	Yes	Yes	NR	NR	32.2 ±5.7	52 weeks
ELIXA Trial	2015	Lixisenatide	Placebo	6068	Adults with DM2 who had had MI or who had been hospitalized for UA within the previous 180 days	59.9 ±9.7	60.6 ±9.6	30.4	30.9	No	Yes	No	Antiplatelet therapy 97.5%, insulin 39.1%, metformin 66%, sulfonylureas 33%, thiazolidinediones 1.5%, other antidiabetic agents 5%	NR	30.1 ±5.6 (lixisenatide) 30.2 ±5.8 (placebo)	25 months
LEADER Trial	2016	Liraglutide	Placebo	9340	Patients with T2DM and high CVD risk	64.2 ±7.2	64.4 ±7.2	35.5	36	No	Yes	No	Aspirin 63%, clopidogrel/ticlopidine/prasugrel/ticagrelor 15.5%, metformin 76%, insulin 44%, sulfonylureas 50%, thiazolidinediones 6%,	NR	32.5 ±6.3 (liraglutide) 32.5 ±6.3 (placebo)	3.8 years

Table I. Cont.

Trial name	Year	Drug	Control	Patients, <i>n</i>	Population	Age [years]*		Female, %		CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo RA	GLP-1 RA	Placebo RA							
FIGHT Study	2016	Liraglutide	Placebo	300	Patients (with or without diabetes) with established HF and reduced LVEF who were recently hospitalized	62 (52–68)	61 (51–67)	62	53	No	No	No	Antiplatelet therapy 72%, antidiabetic agents NA	Yes	31 (26–36) (liraglutide) 33 (25–38) (placebo)	180 days
Zhang (2017)	2017	Liraglutide	Placebo	52	Patients with HF (LVEF < 50%)	58.7 ±11.4	59.1 ±11.8	NR	NR	No	No	No	NA	Yes	24.8 ±3.8 (placebo), 25.3 ±3.4 (liraglutide)	3 months
Chen (2016)	2016	Liraglutide	Placebo	83	NSTEMI	59.0 ±12.1	58 ±11.7	NR	NR	No	No	No	Aspirin 100%, clopidogrel 100%, metformin 10%, sulfonylureas 3%, insulin 3%, Acarbose 7%	NR	NA	6 months
LIVE-Jorsal (2016)	2016	Liraglutide	Placebo	241	Patients aged 30–85 years with CHE, had an LVEF ≤ 45% and were in NYHA functional class I–III.	65 ±9.2	65 ±10.7	NR	NR	No	No	No	Antiplatelet NA, metformin 70%, sulfonylureas 13%, insulin 15%	Yes	28.0 (3.8) (liraglutide), 29.8 (4.6) (placebo)	24 weeks

Table I. Cont.

Trial name	Year	Drug	Control	Patients, <i>n</i>	Population	Age [years]*			CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo	Female, %							
EXSCEL Trial	2017	Extended-release exenatide	Placebo	14752	Patients with T2DM, with or without previous CVD disease	62 (56–68)	62 (56–68)	38	No	Yes	No	Aspirin 63%, clopidogrel/ticlopidine 17%, insulin 46%, metformin 76%, sulfonylureas 4%, DPP-4 inhibitors 14%, SGLT2 inhibitors 1%, thiazolidinediones 4%, other antidiabetic agents 0.7%	NR	31.8 (28.2, 36.2) (exenatide)	3.2 years (IQR 2.2–4.4)
Kyhl 2015	2015	Exenatide	Placebo	334	Patients with a suspected first STEMI and symptom duration ≤ 12 hours were enrolled.	63 ± 12	62 ± 11	NR	No	No	No	Aspirin or clopidogrel 13%, antidiabetic agents NA	NR	27 ± 4 (both)	5.2 years (IQR: 5.0–5.5)
PIONER-6 Trial	2019	Semaglutide	Placebo	3183	At least 50 years old with T2DM and established CVD or CKD, or at least 60 years old with CV risk factors only	66 ± 7	66 ± 7	31.9	No	Yes	No	Antiplatelet/antithrombotic therapy 79%, insulin 60%, metformin 77%, sulfonylureas 32%, DPP-4 inhibitors 0.1%, SGLT2 inhibitors 1%, thiazolidinediones 4%, other antidiabetic agents 1.6%	NR	32.3 ± 6.6 (semaglutide) 32.3 ± 6.4 (placebo)	15.9 months (IQR 0.4 to 20.0)

Table I. Cont.

Trial name	Year	Drug	Control	Patients, <i>n</i>	Population	Age [years]*		Female, %		CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo RA	GLP-1 RA	Placebo RA							
STEP-HFpEF Trial	2023	Semaglutide	Placebo	529	Patients with HFpEF and a BMI of 30 or higher	70 (62–75)	69 (62–75)	97	94.7	No	No	Yes	Antiplatelet therapy 28%, metformin 1.8%	NR	37.2 (33.9–41.1) (semaglutide), 36.9 (33.3–41.6) (placebo)	5 weeks
STEP-HFpEF DM Trial	2024	Semaglutide	Placebo	616	Patients with HFpEF, a BMI of 30 or more, and type 2 diabetes	69.0 (62.0–74.0)	70.0 (63.0–75.0)	41.3	47.4	No	Yes	Yes	SLGT2 inhibitors 32%	NR	36.9 (33.6–41.5) (semaglutide), 36.9 (33.5–41.1) (placebo)	5 weeks
SUSTAIN-6	2016	Semaglutide	Placebo	3,297	Patients with T2DM who were on a standard-care regimen with clinical or subclinical evidence of CVD	64.6 ± 7.2	64.7 ± 7.6	38.6	40.1	No	Yes	No	Insulin 58%, metformin 73%, sulfonylureas 42.3%, DPP-4 inhibitors 0.1%, SLGT2 inhibitors 0.1%, thiazolidinediones 2%, aspirin 5%, ADP receptor inhibitors 6%	NR	32.9 (6.18) (semaglutide 1.0 mg) 32.7 (5.97) (placebo 1.0 mg)	5 weeks

Table 1. Cont.

Trial name	Year	Drug	Control	Patients, n	Population	Age [years]*			CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo	Female, %							
SELECT	2023	Semaglutide	Placebo	17,604	Patients 45 years of age or older with CVD and a BMI of 27 or greater but no history of diabetes	61.6 ±8.9	61.6 ±8.8	83.9	No	No	Yes	Aspirin 78%, P2Y12 inhibitors 33%, antidiabetic agents NA	NR	33.3 ±5.0 (semaglutide), 33.4 ±5.0 (placebo)	39.8 ±9.4 months
AMPLITUDE-O Trial	2021	Efpeglenatide	Placebo	4076	Adults with T2DM and either a history of CVD or current CKD plus at least one other CV risk factor	64.6 ±8.2	64.4 ±8.3	34	No	Yes	No	Insulin 64%, metformin 73%, sulfonylureas 25%, DPP-4 inhibitors 1.5%, SGLT2 inhibitors 19%, aspirin 68%	NR	NA	1.81 years (IQR = 1.69 to 1.98)
REWIND	2019	Dulaglutide	Placebo	9901	Men and women aged at least 50 years with T2DM who had either a previous CV event or CV risk factors	66.2 ±6.5	66.2 ±6.5	46.6	No	Yes	No	Antiplatelet 54%, insulin 24%, metformin 81%, sulfonylureas 46%, DPP-4 inhibitors 6%, thiazolidinediones 1.6%	NR	32.3 (5.7) (dulaglutide) 32.3 (5.8) (placebo)	5.4 years (IQR 5.1–5.9)

Table I. Cont.

Trial name	Year	Drug	Control	Patients, <i>n</i>	Population	Age [years]*		Female, %		CKD	T2DM	Obesity	Concomitant antiplatelet and anti-diabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo	GLP-1 RA	Placebo							
HARMONY OUTCOMES	2018	Albiglutide	Placebo	9463	Patients aged 40 years and older with T2DM and CVD	64.1 ±8.7	64.2 ±8.7	30	31	No	Yes	No	P2Y12 26%, insulin 59%, metformin 73.5%, sulfonylureas 28.5%, DPP-4 inhibitors 15.5%, thiazolidinediones 2%	NR	32.3 ±5.9 (albiglutide) 32.3 ±5.9 (placebo)	1.5 years
FLOW	2024	Semaglutide	Placebo	3533	Adults with T2DM and high risk CKD	66.6 ±9.0	66.7 ±9.0	29.4	31.1	Yes	Yes	No	SGLT2 inhibitors 15.6%	NR	31.9 ±6.1 (semaglutide) 32 ±6.5 (placebo)	3.4 years
SUMMIT	2025	Tirzepatide	Placebo	731	Patients with heart failure, BMI > 30	65.5 ±10.5	65 ±10.9	70.3	69.8	No	No	Yes	SGLT2 inhibitors (17.2%)	NR	38.3 ±6.4 (tirzepatide) 38.2 ±7 (placebo)	104 weeks
SOUL	2025	Semaglutide	Placebo	9650	Patients who were 50 years of age or older, had T2DM with a glycaated haemoglobin level of 6.5 to 10.0%, and had known ASCVD, CKD or both	66.1 ±7.6	66.1 ±7.5	28.5	29.3	No	Yes	No	Antiplatelet medication 77%, metformin 76%; insulins 50.5%; sulfonylureas 29% SGLT2 inhibitors 26.9%, thiazolidinediones 4.3%, a-glucosidase inhibitors 2%, other glucose-lowering medication 1.3%.	NR	31.0 (semaglutide) 31.2 (placebo)	49.5 months

Table I. Cont.

Trial name	Year	Drug	Control	Patients, n	Population	Age [years]*			CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo	Female, %							
STRIDE	2025	Semaglutide	Placebo	792	Adults with T2DM and symptomatic PAD with intermittent claudication (Fontaine IIa), ABI ≤ 0.90 or toe-brachial index ≤ 0.70 , able to walk > 200 m pain-free and with maximum walking distance < 600 m on a constant-load treadmill.	68.0 (60.0–73.0)	68.0 (62.0–73.0)	27	No	Yes	No	Antiplatelet (semaglutide vs placebo): · Acetylsalicylic acid: 52% vs. 52% · P2Y12 inhibitors: 21% vs. 22% · Cilostazol: 11% vs. 11% · Glucose-lowering therapy (semaglutide vs placebo): · Metformin: 80% vs. 81% · SGLT2 inhibitors: 37% vs. 33% · Sulfonylureas: 22% vs. 22% · DPP-4 inhibitors: 20% vs. 16% · Thiazolidinedione: 7% vs. 3% · Insulin: 30% vs. 34%	NR	28.7 (semaglutide) 28.5 (placebo)	13.2 months

Table I. Cont.

Trial name	Year	Drug	Control	Patients, n	Population	Age [years]*		Female, %		CKD	T2DM	Obesity	Concomitant antiplatelet and antidiabetic therapy	Reduced LVEF	Baseline BMI [kg/m ²]	Follow-up
						GLP-1 RA	Placebo RA	GLP-1 RA	Placebo RA							
RUFF	2022	Exenatide	Placebo	4,156 (2,075 vs. 2,081)	T2DM with/ at risk for ASCVD: age 63 (IQR 58–68 vs. 57–68); HbA1c 8.0% (7.2–9.3 vs. 7.2–9.2); T2DM duration 10.4 (5.9–15.6) vs. 10.2 (5.77–15.2) years; 76.0% high CV risk	63 (58–68)	63 (57–68)	37.5	35.9	eGFR 79.0 (68.0–93.0) vs. 80.0 (68.0–93.0) ml/min/1.73 m ²	100%	Yes	Metformin 84.8% vs. 84.9%, sulfonylureas 44.1% vs. 44.9%, insulin 35.8% vs. 35.2%; aspirin 59.1% vs. 59.4%, ACEi/ARB 76.9% vs. 74.9%, statin 66.5% vs. 67.9%, beta-blocker 52.6% vs. 53.5%	NR	32.4 (28.8–36.6) vs. 31.9 (28.6–36.1)	Median 16 months (IQR 10–22)

T2DM – type 2 diabetes mellitus, CKD – chronic kidney disease, CVD – cardiovascular disease, CV – cardiovascular, ASCVD – atherosclerotic cardiovascular disease. Heart failure-related abbreviations include HF (heart failure), HFpEF (heart failure with preserved ejection fraction), CHF (congestive heart failure), LVEF (left ventricular ejection fraction), and NYHA (New York Heart Association). Other cardiovascular abbreviations include PAD (peripheral artery disease), MI (myocardial infarction), UA (unstable angina), NSTEMI (non-ST-elevation myocardial infarction), STEMI (ST-elevation myocardial infarction), ABL (ankle-brachial index), P2Y12 (P2Y12 adenosine diphosphate receptor), and ADP (adenosine diphosphate). BMI (body mass index), HbA1c (haemoglobin A1c or glycated haemoglobin), eGFR (estimated glomerular filtration rate), and GLP-1 RA (glucagon-like peptide-1 receptor agonist). Medication-class abbreviations include SGLT2 (sodium-glucose cotransporter-2 inhibitor), DPP-4 (dipeptidyl peptidase-4 inhibitor), ACEi (angiotensin-converting enzyme inhibitor), and ARB (angiotensin receptor blocker). Statistical and reporting abbreviations include IQR (interquartile range), NR (not reported), NA (not available or not applicable), and vs. (versus).

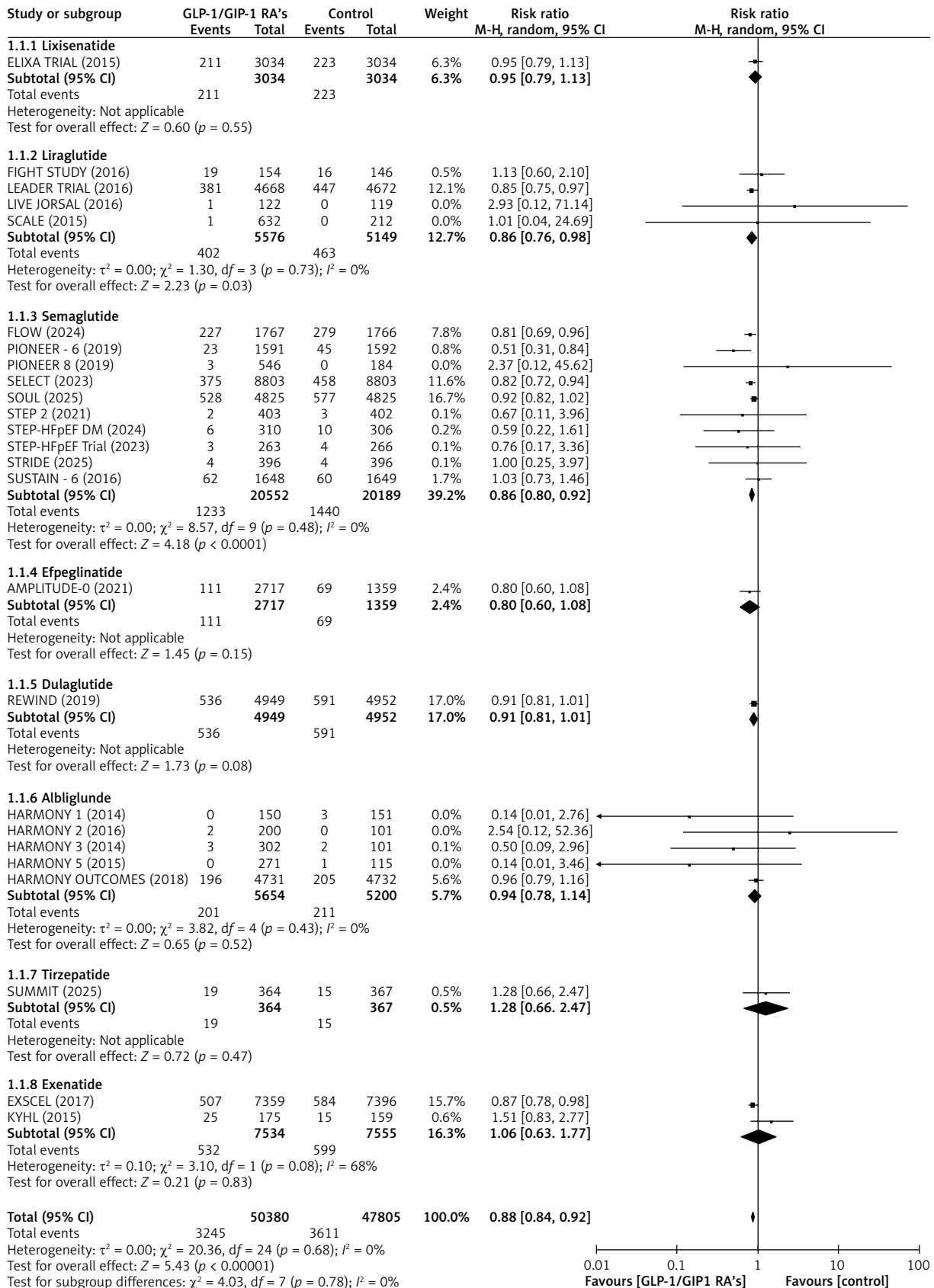


Figure 2. Forest plot for the outcome all-cause mortality. Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

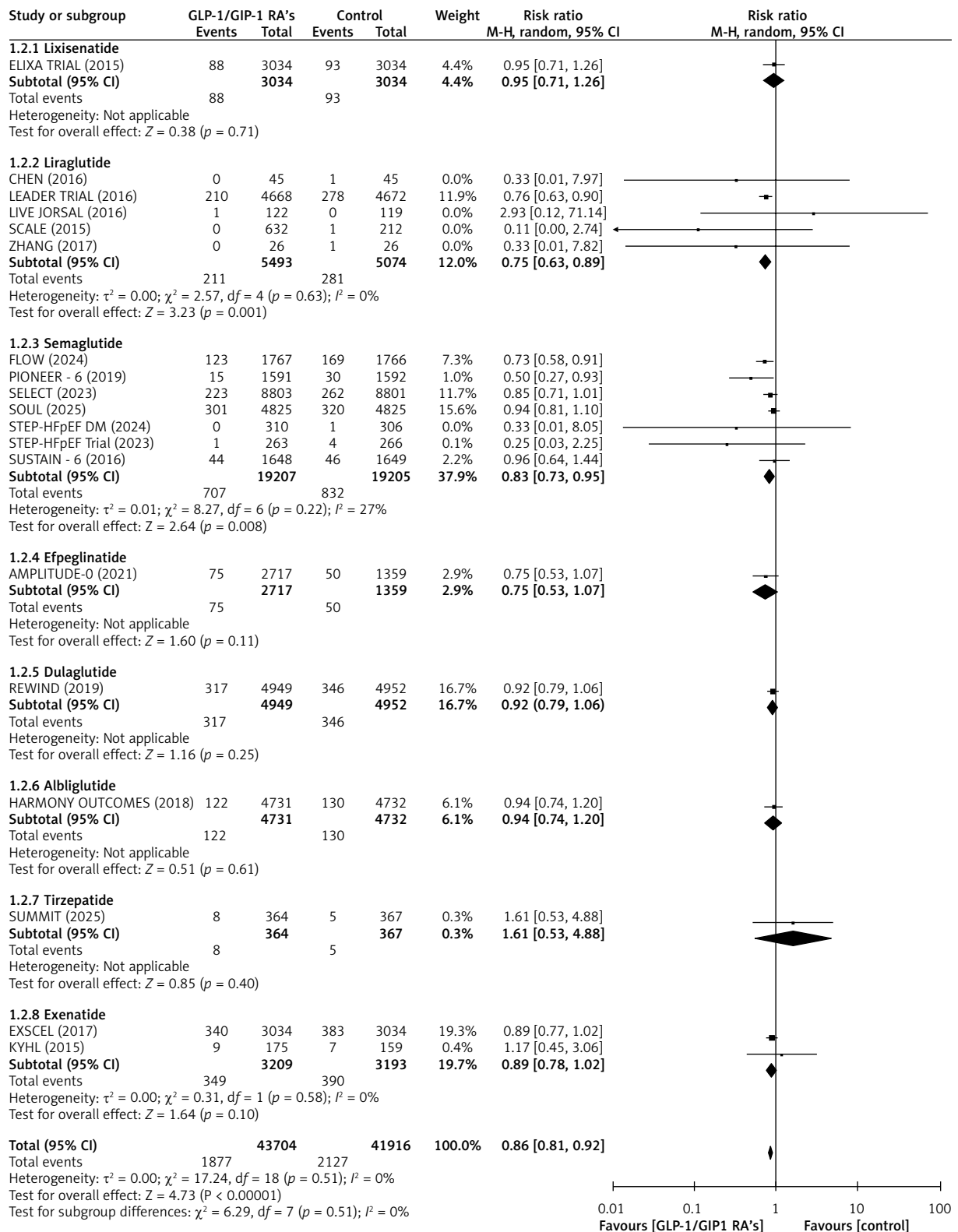


Figure 3. Forest plot for the outcome cardiovascular mortality. Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

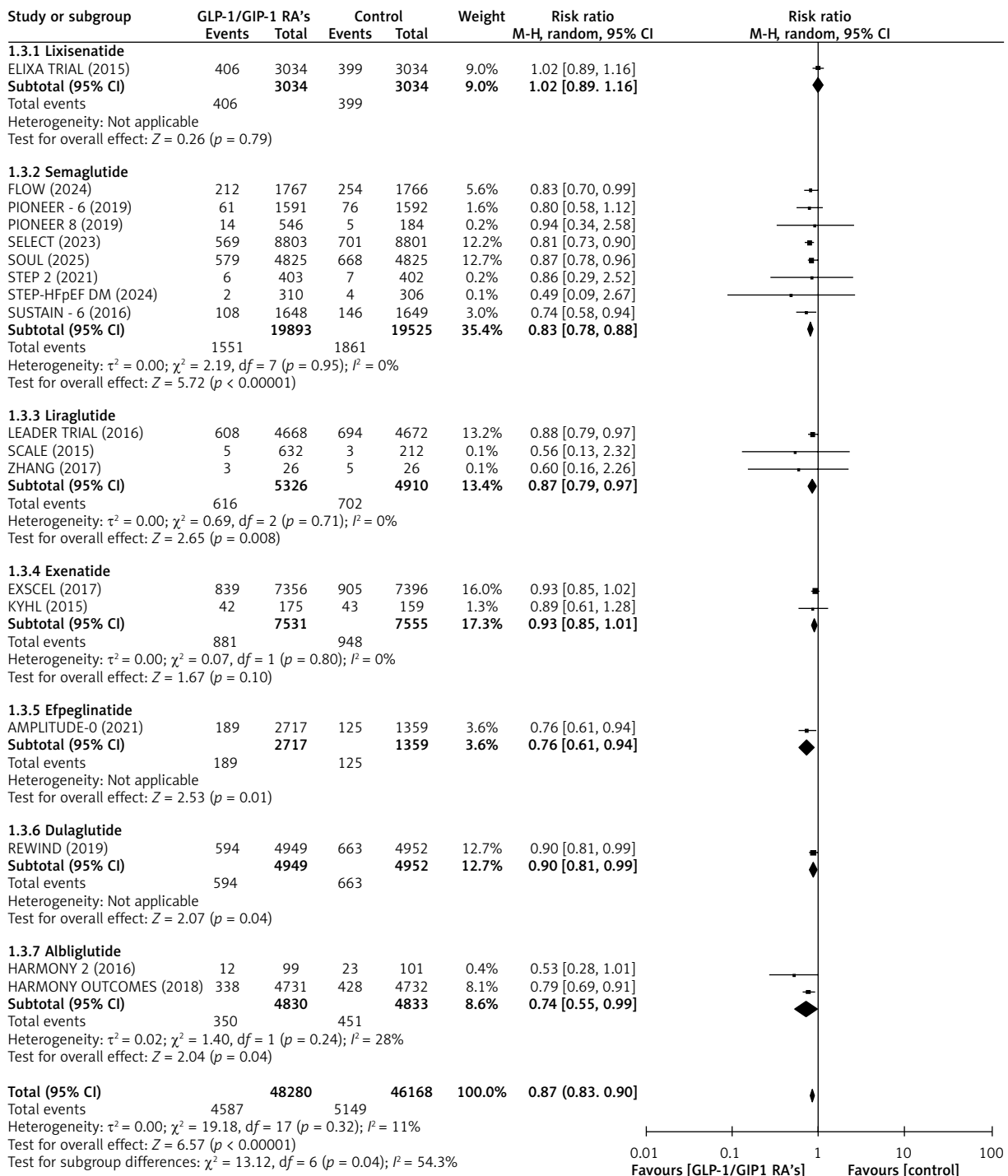


Figure 4. Forest plot for the outcome major adverse cardiovascular events (MACE). Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

ure 6). All included studies reporting this outcome were reported to have a low risk of publication bias (Supplementary Figure S6).

Risk of myocardial infarction

A total of 15 randomized controlled trials including 47,702 participants in the GLP-1 RA group and 45,612 in the control group were analysed for

risk of myocardial infarction (MI). GIP/GLP-1 receptor agonists were associated with a statistically significant reduction in the risk of MI (RR = 0.86; 95% CI: 0.78–0.94; $I^2 = 44\%$; $p = 0.001$).

In subgroup analyses, semaglutide, evaluated across six trials, was significantly associated with lower MI risk (RR = 0.77; 95% CI: 0.69–0.85; $I^2 = 0\%$; $p < 0.00001$). In contrast, liraglutide, assessed across four trials, did not show a statistically

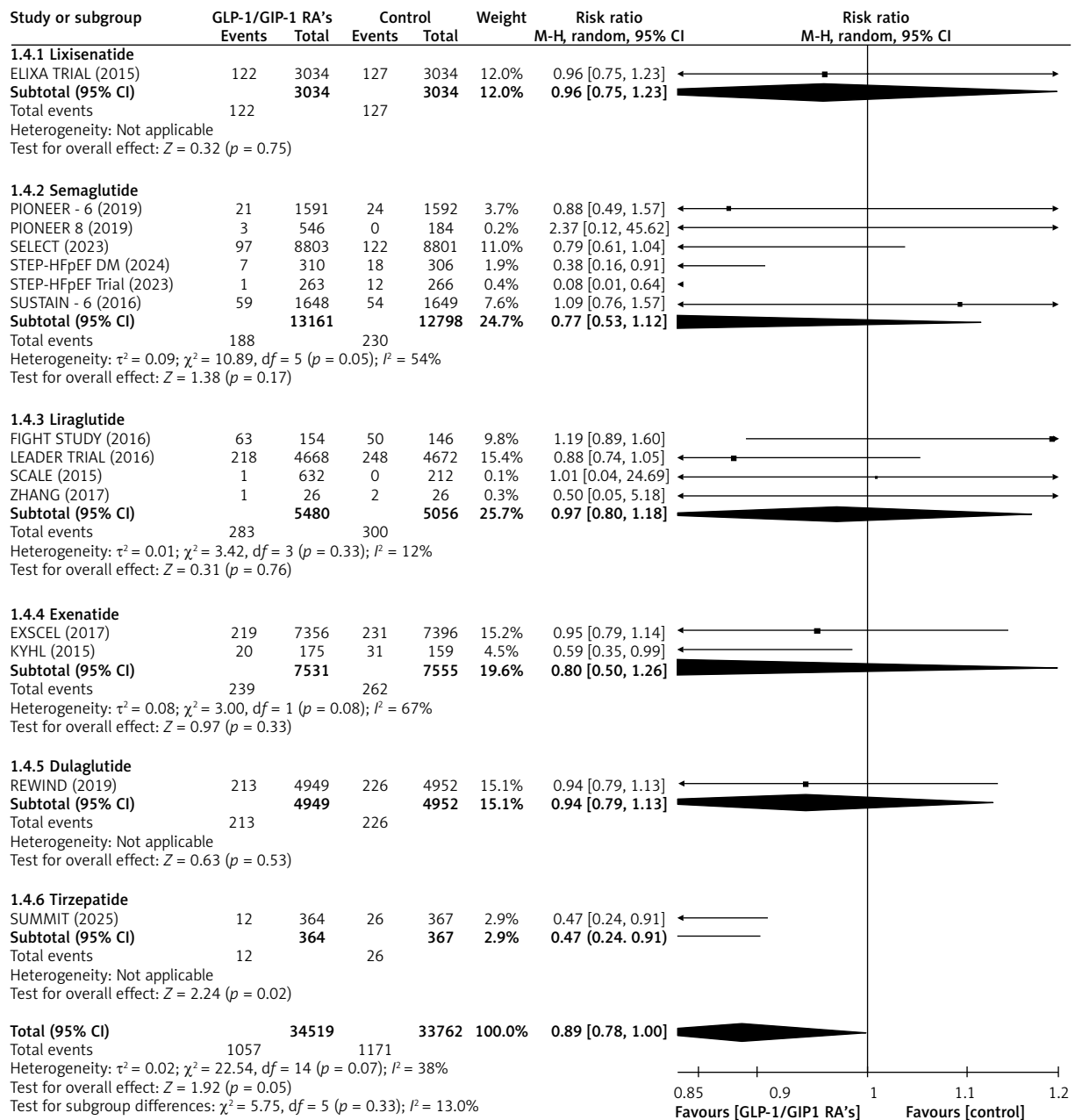


Figure 5. Forest plot for the outcome heart failure hospitalizations (HHF). Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

significant association with MI risk (RR = 0.88; 95% CI: 0.75–1.02; $I^2 = 0\%$; $p = 0.09$) (Figure 7). All included studies reporting this outcome were reported to have a low risk of publication bias (Supplementary Figure S7).

Risk of pancreatitis

A total of 12 randomized controlled trials including 39,351 participants in the GLP-1 RA group and 37,999 in the control group were analysed for pancreatitis. GLP-1 receptor agonists were not significantly associated with pancreatitis (RR = 0.92; 95% CI: 0.71–1.19; $I^2 = 0\%$; $p = 0.53$).

In subgroup analyses, semaglutide, evaluated across seven trials, was not significantly associated with pancreatitis (RR = 0.81; 95% CI: 0.56–1.17; $I^2 = 0\%$; $p = 0.26$) (Figure 8). All included studies reporting this outcome were reported to have a low risk of publication bias (Supplementary Figure S8).

Acute kidney injury

A total of 9 randomized controlled trials including 30,723 participants in the GLP-1 RA group and 29,368 in the control group were analysed for AKI. GLP-1 receptor agonists were not significant-

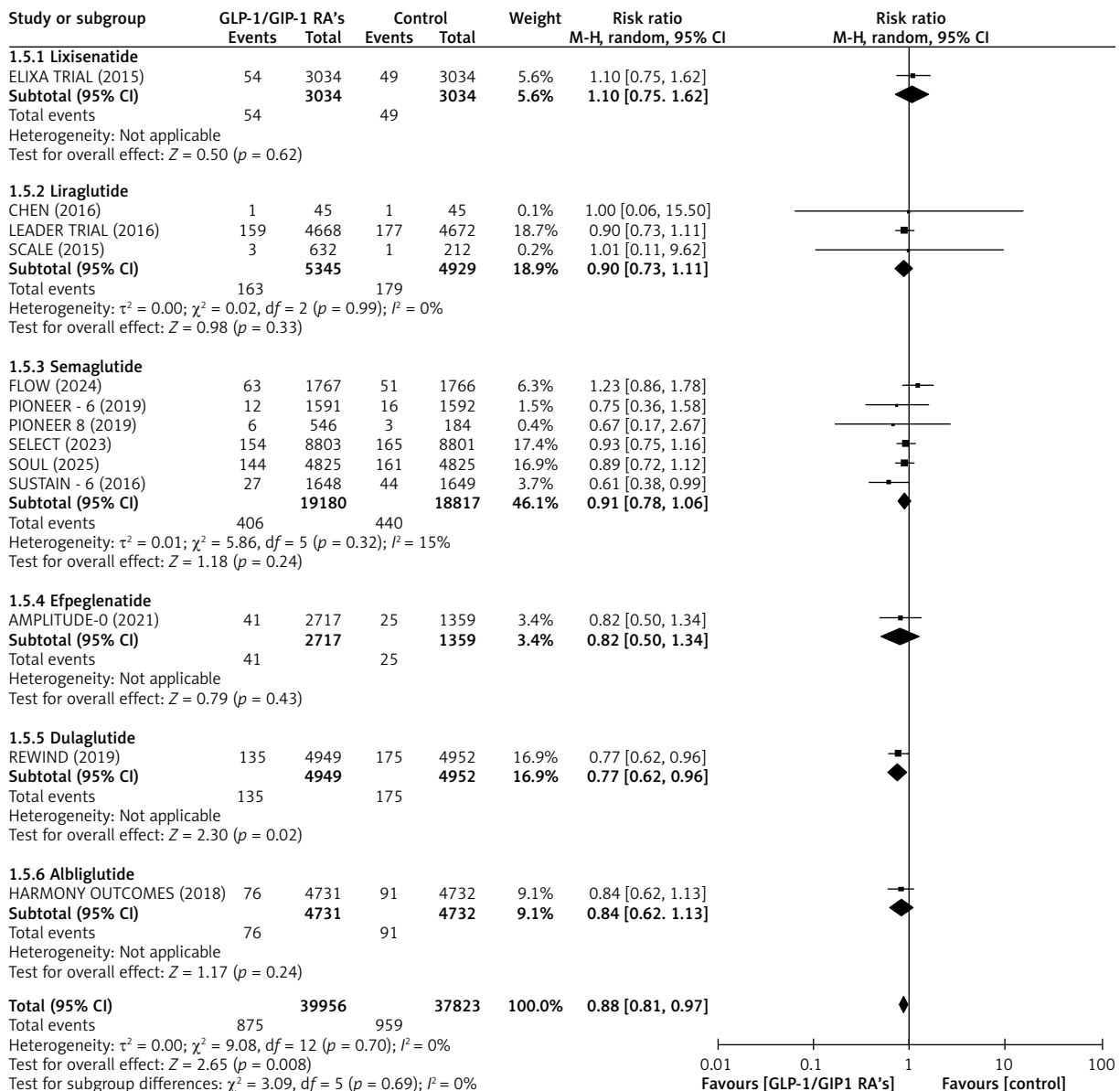


Figure 6. Forest plot for the outcome of risk of stroke. Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

ly associated with acute kidney injury (RR = 0.91; 95% CI: 0.83–1.00; $I^2 = 0\%$; $p = 0.06$).

In subgroup analyses, semaglutide, evaluated across multiple trials, did not demonstrate a statistically significant association with acute kidney injury (RR = 0.90; 95% CI: 0.79–1.02; $I^2 = 10\%$; $p = 0.09$) (Figure 9).

Risk of infections

A total of 13 randomized controlled trials including 42,386 participants in the GLP-1 RA group and 41,067 in the control group were analysed for risk of infections. GLP-1 RAs were associated with a statistically significant reduction in the risk of infections (RR = 0.90; 95% CI: 0.85–0.95; $I^2 = 43\%$; $p = 0.0004$).

In subgroup analyses, semaglutide, evaluated across seven trials, demonstrated a statistically significant reduction in the risk of infections (RR = 0.85; 95% CI: 0.77–0.93; $I^2 = 47\%$; $p = 0.0009$) (Figure 10). All included studies reporting this outcome were reported to have a low risk of publication bias (Supplementary Figure S9).

Risk of bias

Using the ROB 2 tool, the majority of included RCTs were assessed as having low risk of bias, including ELIXA, EXSCEL, PIONEER 6, STEP-HFpEF, STEP-HFpEF DM, SUSTAIN-6, SELECT, AMPLITUDE-O, REWIND, HARMONY OUTCOME, FLOW, SUMMIT, SOUL, PIONEER 8, SCALE Diabetes, HARMONY 1, FIGHT and HARMONY 5. Ten studies were

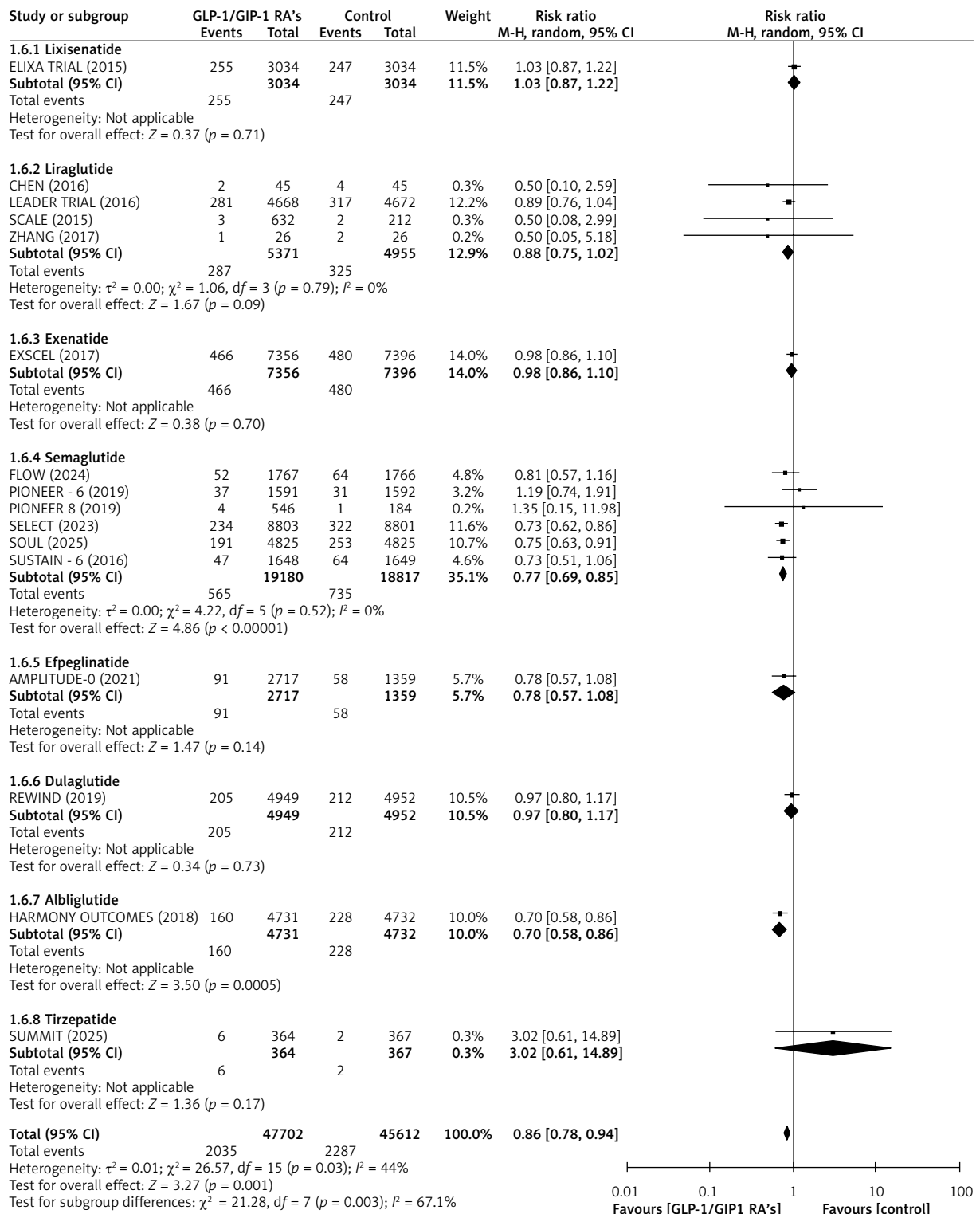


Figure 7. Forest plot for the outcome risk of myocardial infarction. Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

rated as having some concerns (LEADER, Zhang *et al.*, Chen *et al.*, LIVE, Kyhl *et al.*, STRIDE, Ruff 2022, STEP 2, HARMONY 2, and HARMONY 3), most commonly due to concerns in deviations from intended interventions (D2) and in outcome

measurement (D4), while the randomization process (D1), missing outcome data (D3), and selection of reported results (D5) were generally reported as low risk across all included trials (Supplementary Figure S1).

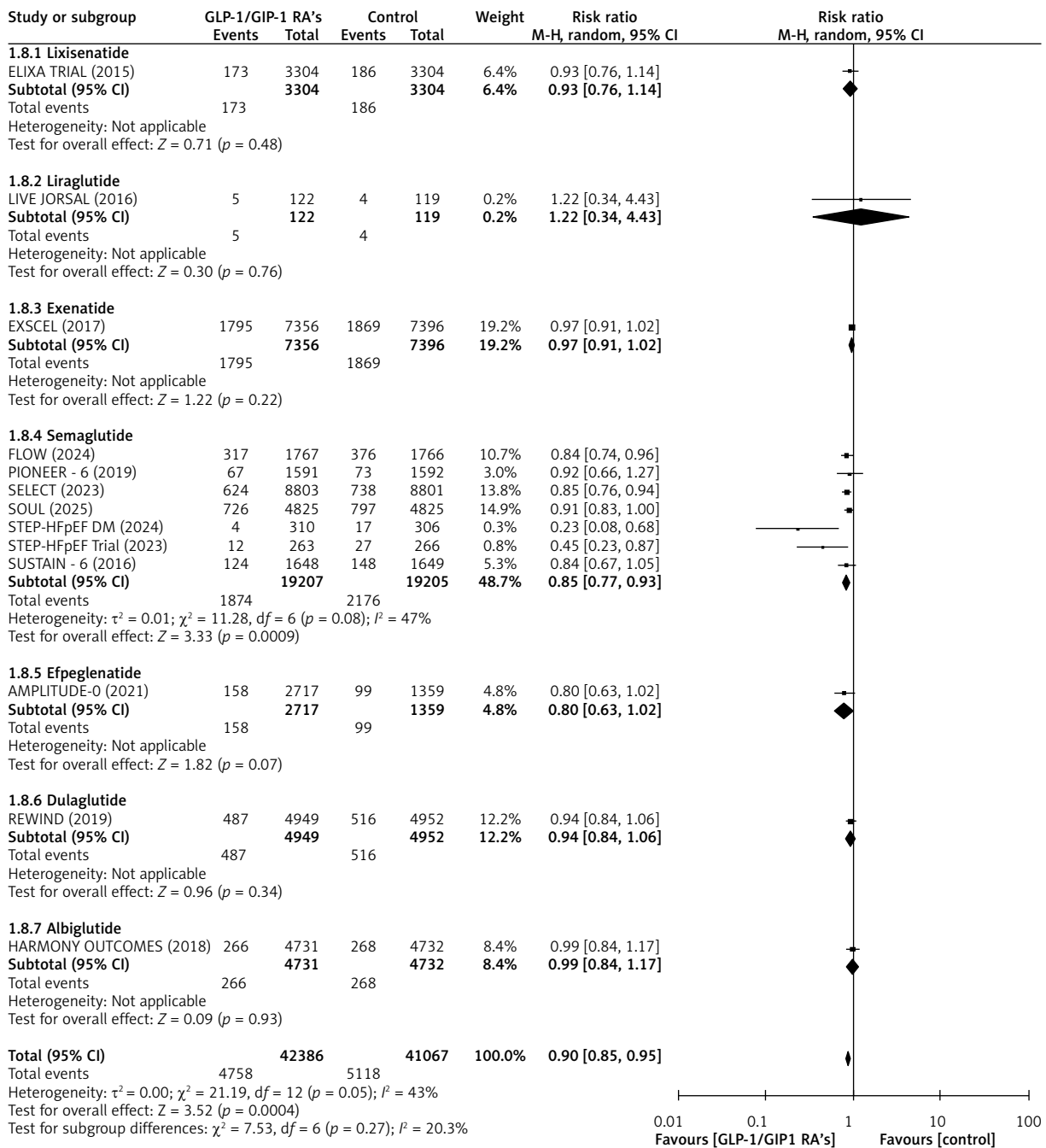


Figure 8. Forest plot for the outcome risk of pancreatitis. Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

Discussion

In this comprehensive meta-analysis of 28 randomized controlled trials including a large population of patients with obesity, type 2 diabetes mellitus, and/or elevated cardiovascular risk, treatment with GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists was associated with significant improvements in major clinical outcomes. Compared with control therapy, these agents were associated with lower all-cause mortality, cardiovascular mortality, and MACE, while

also being associated with lower risks of stroke and myocardial infarction. No statistically significant reduction was observed for HHF. In addition to these cardiometabolic benefits, these therapies were associated with a lower risk of infections, whereas the risks of acute kidney injury and pancreatitis were comparable between treatment and control groups.

With regard to previous meta-analyses, our findings are consistent with earlier evidence supporting the associations of GLP-1 receptor agonists with cardiovascular and mortality out-

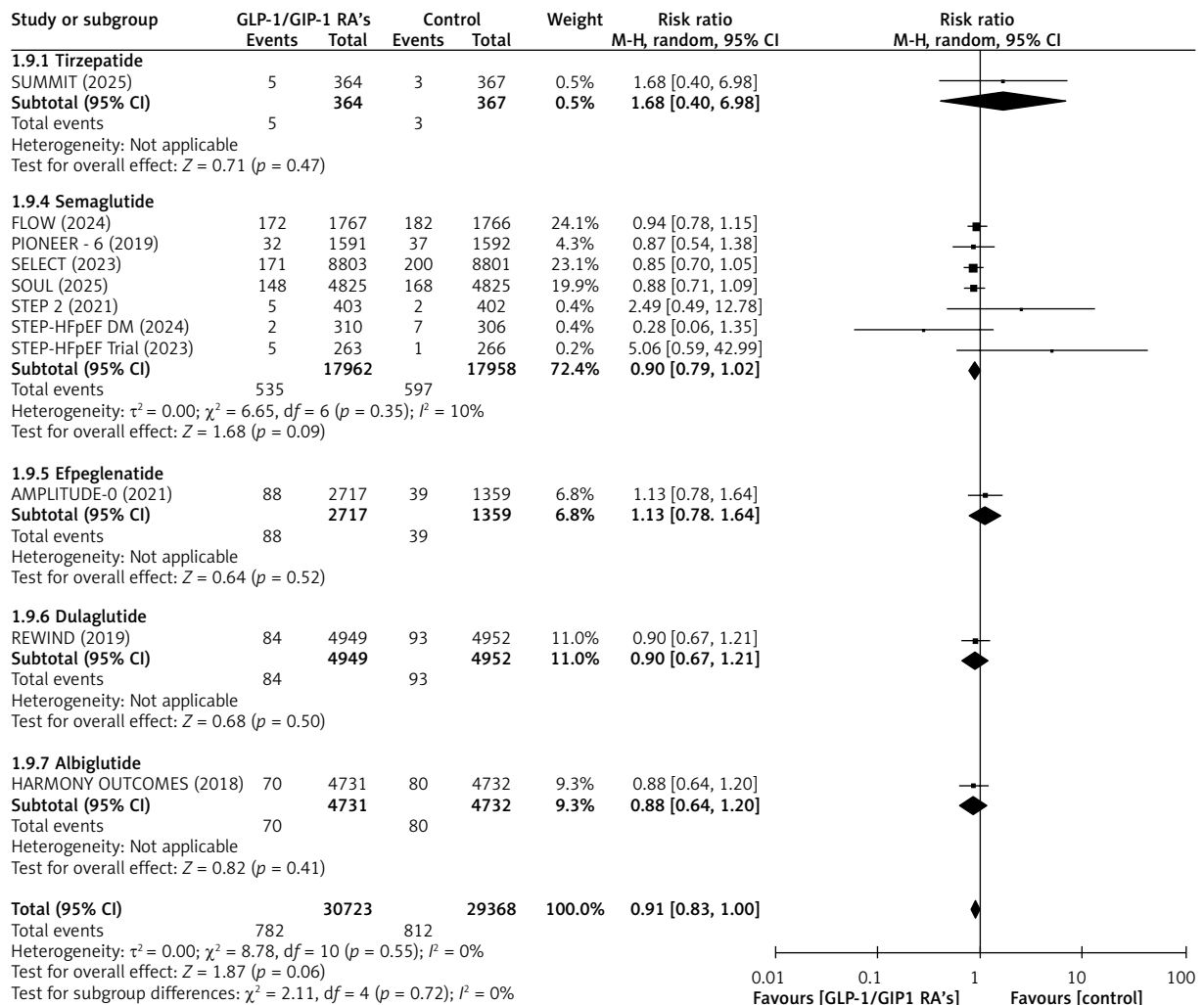


Figure 9. Forest plot for the outcome risk of acute kidney injury (AKI). Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

comes. Shuja *et al.* reported that GLP-1 receptor agonists were significantly associated with lower all-cause mortality ($p = 0.04$) and MACE ($p = 0.02$), while also being associated with improvements in HbA1c levels ($p = 0.02$). However, no significant associations were observed for body weight, major adverse limb events, cardiovascular mortality, myocardial infarction, or stroke [47]. Similarly, Badve *et al.* observed significant associations between GLP-1 receptor agonists and renal and cardiovascular outcomes. Compared with placebo, these agents reduced the composite kidney outcome (HR = 0.82), kidney failure (HR = 0.84), MACE (HR = 0.87), and all-cause mortality (HR = 0.88). Similar findings were also observed in analyses restricted to patients with T2DM, with reductions in the composite kidney outcome (HR = 0.81), kidney failure (HR = 0.84), MACE (HR = 0.86), and all-cause mortality (HR = 0.87) [48]. Likewise, Galli *et al.* found that GLP-1 receptor agonists were associated with lower rates of all-cause mortality (IRR = 0.88), cardiovascular mor-

tality (IRR = 0.86), MACE (IRR = 0.87), and serious adverse events (IRR = 0.92) compared with placebo. Additional benefits included reductions in myocardial infarction, stroke, and heart failure, although increased risks of gallbladder disorders and pancreatitis were also reported [49].

With regard to cardiovascular and mortality outcomes, our analysis demonstrated significant reductions in all-cause mortality, cardiovascular mortality, and MACE, along with significantly lower risks of stroke and myocardial infarction. These findings are consistent with those reported by Kristensen *et al.*, who found that GLP-1 receptor agonist therapy was associated with a 12% reduction in MACE by ($p < 0.0001$). In their analysis, significant reductions were also observed for cardiovascular death ($p = 0.003$), fatal or non-fatal stroke ($p < 0.0001$), and fatal or non-fatal myocardial infarction ($p = 0.043$). Additionally, GLP-1 receptor agonist treatment was associated with a 12% reduction in all-cause mortality ($p = 0.001$) [13].

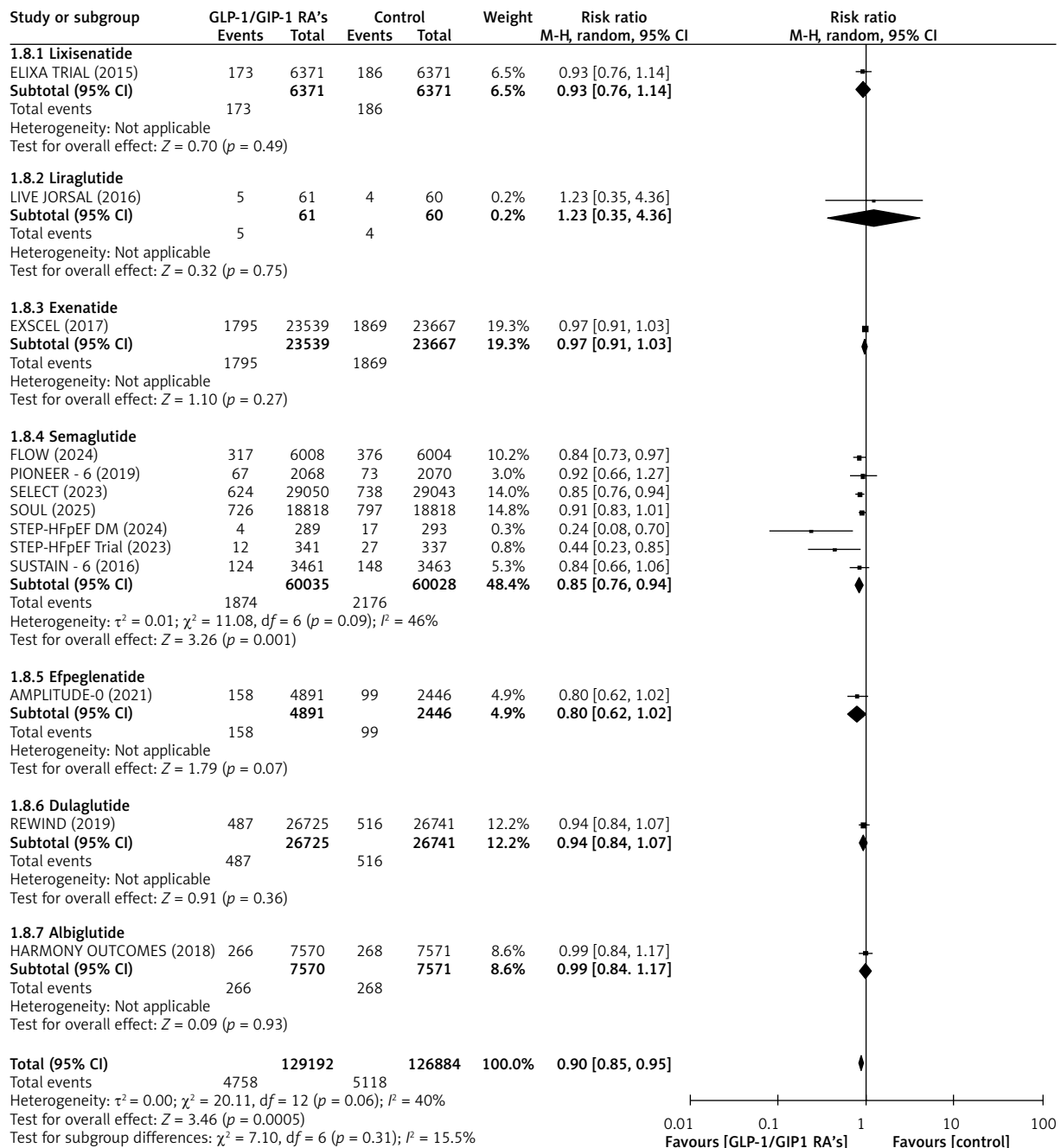


Figure 10. Forest plot for the outcome risk of infections. Risk ratios (RR) with 95% confidence intervals (CI) are shown for individual studies and the pooled estimate

The cardiovascular protective effects of GLP-1 receptor agonists are supported by multiple clinical and preclinical studies. A meta-analysis by Sun *et al.* showed improvements in lipid profiles, including reductions in LDL-C, triglycerides, and apolipoprotein B, along with increases in HDL-C [50]. Consistently, an RCT by Rizzo *et al.* reported that semaglutide was associated with a 5–10% reduction in LDL-C level, while liraglutide semaglutide was associated with a reduction in apolipoprotein B level by about 8%, indicating a reduction in atherogenic lipids [51].

Beyond lipid effects, GLP-1 receptor agonists may have direct vascular benefits. They have been reported to reduce foam cell formation and down-regulate endothelial adhesion molecules such as VCAM-1 and ICAM-1, thereby potentially reducing monocyte adhesion and early atherogenesis, as shown by Gaspari *et al.* [52]. They also may enhance eNOS activation and increase nitric oxide production, which may promote vasodilation, reduce vascular stiffness, and improve endothelial function [53]. This is supported clinically by Irace *et al.*, who found that exenatide was associated

with improved flow-mediated dilation in patients with type 2 diabetes as compared to glimepiride [53]. GLP-1 receptor agonists may also provide neurovascular protection by preserving blood–brain barrier integrity through the upregulation of tight junction proteins and reduced MMP-9 activity, as demonstrated in rodent models by Salcedo *et al.* [54]. Furthermore, according to a meta-analysis by Michaelsen *et al.*, GLP-1 RAs were associated with reduced infarct volume reduction compared with vehicle (placebo) in preclinical animal stroke models [55]. In addition, they may reduce infarct size via activation of pro-survival signalling pathways, including PI3K/Akt and PKA, suggesting a direct cardiomyocyte protective effect independent of glycaemic control [56].

Second, our analysis demonstrated that GLP-1 receptor agonists were not associated with significant reductions in HHF. A meta-analysis by Villaschi *et al.* found that GLP-1 receptor agonists were associated with lower rates of HHF, cardiovascular death, and the composite of HHF plus cardiovascular death only in patients without a prior history of heart failure. In contrast, no significant associations were observed among patients with established heart failure, although a significant interaction according to heart failure history was detected only for the composite outcome [57]. Furthermore, Waqas *et al.* reported that in patients with heart failure with mildly reduced or preserved ejection fraction, GLP-1 receptor agonists were associated with lower rates of the composite of cardiovascular death or worsening heart failure events, as well as worsening heart failure events alone, while no significant reduction was observed for cardiovascular death alone [58].

These findings suggest that although GLP-1 receptor agonists may not consistently be associated with lower rates of HHF across broader populations, they may have greater effects on heart failure outcomes in selected phenotypes. Recent evidence has primarily evaluated their use in patients with the metabolic phenotype of heart failure with preserved ejection fraction (HFpEF) and NYHA class II–IV symptoms, particularly among patients with obesity (BMI ≥ 30 kg/m²) with or without type 2 diabetes. In these populations, the STEP-HFpEF, STEP-HFpEF DM, and SUMMIT trials reported improvements in several clinical outcomes. Agents studied in these trials, including higher-dose semaglutide (2.4 mg) and the dual GLP-1/GIP receptor agonist tirzepatide, have been associated with improvements in heart failure-related outcomes [29, 36, 59]. The reduction in HHF may partly reflect the expression of GLP-1 receptors in the proximal convoluted tubule, where their activation has been proposed to promote natriuresis and diuresis via the inhibition of so-

dium-hydrogen exchanger 3. This may influence RAAS activity, thereby contributing to a reduction in blood pressure, afterload and the overall myocardial oxygen demand [60–62].

Lastly, regarding safety outcomes, GLP-1 receptor agonists were associated with a significant reduction in the incidence of infections, while no statistically significant associations with pancreatitis or acute kidney injury were observed. In accordance with a meta-analysis by Han *et al.*, GLP-1 RA use was associated with a lower risk of serious infections, particularly involving the respiratory, skin, musculoskeletal, and vascular systems, as well as COVID-19, which may be partly explained by weight loss and improved glycaemic control [63]. Similarly, in a retrospective study by Ayoub *et al.* in a comorbidity-free U.S.-based population with type 2 diabetes, GLP-1 RA use was not associated with an increased risk of pancreatitis and was, in that study, associated with a lower lifetime risk [64]. The absence of statistically significant associations with pancreatitis and acute kidney injury observed in our analysis may reflect several factors. First, limited statistical power may have reduced the ability to detect small between-group differences. Second, most included trials were not primarily designed or adequately powered to assess these safety endpoints, which were typically reported as secondary outcomes.

This meta-analysis, though comprehensive, has several limitations. First, considerable heterogeneity existed among included trials regarding design, follow-up duration, participant characteristics, and types/doses of GLP-1 RAs, which may impact the generalizability of findings. Second, while subgroup and sensitivity analyses were conducted, some residual heterogeneity likely remains. Third, a key limitation was the variability in follow-up durations as well as dosing regimens, which may have potentially influenced the pooled estimates. Lastly, the lack of individual patient data (IPD) limited detailed subgroup analyses (e.g., by age, sex, cardiovascular risk, renal function, or HF phenotype) and adjustment for confounders influencing treatment response.

In conclusion, this meta-analysis of randomized controlled trials found that GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists are associated with lower risks of mortality, MACE, myocardial infarction, and stroke. However, no significant association with HHF was observed. Safety outcomes were generally favourable, with a lower risk of infections and no statistically significant associations with pancreatitis or acute kidney injury. Overall, these findings support an association between GLP-1-based therapies and improved cardiovascular outcomes in high-risk populations.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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