

Clinical Outcomes Associated With GLP-1 Receptor Agonists for Diabetes and Obesity: A High-Throughput Meta-Analysis of 35 Randomized Placebo-Controlled Trials

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Background

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed the management of type 2 diabetes (T2D) and obesity by improving glycemic control, promoting weight loss, and reducing cardiovascular risk^{1–4}. Several large cardiovascular outcome trials have demonstrated that GLP-1RAs reduce major adverse cardiovascular events and improve a range of cardiometabolic outcomes^{5–7}. More recently, their therapeutic indications have expanded beyond glycemic management to include obesity, cardiovascular disease, chronic kidney disease, and heart failure^{8–10}. As the use of GLP-1RAs continues to increase globally, a comprehensive understanding of their overall benefit and risk profile has become increasingly important. Most randomized trials and conventional meta-analyses have focused on prespecified efficacy endpoints and a limited number of commonly recognized adverse events, such as gastrointestinal intolerance and pancreatitis^{11–13}. However, these approaches may overlook less frequent but potentially clinically important adverse outcomes that emerge only when large datasets are systematically examined. High-throughput approaches that evaluate the full spectrum of reported adverse events across clinical trials provide an opportunity to identify both established and emerging safety signals. Therefore, we conducted a high-throughput meta-analysis of randomized placebo-controlled trials to systematically evaluate the broad spectrum of clinical outcomes associated with GLP-1RAs in adults with T2D or overweight/obesity.

Methods

We conducted a systematic search of ClinicalTrials.gov from database inception through March 31, 2026, to identify placebo-controlled randomized clinical trials evaluating GLP-1RAs in adults with T2D or overweight/obesity. Eligible studies enrolled at least 500 participants, reported trial results, and included serious adverse event data. GLP-1RAs evaluated including semaglutide, tirzepatide, liraglutide, dulaglutide, exenatide, and lixisenatide, across multiple therapeutic indications. Serious adverse events were extracted and harmonized using the Medical Dictionary for Regulatory Activities (MedDRA), version 26.0, at the preferred-term level¹⁴. To ensure sufficient statistical power and reliability, outcomes were eligible for meta-analysis if they were reported in at least three trials and included a minimum of 10 total events across studies.

We performed a high-throughput meta-analysis by separately evaluating each eligible serious adverse event. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using random-effects models to account for between-study variability. Between-study heterogeneity was assessed and quantified using the I^2 statistic¹⁵. To improve the robustness of inference, particularly for outcomes with a limited number of contributing trials, we applied the Hartung–Knapp–Sidik–Jonkman (HKSJ) method to calculate confidence intervals^{16,17}. For studies with zero events in one treatment arm, a continuity correction of 0.5 was applied¹⁸. Given the large number of outcomes evaluated, statistical significance was assessed using both nominal P values and false

discovery rate (FDR) correction at 5% to account for multiple testing¹⁹. Outcomes that remained significant after FDR adjustment were considered robust associations. All analyses were conducted using R software.

Results

Of 2,123 GLP-1RA trials identified in ClinicalTrials.gov, a total of 35 placebo-controlled randomized trials involving 103,230 participants met the inclusion criteria. Across these studies, 737 serious adverse event outcomes were eligible for evaluation. Of these, 82 outcomes reached nominal statistical significance ($P < 0.05$), and 29 remained significant after controlling the FDR at 5% (**Figure 1**).

GLP-1RA therapy was associated with significant reductions in several major cardiovascular outcomes. The risk of acute myocardial infarction was reduced by 23% (RR 0.77, 95% CI 0.71–0.84), while the risk of cerebrovascular accident was reduced by 21% (RR 0.79, 95% CI 0.70–0.90). GLP-1RAs were associated with reduced risk of diabetic metabolic decompensation (RR, 0.43; 95% CI, 0.32–0.57; FDR = .02), poorly controlled diabetes (RR, 0.59; 95% CI, 0.46–0.77; FDR = .01), and obesity (RR, 0.47; 95% CI, 0.28–0.77; FDR = .046). Beyond cardiometabolic outcomes, GLP-1RAs were associated with substantially lower risks of severe infectious complications. The risk of sepsis was reduced by 63% (RR 0.37, 95% CI 0.29–0.47), and the risk of septic shock was reduced by 35% (RR 0.65, 95% CI 0.54–0.78).

Consistent with previous evidence, GLP-1RA therapy was associated with an increased risk of gastrointestinal adverse events, including vomiting (RR 1.69, 95% CI 1.32–2.17) and diarrhea (RR 1.54, 95% CI 1.21–1.96). An elevated risk of pancreatitis (RR 1.56, 95% CI 1.22–1.99) and inguinal hernia (RR, 1.53; 95% CI, 1.21–1.92) was also identified. Our analysis identified several less common but potentially important safety signals. These included retinal artery occlusion (RR, 2.68; 95% CI, 1.86–3.86), craniofacial fractures (RR, 3.63; 95% CI, 2.51–5.25), pelvic fractures (RR, 1.85; 95% CI, 1.31–2.62), dehydration (RR, 1.44; 95% CI, 1.23–1.6), syncope (RR, 1.22; 95% CI, 1.09–1.36), and increased amylase levels RR, 2.95; 95% CI, 1.88–4.62).

Conclusion

In this high-throughput meta-analysis of 35 randomized trials involving more than 100,000 participants, GLP-1RAs showed a favorable benefit–risk profile, with significant reductions in cardiovascular and severe infectious outcomes but increased risks of gastrointestinal adverse events, pancreatitis, and several less common adverse outcomes. These findings confirm established benefits and risks while identifying emerging safety signals that warrant further investigation. Continued pharmacovigilance, mechanistic studies, and real-world evaluations are needed to clarify the clinical significance of these associations and inform the safe and effective use of GLP-1RAs.

References

1. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients With Type 2 Diabetes. *Circulation*. 2022;146(24):1882-1894.
2. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. *BMJ*. 2024;384:e076410.
3. Rosen CJ, Ingelfinger JR. GLP-1 Receptor Agonists. *N Engl J Med*. 2026;394(13):1313-1324.
4. Drucker DJ. The expanding landscape of GLP-1 medicines. *Nat Med*. 2026;32(1):47-57.
5. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2019;381(9):841-851.
6. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
7. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(13):1228-1239.
8. eClinicalMedicine. GLP-1 receptor agonists beyond diabetes management. *eClinicalMedicine*. 2024;78.
9. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023;389(12):1069-1084.
10. Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *N Engl J Med*. 2024;391(2):109-121.
11. Tang H, Zhang B, Lu Y, et al. Assessing the benefit–risk profile of newer glucose-lowering drugs: A systematic review and network meta-analysis of randomized outcome trials. *Diabetes Obes Metab*. 2025;27(3):1444-1455.
12. Lu Y, Tang H, Kotecha P, et al. Newer Glucose-Lowering Drugs and risk of Suicidal Ideation and Behaviors: a Network Meta-Analysis of Randomized Outcome Trials. *Diabetes Obes Metab*. 2024;26(10):4783.
13. Tang H, Lu Y, Okun MS, et al. Meta-analysis of Association between Newer Glucose-Lowering Drugs and Risk of Parkinson’s Disease. *Mov Disord Clin Pract*. 2023;10(11):1659-1665.
14. MedDRA. What’s New MedDRA Version 26.0. Published online March 2023. https://admin.meddra.org/sites/default/files/guidance/file/whatsnew_26_0_English.pdf
15. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods*. 2006;11(2):193-206.
16. Int’Hout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25.
17. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med*. 2014;160(4):267-270.

18. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol.* 2007;7:5.
19. Mehrotra DV, Adewale AJ. Flagging clinical adverse experiences: reducing false discoveries without materially compromising power for detecting true signals. *Stat Med.* 2012;31(18):1918-1930.