Cardiovascular Diabetology

REVIEW

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Glucagon-like peptide-1 receptor agonist in myocardial infarction and atherosclerotic cardiovascular disease risk reduction: a comprehensive meta-analysis of number needed to treat, efficacy and safety

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Abstract

Background Glucagon like peptide-1 receptor agonist (GLP-1RA) use in individuals with high atherosclerotic cardiovascular disease (ASCVD) risk reduces major adverse cardiovascular events (MACE). However, its clinical impact, in terms of numbers needed to treat (NNT), efficacy and safety profile in reducing the risk of myocardial infarction (MI) and the individual ASCVD constituents remain unclear.

Methods Electronic databases, Medline and Embase were reviewed for randomized trials from inception to 29 May 2025. Risk-reduction effect of GLP-1RA were pooled using pairwise meta-analysis with random-effects model. The primary outcome was MI, and secondary outcomes were the individual ASCVD constituents.

Results 109,846 patients from 25 unique studies were included. Over a follow-up duration of 3.48 ± 1.51 (1.55 to 5.47) years, GLP-1RA reduced the risk of total MI (RR: 0.86, $p < 0.01$), with numbers needed to benefit (NNTB) of 207 to prevent one event of MI. Higher body mass index was associated with greater MI risk reduction (β: -0.09, $p = 0.03$) in GLP-1RA users. GLP-1RA reduced cardiovascular mortality (RR: 0.87, $p < 0.01$, NNTB 170), MACE (RR: 0.87, $p < 0.01$, NNTB 67) and stroke (RR: 0.88, $p < 0.01$, NNTB 335) compared to placebo. GLP-1RA commonly resulted in gastrointestinal side-effects amongst other systems (RR: 1.55, $p < 0.01$, NNTH 9).

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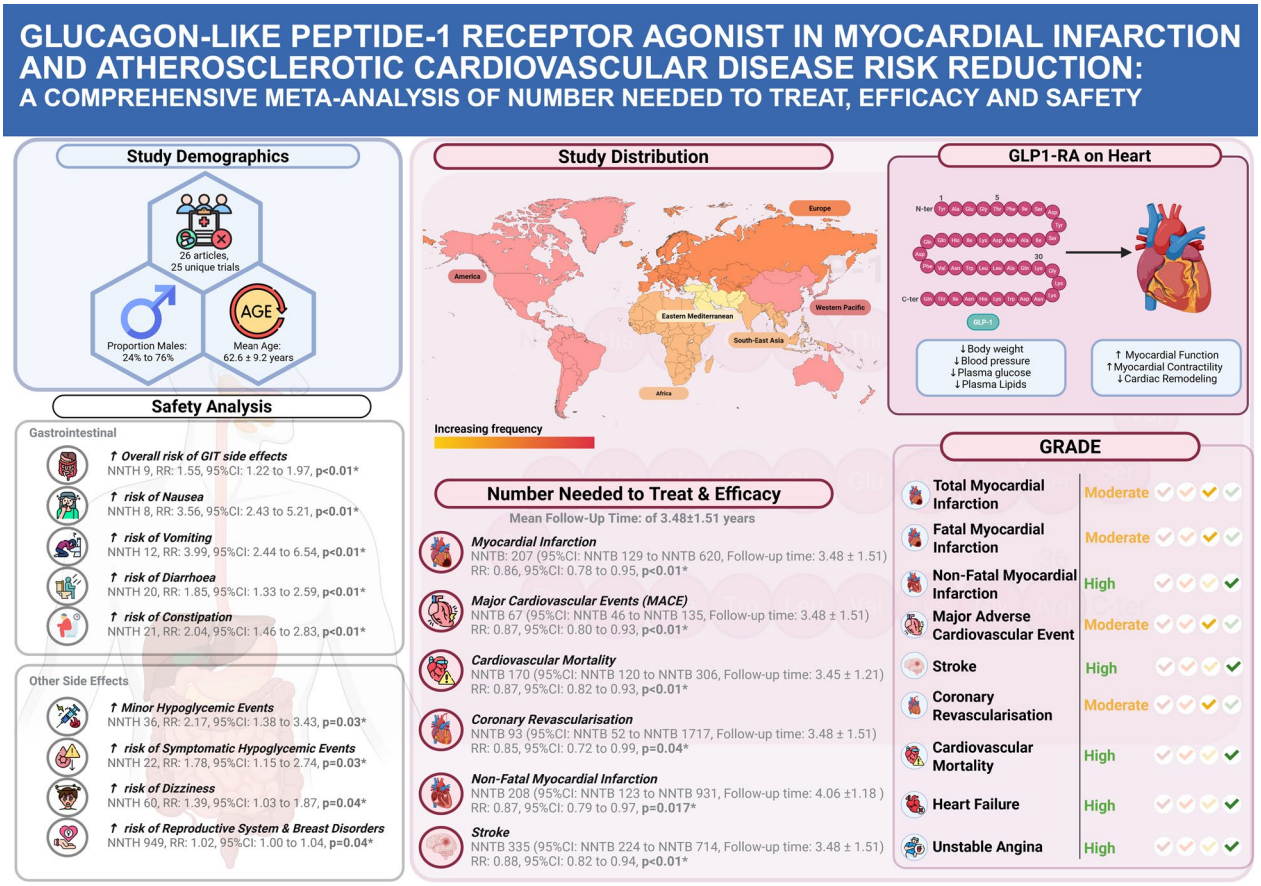
Conclusion GLP-1RA reduced the risk of MI, stroke, cardiovascular mortality and MACE in a broad range of patients with and without T2DM and/or prior ASCVD, supporting its role in ASCVD prevention, especially in the cohort with high BMI.

Trial registration: Open Science Framework (https://doi.org/10.17605/OSF.IO/7VXN5**).**

Keywords GLP-1 receptor agonist, GLP-1RA, Myocardial infarction, Stroke, Cardiovascular mortality, Cardiovascular disease, Numbers-needed-to-treat

Graphical Abstract



Research insights

What is currently known about this topic?

- Landmark cardiovascular outcome trials like LEADER and SELECT have demonstrated the cardiometabolic benefits of GLP1-RA in the reduction of MACE events in populations with T2DM as well as populations with overweight or obesity in the absence of T2DM. This was further substantiated by systematic reviews, which have described pooled overall MACE risk reductions in both the abovementioned population groups.

What is the key research question?

- What is the NNT, efficacy and safety profile of GLP-1RA in reducing the risk of myocardial infarction (MI) and individual ASCVD constituents, namely non-fatal MI, unstable angina, coronary revascularization, and/or cardiovascular mortality?

What is new?

- GLP-1RA use was associated with a 13% risk reduction in total MI with an NNT of 207 to prevent one event of MI over a follow-up of 3.48 ± 1.51 (range: 1.55 to 5.46) years. However, MI risk reduction was attenuated in the population with T2DM and in the secondary preventative cohort with prior ASCVD. The former is likely attributable to the competing multimorbid status in the generally

higher risk population with T2DM, that can attenuate the overall beneficial effects of GLP-1RA.
- Increased BMI is associated with significantly larger MI risk reduction with GLP-1RA, implying that weight reduction may further reduce residual ASCVD risk with GLP-1RA use.
- In the secondary preventative cohort, GLP-1RA may be considered for its significant reduction in unstable angina and coronary revascularization risk. Relative to its clinical impact on MI reduction, measured by NNT, GLP-1RA was more effective in preventing one event of cardiovascular mortality and MACE.

How might this study influence clinical practice?

- Evidence supports the role of GLP-1RA as part of therapy in overall ASCVD risk reduction, especially in the cohort with high BMI.

Introduction

Cardiovascular disease (CVD)-related mortality [1, 2] and morbidity have surged in recent decades[3], despite advancements in medical and healthcare resources [4]. The global CVD burden is expected to see a 3.6% year-on-year increase from 2025 to 2050 [5], thus emphasizing the need for effective strategies in cardiometabolic prevention within the global health conundrum [6–9]. With the success of landmark cardiovascular outcome trials on glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) [10], this has transformed the landscape of cardiometabolic disease management [11]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial (LEADER) led to a paradigm shift in the wider use of GLP-1RA from promising antihyperglycemic agents to cornerstone cardiometabolic therapies, demonstrating the significant reduction of major adverse cardiovascular events (MACE) with the use of liraglutide in the population with type 2 diabetes mellitus (T2DM) [12, 13]. The overall cardiometabolic benefit of GLP-1RA rapidly expanded beyond the T2DM population, with the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial describing MACE reduction in the population with overweight and obesity, even in the absence of T2DM [14].

In the era of precision prevention, together with updated pooled cohort equations such as the Predicting Risk of Cardiovascular Disease Events (PREVENT) calculator [15, 16] that distinguish the individual's risk of atherosclerotic cardiovascular disease (ASCVD) and/or heart failure (HF), primary preventative strategies could be tailored in accordance to the individual's risk profile [17–19]. Clinical practice guidelines[20, 21] have recommended the use of SGLT2i in individuals at higher risk of HF, while GLP-1RA may be prioritized in those with T2DM at higher ASCVD risk (calculated 10-year ASCVD risk ≥ 10%, Class IIa, level of evidence: B) given their neutral effect on HF hospitalization [22]. While other reviews have described the MACE risk reduction in the general population with T2DM [23, 24], non-T2DM [25], or both [26], the present study seeks to address the gap in the literature in providing a comprehensive meta-analysis on the number need to treat (NNT), efficacy and safety profile of GLP-1RA in reducing the risk of myocardial infarction (MI) and individual ASCVD constituents, namely non-fatal MI, unstable angina, coronary revascularization, and/or cardiovascular mortality.

Methods

Study design and search strategy

This systematic review and meta-analysis was conducted with reference to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020. Two electronic databases, Embase and Medline, were searched for randomized controlled trials (RCTs) relating to treatment with GLP-1RA and prevention of MI from inception to 22 May 2025. Key search terms including "glucagon-like peptide 1 receptor agonist" and "myocardial infarction" were used in the search strategy and the full search strategy can be found in Supplementary Material 1. This review was prospective registered in Open Science Framework (https://doi.org/https://doi.org/10.17605/OSF.IO/7VXN5).

Eligibility and selection criteria

References were imported into Covidence (Melbourne, Victoria, Australia) for the compilation and removal of duplicates. Abstracts were independently screened by two pairs of authors (FS, JTYH, SKSC, GS). Any discrepancies were resolved by consensus or in consultation with a senior author (ASPT, JQ, YHC, NWC). Subsequently, full text reviews were conducted to check for eligibility of studies for inclusion in this review. Only original randomized trials with published results in English or professionally translated into English were included in this study. The inclusion of each study was contingent on the use of a GLP-1RA arm and the incidence of MI both groups during the trial. Non-randomized controlled trials and observational studies, including cohort and cross-sectional studies, were excluded from this study. Reviews, study protocols, letters, commentaries, conference abstracts were also excluded. Studies in pediatric populations were also excluded in this study. References of related reviews and grey literature were screened to ensure a comprehensive review.

Data extraction and outcomes

Two pairs of authors (FS, JTYH, SKSC, GS) independently extracted data including, but not limited to: (1) study characteristics (e.g. author, title, publication year, trial name, trial registry), (2) patient demographics (e.g. age, sex, ethnicity, body mass index [BMI]), (3) baseline comorbid status (e.g. T2DM, hypertension, obesity, hyperlipidemia), (4) treatment characteristics (e.g. drug formulation, dosage, duration of intervention), (5) prognostic outcomes, (6) safety data (e.g. general, gastrointestinal, endocrine, and neurological side-effects). Any discrepancies were resolved by consensus or in consultation with a senior author (ASPT, JQ, YHC, NWC). The primary outcome of interest was the incidence of MI. Secondary outcomes were the incidence of MACE, stroke, unstable angina, coronary revascularization and cardiovascular mortality. Where available, the hazard ratios of these outcomes were also collated. MACE outcomes were collated, with most adhering to the MACE-3 definition (comprising non-fatal MI, non-fatal stroke and cardiovascular mortality). A list of MACE definitions used across the included studies are summarized in Supplementary Material 2. Cardiovascular mortality was defined as deaths resulting from any cardiovascular causes, which include, but are not limited to, cardiac arrest, MI, and arrhythmia.

Statistical methods

All statistical analysis was conducted in RStudio (version 4.4.0). Statistical significance was considered for outcomes with a p value of ≤ 0.05. To assess the cardioprotective impact of GLP-1RA on MI, secondary cardiovascular outcomes and safety profile, pairwise meta-analysis was conducted using the Paul-Mandel estimator to obtain the risk ratio (RR) and corresponding 95% confidence interval [27]. Due to the differing mechanisms of tirzepatide, a dual gastric inhibitory polypeptide (GIP) and GLP-1RA, compared with the rest of the GLP-1RA medications, the results of studies examining tirzepatide were systematically reviewed without inclusion in the meta-analysis. Statistical heterogeneity was assessed via I^2, where a value of 25%, 50% and 75% indicated low, moderate and high heterogeneity respectively, and Cochran Q test, where $p < 0.10$ was considered significant for heterogeneity [28]. Hartung-Knapp adjustments were employed to adjust for confidence intervals by controlling for the heterogeneity arising from between-study estimations [29]. Zero total event trials for each outcome were accounted in our analysis using the continuity correction of 0.5 [30]. The random effects model was used regardless of heterogeneity scores, based on evidence of more robust estimates when compared to fixed-effect models [31–33].

To estimate the absolute risk reduction and its corresponding numbers needed to treat, data extracted for the efficacy outcomes mentioned in Sect. "Data Extraction and Outcomes" were used to calculate NNT, which yielded either numbers needed to benefit (NNTB) and number needed to harm (NNTH) based on formulas recommended by the Cochrane guidelines [34].

$$\text{NNT} = 1/\text{absolute value of risk difference.}$$

Subgroup analyses (duration of trial, type of medication) and sensitivity analyses (secondary prevention, T2DM only) were conducted. To assess the modulatory effect of demographic factors, such as age, sex, ethnicity, BMI and comorbid status, mixed-model meta-regression with Hartung-Knapp estimator was conducted [35]. In view of limited information ($n < 3$) when making head-to-head comparisons of identified outcomes with other glucose lowering agents, the results were systematically reported.

Study quality, publication bias and certainty of outcomes

Each study was independently screened by two pairs of authors (FS, JTYH, SKSC, GS). Any discrepancies were resolved by consensus or in consultation with a senior author (ASPT, JQ, YHC, NWC). Quality assessment of included articles was conducted using the Cochrane Risk of Bias 2 (ROB-2) tool [34]. RoB2 analyses the risk of bias by grading the quality of evidence through five bias domains including randomization process, deviation from intended intervention, missing outcome data, outcome measurement and reported result selection. A final grade of low risk of bias, some concerns of bias and high risk of bias was attributed to each article considering the score in each section. Publication bias was examined with Egger's [36] regression, where ≥ 10 studies were present. Funnel plots were generated for analyses involving ≥ 10 studies for visual inspection of asymmetrical distribution of data points across the vertical treatment effect axis. Grading of Recommendations Assessment, Development and Evaluation (GRADE) scoring was also performed for each of the main outcomes analyzed. GRADE is a system of grading used to assess the overall quality and certainty of the evidence obtained from the specific outcome or intervention [37]. This helps the reader determine the level of confidence and robustness the data estimates have in each of the specific outcomes.

Results

Summary of included articles

The initial search of the literature yielded a total of 2218 articles. After the removal of 559 duplicates and automated removal by Covidence of 399 ineligible articles, 1260 articles remained for title and abstract screening. Further removal of 986 articles resulted in 274 articles being sought for retrieval and full-text review. A total of 26 articles [12, 14, 38–61], derived from 25 unique trials,

published between 2013 and 2025, involving 109,846 patients were selected for inclusion in this study. The selection process is depicted in Fig. 1. All trials were randomized trials conducted in adult patients (≥ 18 years). Most studies were conducted in a multi-national setting, except for two studies conducted only in Japan. Majority of studies were also conducted in patients with T2DM, except for one study conducted in a cohort with obesity in the absence of T2DM [62]. In addition, the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial [60] recruited participants with chronic kidney disease. The proportion of males ranged from 24 to 76%, and the mean age was 62.6 ± 9.2 years. Based on the ROB 2 tool, most studies were of low risk of bias, while only a minority was of some concern or higher. Majority of studies compared GLP-1RA to placebo [12, 14, 38–40, 44, 47, 48, 51–61], while others used insulin regiments and other anti-diabetic medications [41–43, 45–47, 49, 50] as the comparators. A summary of the study characteristics and study quality can be found in Table 1 and Supplementary Material 3 respectively.

Number needed to treat

When compared to placebo, the NNT in the overall study is based on studies with a mean follow-up time in years of 3.48 ± 1.51 (range: 1.55 to 5.46). The current results show that number needed to benefit (NNTB) was 207 (95%CI: NNTB 129 to NNTB 620, Follow-up time: 3.48 ± 1.51 years) for total MI, NNTB 67 (95%CI: NNTB 46 to NNTB 135, Follow-up time: 3.48 ± 1.51 years) for MACE, NNTB 170 (95%CI: NNTB 120 to NNTB 306, Follow-up time: 3.48 ± 1.51 years) for cardiovascular mortality, and NNTB 93 (95%CI: NNTB 52 to NNTB 1717, Follow-up time: 3.45 ± 1.21 years) for coronary revascularization. These findings are summarized in Table 2.

Subgroup analysis based on GLP-1RA type showed that NNTB for albiglutide was 51, followed by semaglutide (NNTB 82), whilst the NNT for efpeglenatide, liraglutide, dulaglutide and exenatide was insignificant (Supplementary Material 4).

Efficacy

Comparison to placebo

Table 3; Fig. 2 summarize the comparison of GLP-1RA and placebo on the effect of cardiovascular outcomes. Across the main outcomes, GLP-1RA significantly reduced the rates of most outcomes, including total MI (RR: 0.86, 95%I 0.78 to 0.95, $p < 0.01$), non-fatal MI (RR: 0.87, 95%CI: 0.79 to 0.97, $p = 0.02$), MACE (RR: 0.87, 95%CI: 0.80 to 0.93, $p < 0.01$), stroke (RR: 0.88, 95%CI: 0.82 to 0.94, $p < 0.01$), rates of coronary revascularization (RR: 0.85, 95CI: 0.72 to 0.99, $p = 0.04$) and cardiovascular mortality (RR: 0.87, 95%CI: 0.82 to 0.93, $p < 0.01$).

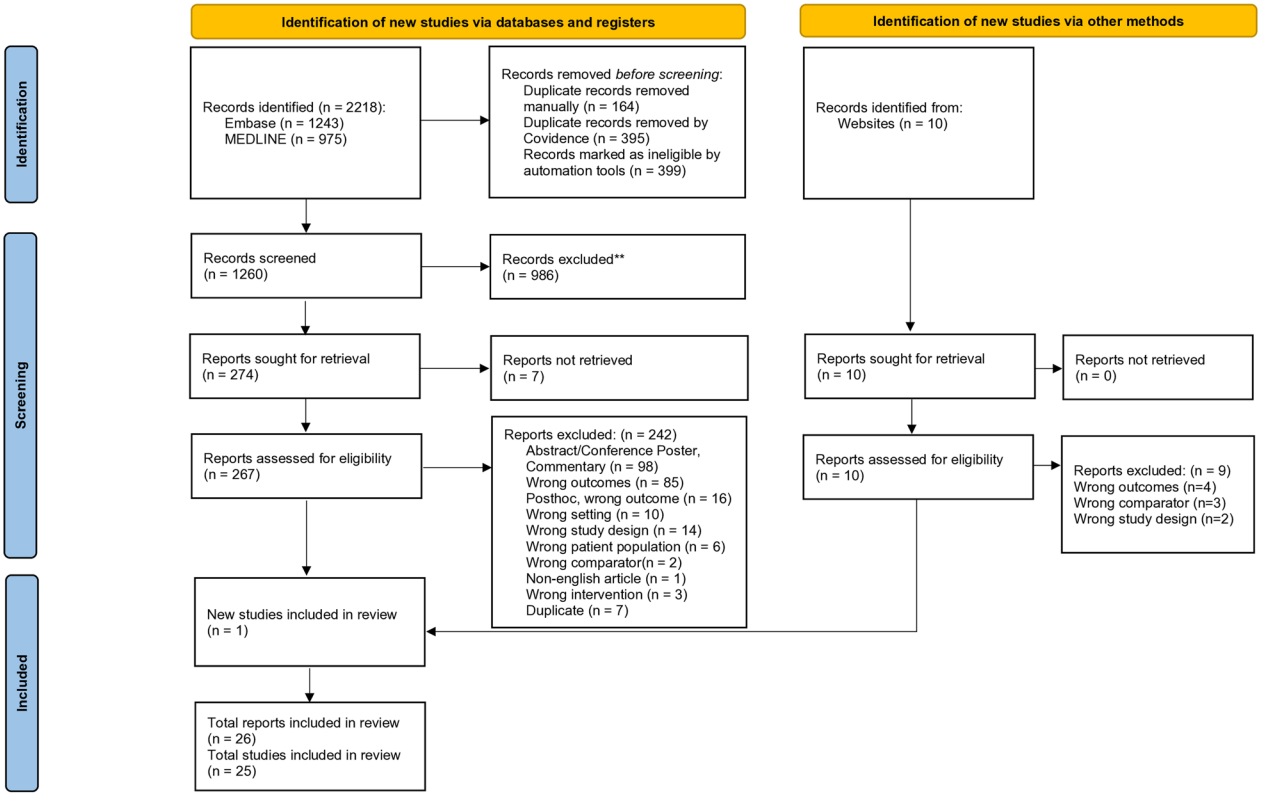


Fig. 1 PRISMA flowchart

Table 1 Summary of included studies

Study	Trial name	Trial registry number	Intervention arms	Sample size	Sex (male)	Age (years)		Risk of bias
						Mean	SD	
Lincoff et al. 2023	SELECT	NCT03574597	- Semaglutide - Placebo	17,604	0.72	61.60	8.85	High
Ruff et al. 2022	FREEDOM CVO	NCT01455896	- Exenatide - Placebo	4156	0.63	62.83	7.7993	Low
Perkovic et al. 2024	FLOW	NCT03819153	- Semaglutide - Placebo	3533	0.70	66.60	9.00	Low
Gerstein et al. 2019	REWIND	NCT01394952	- Dulaglutide - Placebo	9901	0.54	66.20	6.50	Low
Pfeffer et al. 2015	ELIXA	NCT01147250	- Lixisenatide + standard of care - Placebo + standard of care	6068	0.69	60.25	9.66	Low
Green et al. 2024	GRADE	NCT01794143	- Liraglutide + metformin - Insulin Glargine + metformin - Glimepiride + metformin - Sitagliptin + metformin	5047	0.64	57.20	10.00	Some concerns
Del Prato et al. 2022	SURPASS-4	NCT03730662	- Tirzepatide (± metformin, sulfonylurea, SGLT2 inhibitor) - Insulin Glargine (± metformin, sulfonylurea, SGLT2 inhibitor)	1995	0.62	63.60	8.60	Low
Pei et al. 2021	DUAL II China	NCT03175120	- IDegLira (Degludec, Liraglutide) + basal insulin + metformin ± oral antidiabetic drugs (OADs) - Insulin degludec + basal insulin + metformin ± oral antidiabetic drugs (OADs)	453	0.60	54.70	9.90	Low
Frias et al. 2019			- Dulaglutide + metformin - Placebo + metformin	317	0.50	56.80	9.74	Low
Philis-Tsimikas et al. 2019	DUALTM IX	NCT02773368	-Insulin Degludec/Liraglutide (IDegLira) + SGLT2 inhibitor -Insulin Glargine + SGLT2 inhibitor	420	0.59	56.65	10.30	Low
Seino et al. 2018		NCT02254291	-Semaglutide -Sitagliptin	308	0.76	58.30	10.70	Low
Jabbour et al. 2018	DURATION-8	NCT02229396	-Exenatide/Dapagliflozin + metformin -Exenatide/Placebo + metformin -Dapagliflozin/Placebo + metformin	685	0.48	54.17	9.53	Low
Le Roux et al. 2017	SCALE	NCT01272219	-Liraglutide + reduced-calorie diet and increased physical activity -Placebo + reduced-calorie diet and increased physical activity	2254	0.24	47.43	11.73	High
Araki et al. 2015		NCT01584232	-Dulaglutide + sulphonylureas (± biguanides) -Insulin Glargine + sulphonylureas (± biguanides)	361	0.71	56.80	10.90	Low
Gough et al. 2014	DUAL I	NCT01336023	-Insulin Degludec/Liraglutide + metformin (± pioglitazone) -Liraglutide + metformin (± pioglitazone) -Insulin Degludec + metformin (± pioglitazone)	1663	0.51	55.03	9.92	Low
Pan et al. 2014	GetGoal-M-Asia	NCT01169779	-Lixisenatide + metformin (± sulfonylurea) -Placebo + metformin (± sulfonylurea)	390	0.49	54.80	10.39	Low
Pinget et al. 2013	GETGOAL-P	NCT00763815	-Lixisenatide + pioglitazone (± metformin) -Placebo + pioglitazone (± metformin)	484	0.52	55.77	9.50	Low
Riddle et al. 2013	GetGoal-Duo1	NCT00975286	-Insulin Glargine + metformin (± TZDs) + lixisenatide -Insulin Glargine + metformin (± TZDs) + placebo	446	0.50	56.00	10.00	Low
Gerstein et al. 2023	AMPLITUDE O	NCT03496298	- Efpeglenatide - Placebo	4076	0.67	64.50	8.20	Low
Gerstein et al. 2021	AMPLITUDE O	NCT03496298	- Efpeglenatide - Placebo	4076	0.67	64.50	8.20	Low
Holman et al. 2017	EXSCEL	NCT01144338	- Exenatide + usual care - Placebo + usual care	14,752	0.62	62.00	8.90	Low
Hernandez et al. 2018	HARMONY	NCT02465515	- Albiglutide + standard care - Placebo + standard care	9463	0.69	64.15	8.70	Low

Table 1 (continued)

Study	Trial name	Trial registry number	Intervention arms	Sample size	Sex (male)	Age (years)		Risk of bias
						Mean	SD	
Marso et al. 2016	LEADER	NCT01179048	- Liraglutide + standard of care - Placebo + standard of care	9340	0.64	64.30	7.20	Low
Husain et al. 2019	PIONEER 6	NCT02692716	- Semaglutide - Placebo	3183	0.68	66.00	7.00	Low
Marso et al. 2016	SUSTAIN 6	NCT01720446	- Semaglutide + standard-care regimen - Placebo + standard-care regimen	3297	0.61	64.60	7.40	Low
McGuire et al. 2025	SOUL	NCT03914326	- Oral semaglutide - Placebo"	9650	0.71	66.10	7.55	Low

Table 2 Numbers needed to treat for total MI (overall)

Outcome	Number of studies	Numbers needed to treat (95% confidence interval)	Follow-up time (Years)[a]
Total MI	15	NNTB 207 (NNTB 129 to NNTB 620)	3.48 ± 1.51 (Range: 1.55 to 5.47)
Fatal MI	6	NNTB 1744 (NNTB 401 to ∞ to NNTH 312)	4.15 ± 1.70 (Range: 3.27 to 5.47)
Non-Fatal MI	13	NNTB 208 (NNTB 123 to NNTB 931)	4.06 ± 1.18 (Range: 3.32 to 5.47)
MACE	12	NNTB 67 (NNTB 46 to NNTB 135)	3.48 ± 1.51 (Range: 1.55 to 5.47)
Stroke	11	NNTB 335 (NNTB 224 to NNTB 714)	3.48 ± 1.51 (Range: 1.55 to 5.47)
Coronary Revascularization	6	NNTB 93 (NNTB 52 to NNTB 1717)	3.45 ± 1.21 (Range: 3.27 to 3.96)
Cardiovascular Mortality	13	NNTB 170 (NNTB 120 to NNTB 306)	3.48 ± 1.51 (Range: 1.55 to 5.47)
Heart Failure	10	NNTB 551 (NNTB 119 to ∞ to NNTH 153)	4.10 ± 1.52 (Range: 3.27 to 5.47)
Unstable Angina	8	NNTB 2919 (NNTB 659 to ∞ NNTH 1031)	3.03 ± 1.18 (Range: 3.32 to 5.47)

When the numbers needed to benefit crosses infinity, it means that for the current outcome, no clear benefit for the outcome can be seen statistically

Legend: NNTB, Numbers needed to treat; NNTH, Numbers needed to harm; MI, Myocardial Infarction; MACE, Major Adverse Cardiovascular Events; ∞, Infinity

[a] Follow-up Time is presented in Mean ± Standard deviation (Range) unless stated otherwise

There were no significant differences for fatal MI, HF and unstable angina.

Comparison to insulin and glucose-lowering agents

Table 3 summarizes the comparison between the impact of GLP-1RA to other glucose-lowering agents on cardiovascular outcomes. GLP-1RA significantly reduces the rates of MACE (RR: 0.73, 95%CI: 0.69 to 0.79, $p = 0.01$), rates of coronary revascularization (RR: 0.61, 95%CI: 0.40 to 0.94, $p = 0.02$) and cardiovascular mortality RR: 0.43, 95%CI: 0.34 to 0.54, $p < 0.01$). However, no statistical differences were observed for other outcomes (MI, non-fatal MI, stroke, heart failure, unstable angina). Comparison with other glucose-lowering agents, comprising sulfonylurea, dipeptidyl peptidase 4 inhibitors (DPP4-I) and SGLT2i are summarized in Supplementary Material 5.

Sensitivity analysis based on prior ASCVD

Sensitivity analysis was conducted on the population with prior ASCVD events and summarized in Supplementary Material 6. In the secondary prevention population, the use of GLP-1RA led to significant reduction in unstable angina events (RR: 0.88, 95%CI: 0.82 to 0.95, $p = 0.03$) and coronary revascularization (RR: 0.78, 95%CI: 0.69 to 0.87, $p < 0.01$) compared to placebo. However, the rates of total MI and non-fatal MI were not significantly reduced in the prior ASCVD population (Total MI RR: 0.82, 95%CI: 0.49 to 1.36, $p = 0.23$;non-fatal MI RR: 0.87, 95%CI: 0.09 to 7.96, $p = 0.56$).

Sensitivity analysis based on T2DM

The effects of GLP-1RA in the T2DM population were largely congruent with the overall population, except for its effects on the rates of coronary revascularization. While the levels of risk reduction were similar (Overall RR: 0.85 vs. T2DM RR: 0.86), this effect did not achieve statistical significance within this analysis. The results of this sensitivity analysis is summarized in Supplementary Material 6.

Meta-regression on modulators of GLP-1RA effectiveness

Sufficient studies ($n \geq 10$) were available for the conductance of meta-regression on the following baseline, biochemical and demographic factors. Higher BMI was independently associated with reductions in total MI incidence (β: -0.09, 95%CI: -0.18 to -0.01, $p = 0.03$) with GLP-1RA use. On the other hand, the Asian ethnicity was associated with increased risk of total MI incidence with GLP-1RA use (β: 3.49, 95%CI: 0.95 to 6.03, $p = 0.01$).

Table 3 Effect on cardiovascular outcomes compared to placebo and insulin regimen

Outcomes	Number of Studies	Risk Ratio (95% Confidence Interval)	I^2	Cochran Q	*p*-value
Comparison to Placebo					
Total MI	15	0.86 (0.78 to 0.95)	47.10%	0.02	**< 0.01***
Fatal MI	6	0.87 (0.44 to 1.72)	32.80%	0.19	0.62
Non-fatal MI	13	0.87 (0.79 to 0.97)	38.30%	0.08	**0.02***
MACE	12	0.87 (0.80 to 0.93)	52.50%	0.02	**< 0.01***
Stroke	11	0.88 (0.82 to 0.94)	00.00%	0.82	**< 0.01***
Coronary Revascularization	6	0.85 (0.72 to 0.99)	72.00%	< 0.01	**0.04***
Cardiovascular Mortality	13	0.87 (0.82 to 0.93)	00.00%	0.50	**< 0.01***
Heart Failure	10	0.95 (0.75 to 1.19)	35.90%	0.12	0.60
Unstable Angina	8	0.97 (0.87 to 1.08)	00.00%	0.84	0.54

Age, sex and hemoglobin A1c (HbA1c) levels was not associated with total MI risk reduction. These findings are summarized in Table 4.

Safety analysis

Amongst the 16 safety domains (Supplementary Material 7), most of the side-effects were related to the gastrointestinal system. Patients taking GLP-1RA were at elevated risk of nausea (NNTH 8, RR: 3.56, 95%CI: 2.43 to 5.21, $p < 0.01$), vomiting (NNTH 9, RR: 3.99, 95%CI: 2.44 to 6.54, $p < 0.01$), diarrhea (NNTH 20, RR: 1.85, 95%CI: 1.33 to 2.59, $p < 0.01$), and constipation (NNTH 21, RR: 2.04, 95%CI: 1.46 to 2.83, $p < 0.01$). Overall, patients were 55% more likely to develop gastrointestinal side-effects (NNTH 8, RR: 1.55, 95%CI: 1.22 to 1.97, $p < 0.01$) compared to placebo. Other side effects included, but are not limited to, minor (NNTH 36, RR: 2.17, 95%CI: 1.38 to 3.43, $p = 0.03$), symptomatic (NNTH 22, RR: 1.78, 95%CI: 1.15 to 2.74, $p = 0.03$) hypoglycemic events, dizziness (NNTH 60, RR: 1.39, 95%CI: 1.03 to 1.87, $p = 0.04$) (Table 5).

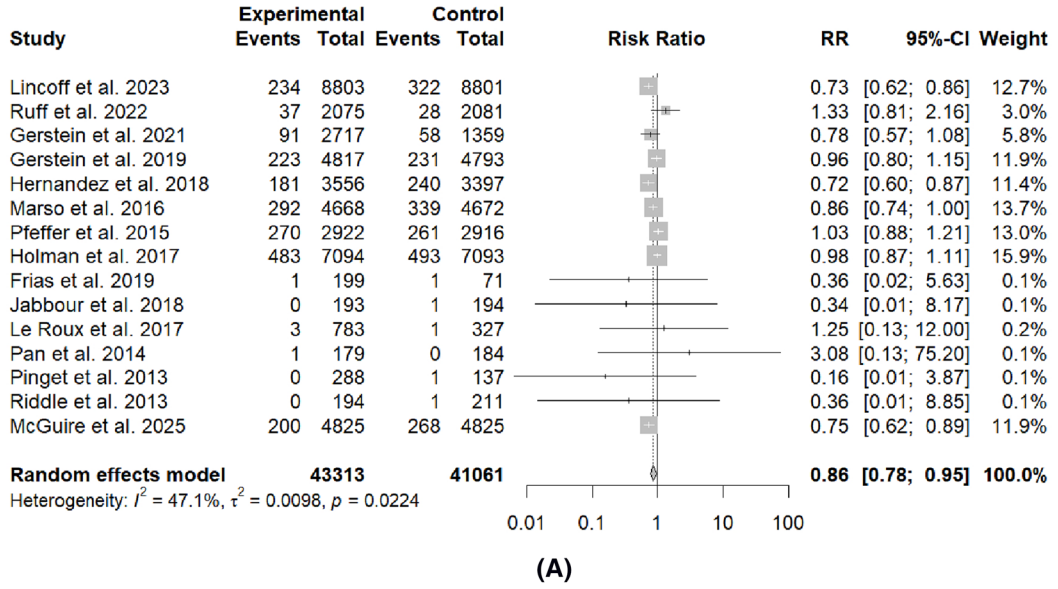
Publication bias and certainty of outcomes

From the visual assessment of funnel plots, there was no significant publication bias in the analysis of cardiovascular outcomes. The funnel plots are shown in Supplementary Material 8. Egger's regression performed also did not reveal any statistically significant publication bias, with $p < 0.05$ as the threshold for significance. The GRADE methodology was employed and the assessment noted moderate to high level of certainty in all the main outcomes Supplementary Material 9). Nonetheless, attenuation of the certainty of outcomes for total MI, fatal MI, MACE and coronary revascularization was attributed to the domain of inconsistency and imprecision.

Discussion

Current clinical practice guidelines [63, 64] recommend the use of GLP-1RA in patients with T2DM at high risk of ASCVD. While these guidelines are informed by the surmounting evidence of MACE reduction in the primary preventative cohort at risk of ASCVD [26], the present study adds to the current evidence by providing an in-depth assessment of clinical impact, in terms of the NNT, efficacy and safety of GLP-1RA on MI risk and the individual constituents of ASCVD risk reduction. There were several principal findings from the comprehensive evaluation of 25 trials enrolling over 109,846 participants. The therapeutic effect of GLP-1RA was observed with 14% risk reduction in total MI, although these effects should be interpreted in the context of the NNT of 207 to prevent one event of MI over a follow-up of 3.48 ± 1.51 years. However, the significant MI risk reduction was slightly attenuated in the population with T2DM (Overall RR: 0.86 vs. T2DM RR: 0.89) and in the secondary preventative cohort with prior ASCVD (Overall $p < 0.01$ vs. Prior ASCVD $p = 0.23$). Importantly, the meta-regression analysis revealed greater effectiveness in MI reduction in individuals with high BMI from early initiation of GLP-1RA. It is also notable that significant reduction in unstable angina and unplanned revascularization with the use of GLP-1RA was observed in the secondary preventative cohort, potentially translating to clinical impact in individuals with prior ASCVD events. The benefits in ASCVD risk reduction with GLP-1RA are evidenced by 14% risk reduction in cardiovascular mortality with an NNTB of 207 to prevent one event, 13% MACE reduction with an NNT of 67 to prevent one event and 12% risk reduction in stroke with an NNT of 335 to prevent one event, along with their favourable safety profile of 6% increased overall adverse events.

The ASCVD risk reduction of GLP-1RA is largely attributed to the 13% reduction of three-point MACE, which comprised of cardiovascular death, non-fatal MI and non-fatal stroke. However, little is known about the weight of each individual component's contribution to the overall composite risk reduction. Prior evidence suggested that, while GLP-1RA exhibits beneficial effects on MACE, the reduction of MI may not be the primary driver to the improvement of overall cardiovascular outcomes. These studies described an insignificant trend towards the risk reduction of fatal and non-fatal



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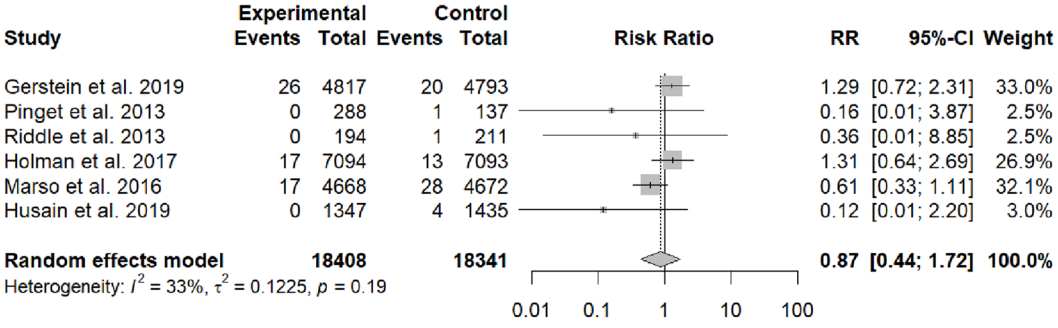

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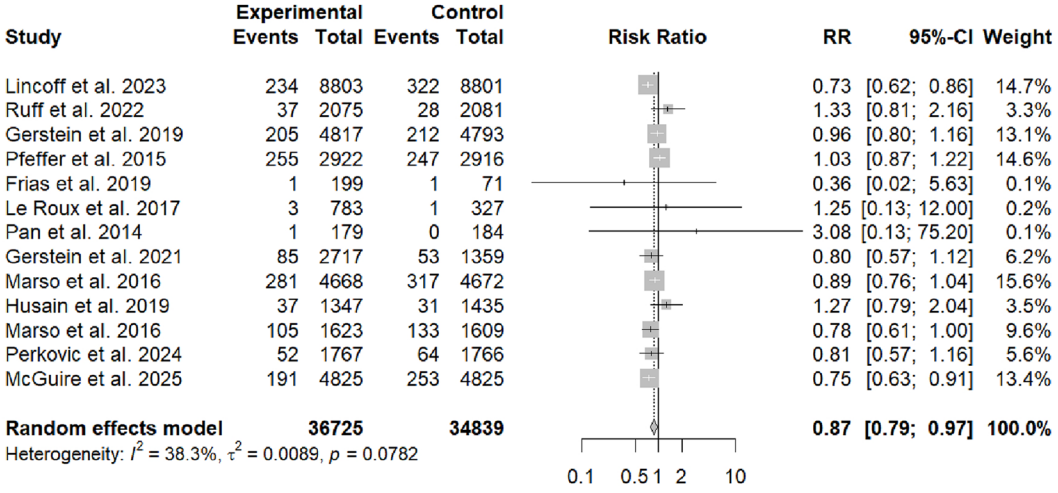
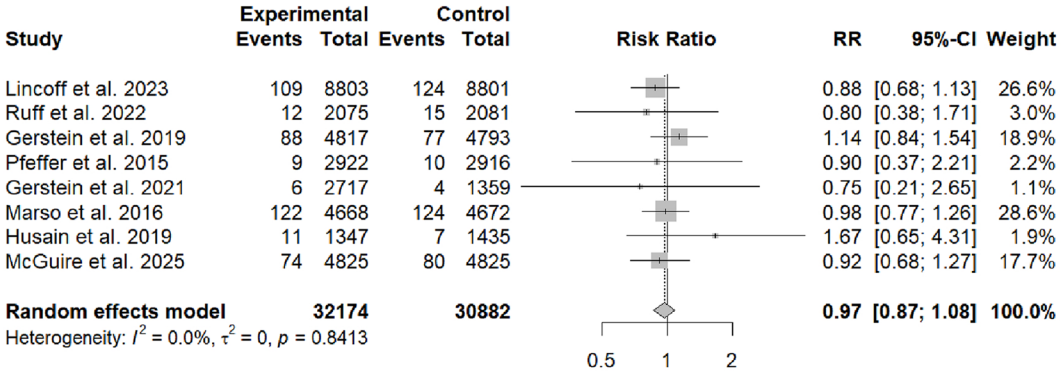


(C)

Fig. 2 Forest plots of cardiovascular outcome prevention compared to placebo



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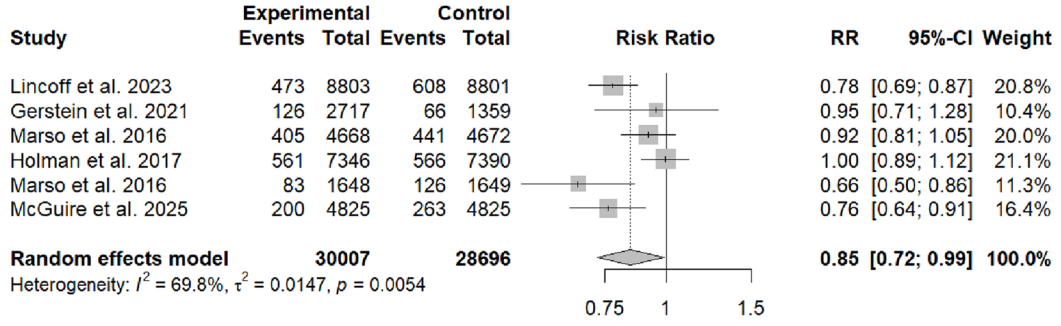

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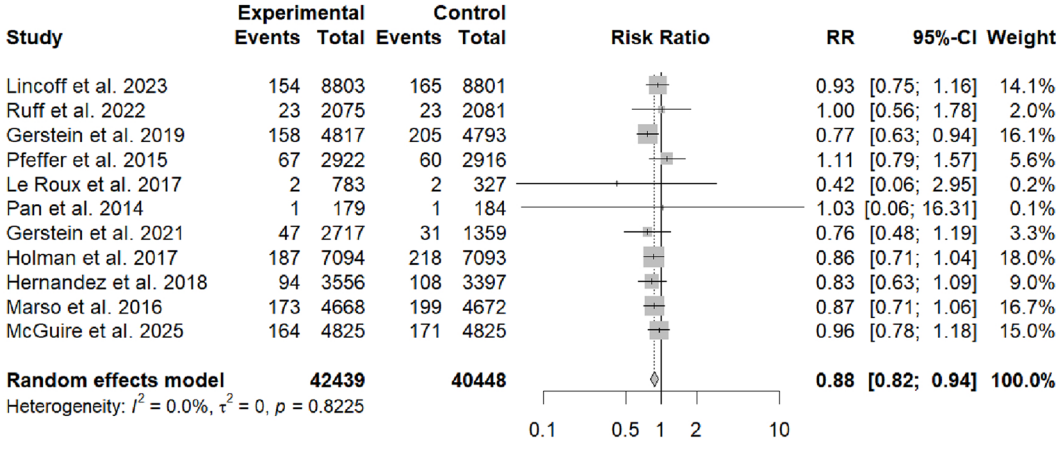
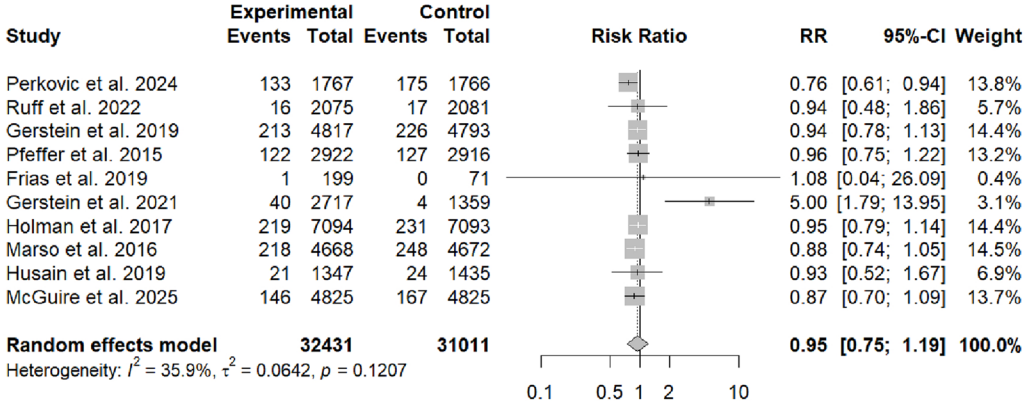


(F)

Fig. 2 (continued)

MI, as well as unstable angina [65–68]. Our study challenges current observations by demonstrating significant risk reduction of MI, with the use of GLP-1RA. Several mechanistic pathways have been hypothesized to underpin these clinical observations, which involves the influence of GLP-1RA on inflammatory, oxidative stress, and angiogenesis pathways in the atherosclerotic process [69–72].

GLP-1RA has comparable efficacy in MI risk reduction compared to current guideline-guided medical therapy in ASCVD prevention. The NNT for MI risk reduction over a course of five years has been reported to be 361 for aspirin [73], 104 for statins [74], and 100



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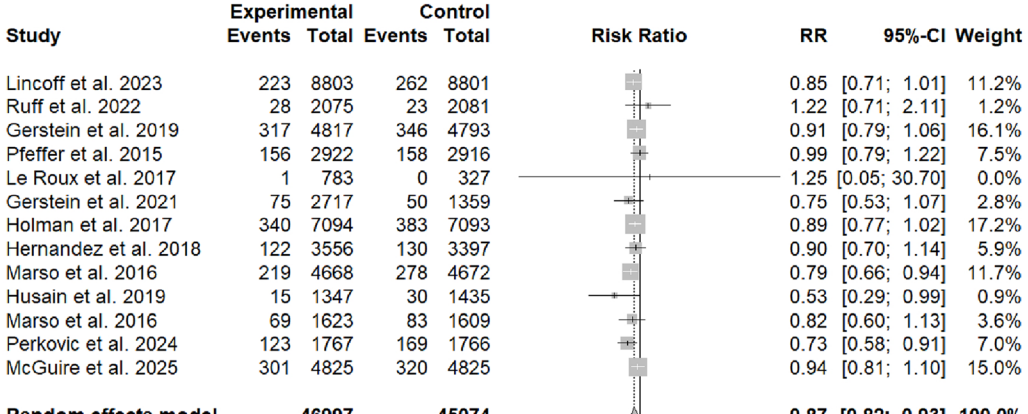

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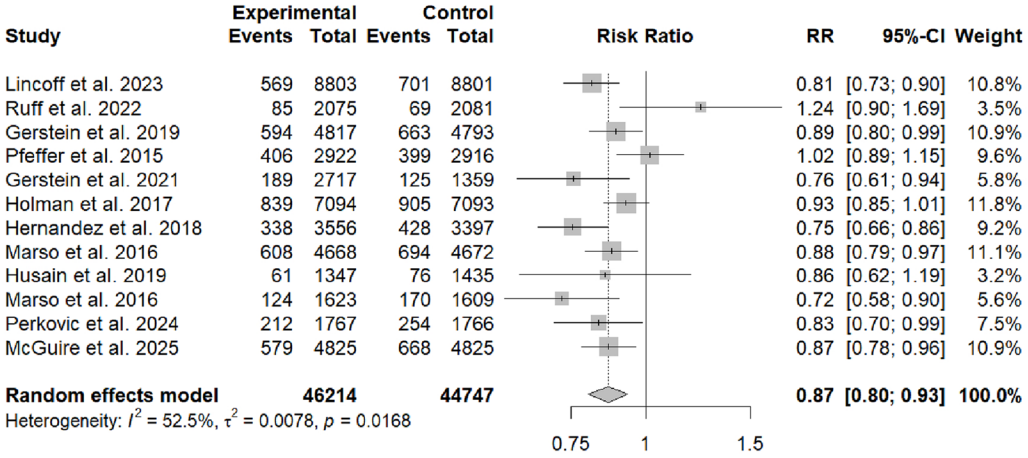

(I)

Fig. 2 (continued)

for anti-hypertensive medications [75], compared to the NNT of 207 for GLP-1RA. In terms of the individual MACE components, the present study informs clinicians that the impact of GLP-1RA, based on the NNT,

Table 4 Meta-regression of demographic factors on myocardial infarction compared to placebo

Demographic Factor	Number of Studies	Sample size	β coefficient (95% Confidence Interval)	*p*-value
Age	15	84,374	-0.02 (-0.06 to 0.03)	0.37
Male	15	84,374	-1.24 (-2.69 to 0.20)	0.09
Caucasian	14	83,969	0.21 (-1.51 to 1.93)	0.79
African American	11	64,727	0.30 (-4.10 to 9.91)	0.37
Asian	11	56,882	3.49 (0.95 to 6.03)	**0.01***
Bodymass Index	14	74,724	-0.09 (-0.18 to -0.01)	**0.03***
HbA1C	13	70,568	0.02 (-0.09 to 0.12)	0.76

Bolded *p* value with asterix (*) are of $p \leq 0.05$, denotingstatistical significance

Legend: HbA1C, hemoglobin A1C;

Table 5 Safety analysis (Numbers needed to Harm)

Outcome	Number of Studies	Numbers Needed to Harm (95% Confidence Interval)
Gastrointestinal		
Gastrointestinal side effects	8	NNTH 8 (NNTH 5 to NNTH 21)
Nausea	12	NNTH 8 (NNTH 5 to NNTH 14)
Vomiting	9	NNTH 12 (NNTH 7 to NNTH 25)
Diarrhea	12	NNTH 20 (NNTH 11 to NNTH 53)
Constipation	4	NNTH 21 (NNTH 12 to NNTH 46)
Endocrinology		
Minor hypoglycaemic events	2	NNTH 36 (NNTH 18 to NNTH 113)
Symptomatic hypoglycaemic events	3	NNTH 22 (NNTH 10 to NNTH 113)
Severe symptomatic hypoglycaemic events	7	NNTH 2307 (NNTH 82 to ∞ to NNTB 125)
Neurology		
Dizziness	4	NNTH 60 (NNTH 27 to NNTH 848)
Headache	6	NNTH 152 (NNTH 45 to ∞ to NNTB 162)
Hepatobiliary		
Overall pancreatitis	s5	NNTH 1743 (NNTH 368 to ∞ to NNTB 1612)
Acute Pancreatitis	5	NNTH 2550 (NNTH 523 to ∞ to NNTB 436)
Cholelithiasis	2	NNTH 459 (NNTH 132 ∞ to NNTB 670)
Rheumatology		
Severe allergic reactions	3	NNTH 425 (NNTH 42 to ∞ to NNTB 105)
Hypersensitivity syndrome or symptoms	2	NNTB 638 (NNTB 589 to NNTB 695)

When the numbers needed to harm crosses infinity, it means that for the current outcome, no clear harm for the outcome can be seen statistically

Legend: NNTH, Numbers needed to harm; TEAE, Treatment-emergent adverse events; ∞, Infinity;

is predominantly in the reduction of coronary revascularization risk, followed by total MI, then cardiovascular mortality, non-fatal MI and stroke. In addition, studies have shown that use of GLP-1RA has significant reduction in MI, CV mortality, and/or MACE in patients with a history of MI [12, 76], with our data demonstrating reduction in unstable angina and coronary revascularization risk in the secondary preventative cohort. The next important step will be to examine the cost effectiveness of GLP-1RA medications in patients following MI, and the role in further ASCVD risk reduction. Future studies are needed to compare the clinical impact of GLP-1RA, in terms of NNT, with other therapies in the pipeline that target the various pathways in the ASCVD process, such as bempedoic acid which has been associated with reduced risk of MI and coronary revascularization due to the improvement in lipid and inflammatory profiles [77]. However, the comparison of NNT across various drug classes must be nuanced given the NNT values are specific to individual trial design, study population baseline characteristics, and the time of outcome measurement.

The possibility that specific GLP-1RAs may differentially impact on MI risk cannot be dismissed. Four GLP-1RAs demonstrated similar degree of protection against total MI, with albiglutide associated with the lowest NNTB for total MI, followed by semaglutide, efpeglenatide, and liraglutide. While lixisenatide was found to be the only GLP-1RA subtype to increase the risk of MI, it is important to consider that the ELIXA trial, which studied lixisenatide in patients with T2DM, had the highest risk population as it included participants with recent acute coronary events in the past 180 days [40]. Moreover, the lack of cardiovascular benefits observed with lixisenatide may be contributed to its relatively short half-life [78]. Interestingly, our analysis revealed that the unfavorable impact of lixisenatide on MI rates was reversed upon the removal of the ELIXA trial [40] in the sensitivity analysis (NNTB: 569, 95%CI: NNTB 252 to ∞ to NNTH 10). In addition, our study revealed that exenatide demonstrated the least favorable NNTB profile in terms of MI risk reduction. This was partly contributed by the relatively higher discontinuation rate observed in the EXSCEL trial [55], which studied once-weekly exenatide on cardiovascular outcomes in T2DM, given that the study did not have a run-in period to optimize medication adherence. Together with the EXSCEL trial's shorter follow-up duration, this could have attenuated the significance in the study outcome. It will be important to consider the specific GLP1-RAs that have shown clear benefit in the reduction of MI risk when integrating them into contemporary primary and secondary ASCVD prevention guidelines.

Specific patient factors can modify the beneficial effect of GLP-1RA in MI risk reduction [79, 80]. The presence of obesity is intricately associated with the risk of ischemic heart diseases [81], associated with a dose–response relationship[82]. Our findings are suggestive that an increased BMI is associated with significantly larger MI

risk reduction with GLP-1RA. With weight reduction, GLP-1RA can improve dysregulated lipid profile and insulin resistance of individuals with obesity, thus reducing residual ASCVD risk [83–85]. In addition, GLP-1RA did not result in improvements in total MI and non-fatal MI compared to placebo, in our sensitivity analysis of the T2DM as well as the secondary prevention populations. This is likely attributable to the competing multimorbid status in the generally higher risk population with T2DM, that can attenuate the overall beneficial effects of GLP-1RA [86–88]. Some studies suggest that the beneficial effects of GLP-1RAs can be dampened by the deleterious effects of long-standing T2DM resulting in the reduced capacity to secrete insulin and diminished incretin effects, resulting in reduced glucose-lowering efficacy of GLP-1RA [89, 90]. While others have reported on the significant MACE reduction with GLP-1RA therapy in the secondary prevention cohort, but not in the primary prevention setting [91], our findings extend the current notion that the beneficial impact on the individual MACE constituents, particularly MI risk reduction, may be attenuated in the higher risk secondary preventative population with established CVD, often characterized by advanced age and multimorbidity status [90]. Taken together, this emphasizes the importance in timely initiation of GLP-1RA, targeting the primary preventive population with overweight/obesity, prior to the manifestation of T2DM and development of ASCVD [92–95].

In the context of heart failure, GLP-1RA were associated with a directionally favorable but statistically non-significant effect. This finding diverges from the results reported by Sattar et al. 2021 [96], wherein GLP-1RA therapy was linked to a statistically significant reduction in heart failure risk. A critical distinction lies in the substantially larger sample size of the present analysis—encompassing over 9,000 additional participants—which may confer greater statistical power and reliability. Furthermore, the current findings are concordant with those of Villaschi et a. 2024 [97], suggesting that earlier signals of cardioprotective benefit may have led to pre-mature conclusions. These inconsistencies underscore the necessity for additional high-powered methodologically rigorous trials to more definitively delineate the effect of GLP-1RA therapy on heart failure outcomes, thereby informing future revisions of clinical practice guidelines.

Moreover, emerging evidence has shown that the SGLT2i and GLP-1RA combination therapy was associated with fewer cardiovascular events in the population with T2DM and MI, compared to either drug used alone [98]. Both these classes can synergistically improve the plethora of metabolic risk factors and reduce peri-infarct tissue inflammation as well as infarct size molecular, thus improving myocardial remodeling post-infarct [99, 100]. This could further position GLP-1RA as part of a comprehensive cardiometabolic strategy, optimizing its potential synergistic cardiovascular benefit with SGLT2i.

GLP-1RA demonstrated mixed evidence on the reduction of MI, coronary revascularization, HF and/or cardiovascular mortality when compared to other glucose-lowering agents [101–104]. Several studies reported larger risk reduction in coronary revascularization by 44% when compared to sulfonylurea[41] and DPP-4I[46]. Our study postulates improved MI rates, albeit statistically non-significant, with the use of GLP-1RA compared to other glucose-lowering agents. Larger head-to-head analysis comparing GLP-1RA and other glucose lowering agents are needed to evaluate the effects on atherosclerosis and plaque regression [95, 105, 106].

Limitations

This study has its limitations. First, in composite outcomes such as MACE, differences in definition introduce heterogeneity in the analysis as seen in Supplementary Material 2. Thus, caution should be taken in the interpretation of the NNT and RRs derived from the MACE analysis. Second, most studies included participants with T2DM, except the SELECT trial. Therefore, generalizing the MI reduction effect on populations without T2DM must be done with caution. Further analyses are warranted to examine the cardioprotective effects of GLP-1RA in this subgroup without T2DM. Third, the included studies consisted mostly of mixed prior and non-prior ASCVD patients, preventing a direct comparison of the utility of GLP-1RA between primary and secondary prevention cohorts. Future study designs with homogeneous inclusion criteria are warranted to delineate primary and secondary prevention cohorts to facilitate more informative interpretation of the effects and safety of GLP-1RA. Fourth, despite the mounting evidence of the clinical impact of GLP-1RA on MACE reduction, the present study extends the current literature on the clinical impact and efficacy of GLP-1RA on the MI risk reduction and its individual ASCVD components. However, comparisons with novel glucose-lowering medications (e.g. SGLT2i) and other newer GLP-1RA medications such as the dual GIP and GLP-1RA medications (tirzepatide and mazdutide) on their effectiveness in ASCVD risk reduction remain lacking. Thus, future studies are warranted to examine a head-to-head or indirect comparison through network meta-analyses to compare the clinical utility in ASCVD risk reduction across these emerging pharmacotherapies. Fifth, other studies have reported high one-year discontinuation rates (64.8% in non-T2DM and 46.5% in T2DM cohorts) and low 1-year re-initiation rates of GLP-1RA (36.3% in non-T2DM and 47.3% in T2DM cohorts), largely contributed by moderate or severe incident gastrointestinal adverse events and lower income status [107–111]. As

such, suboptimal medication adherence and access can underestimate long-term ASCVD risk reduction correlates associated with GLP-1RA therapy. Sixth, the current estimates for NNT show large uncertainty, as seen with wide confidence intervals in some of the NNT results. This is largely owing to trial variability, incorporation of trials with smaller scale trials reporting on MI rates [44, 47, 48, 51, 52, 59], the heterogeneity of the study population, and incorporation of zero total event trials in the current analysis [47, 48, 51, 52, 59]. Though this has been shown to lead to larger variability, numerous simulation papers have shown that this leads to a more conservative estimate and allows for the most generalizable estimate of treatment effect. Nevertheless, larger-scale research with harmonized study endpoints of ASCVD risk should be done to better clarify the overall treatment effect of GLP-1RA in cardiovascular outcomes.

Conclusions

In this meta-analysis of 100,196 patients, across the full spectrum of those with and without prior ASCVD and/or T2DM, GLP-1RA demonstrated significant reduction of MI risk by 12% with NNT of 248 to prevent one event of MI. This benefit was more pronounced in those with higher BMI. In the secondary preventative cohort, GLP-1RA may be considered for its significant reduction in unstable angina and coronary revascularization risk. Relative to its clinical impact on MI reduction, measured by NNT, GLP-1RA was more effective in preventing 1 event of cardiovascular mortality and MACE. Together with its favorable safety profile, the evidence supports the role of GLP-1RA as part of therapy in overall ASCVD risk reduction, especially in the cohort with high BMI.

Abbreviations

GLP1-RA	Glucagon like peptide-1 receptor agonist
ASCVD	Atherosclerotic cardiovascular disease
MACE	Major adverse cardiovascular events
NNT	Numbers Needed to Treat
MI	Myocardial Infarction
CVD	Cardiovascular Disease
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
LEADER	Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results
T2DM	Type 2 Diabetes mellitus
SELECT	Semaglutide effects on cardiovascular outcomes in people with overweight or obesity
PREVENT	Predicting risk of cardiovascular disease events
HF	Heart Failure
PRISMA	Preferred reporting items for systematic review and meta-analyses
RCT	Randomized controlled trial
BMI	Body mass index
RR	Risk ratio
NNTB	Numbers needed to benefit
NNTH	Number needed to harm
ROB-2	Cochrane risk of bias 2 (ROB-2) tool
FLOW	Evaluate renal function with semaglutide once weekly

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02840-3.

Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
Supplementary Material 4
Supplementary Material 5
Supplementary Material 6
Supplementary Material 7
Supplementary Material 8
Supplementary Material 9
Supplementary Material 10

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Author contributions

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures and tables has not been previously published, and the manuscript is not under consideration elsewhere.Conceptualization and Design: MAM, YHC, NWCAcquisition of Data: ASPT, JTYH, SKSC, JQ, GS, FS, KECAnalysis and Interpretation of Data: ASPT, VVA, BC, YHC, NWSCWriting– original draft: ASPT, JTYH, SKSC, JQ, GS, FS, KEC, VVA, BC, AM, SAT, MM, GKD, CWLR, MYC, MAM, YHC, NWSCWriting– review & editing: ASPT, JTYH, SKSC, JQ, GS, FS, KEC, VVA, BC, AM, SAT, MM, GKD, CWLR, MYC, MAM, YHC, NWSC.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from IRB review as no confidential information was involved.

Consent for publication

Not applicable.
All other authors of the manuscript do not have a conflict of interest to declare.

Authorship statement

All authors approve the final version of the manuscript, including the authorship list and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Presentations

No part of this manuscript or its contents have been presented in any capacity outside of this manuscript as of the time of submission.

Registration and protocol
This review was registered on the Open Science Framework (OSF) registries prior to conduction (https://doi.org/10.17605/OSF.IO/7VXN5).

Competing interests
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