[1] Division of Cardiology, Lahey Clinic, Burlington, MA 01805, USA

Correspondence to: S Ganatra
sarju.ganatra@lahey.org

Cite this as: *BMJ* 2026;394:e100366
http://doi.org/10.1136/bmj-2026-100366

Tirzepatide and cardiovascular outcomes

A credible signal, not a causal verdict

Sourbha , S Dani, [1] Arjun Jayakumar, [1] Sarju Ganatra[1]

After the SURPASS-CVOT (A Study of Tirzepatide Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes) trial showed that tirzepatide was non-inferior but not superior to dulaglutide, the unresolved question was not whether tirzepatide matched another effective incretin, but how much cardiovascular benefit it might add over a glucose lowering strategy with neutral cardiovascular effects.[1] In a linked observational study, Krüger and colleagues (doi:10.1136/bmj-2026-100011) address that question using two US claims databases.[2] They compared new users of tirzepatide with new users of sitagliptin among 52 971 adults aged 40 years or older with type 2 diabetes, a body mass index of at least 25, and established atherosclerotic cardiovascular disease—previous myocardial infarction, ischaemic stroke, or coronary, carotid, or peripheral arterial disease documented by diagnosis or revascularisation.[2]

The primary outcome requires careful reading. Major adverse cardiovascular events were defined as myocardial infarction, stroke, and all cause mortality, not cardiovascular death. After propensity score overlap weighting, the one year risk was 2.9% with tirzepatide and 4.4% with sitagliptin (hazard ratio 0.68, 95% confidence interval 0.58 to 0.80; number needed to treat 70).[2] Yet the components tell a more nuanced story: myocardial infarction was lower (hazard ratio 0.67, 0.52 to 0.87), stroke was not (0.91, 0.64 to 1.28), and the composite of myocardial infarction or stroke was 0.74 (0.61 to 0.91). All cause mortality showed the largest association 0.55 (0.42 to 0.72). The expanded atherosclerotic composite, adding revascularisation and unstable angina, yielded 0.92 (0.85 to 0.99).[2] Thus, the study supports a cardiovascular signal, particularly for myocardial infarction, but its magnitude depends substantially on outcome definition.

Methodologically, this is rigorous observational research. Krüger and colleagues pre-registered a target trial protocol, used a new user active comparator design, replicated analyses in two claims databases (Optum and MarketScan), applied overlap weighting, and benchmarked against previous emulations of SURPASS-CVOT and SUSTAIN-6 (comparing semaglutide with the placebo proxy sitagliptin).[2-4] Negative control outcomes were reassuring, and as-started (intention-to-treat analogue) and competing risk analyses were consistent. These safeguards strengthen credibility, but they do not recreate randomisation. Before weighting, tirzepatide users were younger and had fewer comorbidities compared with sitagliptin users; claims cannot fully capture frailty, prognosis, health seeking behaviour, or the ability to obtain and persist with a newer injectable treatment. Median on-treatment follow-up was only four to five months, although risks were estimated to one year. The overlap weighted estimand also applied principally to patients for whom either treatment was plausible, not to every eligible patient.

The mortality and infection findings expose this uncertainty. Tirzepatide was associated with lower all cause mortality, infection related mortality (hazard ratio 0.40), and infections requiring hospital admission (0.64).[2] These findings should neither be dismissed as biologically impossible nor accepted as causal. Weight loss, improved glycaemia, reduced systemic inflammation, better renal metabolic health, and improved obesity related comorbidity could plausibly reduce infection and non-atherosclerotic risk. Glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide signalling may also influence vascular inflammation, endothelial function, thrombosis, and myocardial energetics beyond weight loss.[5 6] But the speed and magnitude of benefit, together with previous benchmarking suggesting preferential sitagliptin prescribing in frailer patients with shorter life expectancy, also fit residual channelling and healthy user effects. Our observational study found favourable cardiovascular outcomes with tirzepatide versus GLP-1 receptor agonists, reinforcing the signal but not resolving causality.[7]

Sitagliptin is both a strength and a limitation. Its cardiovascular neutrality makes it a defensible placebo proxy and avoids comparing tirzepatide with a treatment known to reduce cardiovascular events.[8] However, this is comparative initiation, not random assignment of tirzepatide versus placebo on an identical background regimen, and it does not settle contemporary treatment sequencing. In patients with diabetes and established cardiovascular disease, clinicians must decide how tirzepatide fits alongside metformin, SGLT-2 (sodium-glucose cotransporter-2) inhibitors, and GLP-1 receptor agonists with established outcome data. SGLT-2 inhibitors were used by 21% of the cohort. In post hoc analyses, tirzepatide remained associated with lower major adverse cardiovascular events among users (0.55) and non-users (0.73).[2] This consistency is encouraging, but it does not prove incremental benefit over optimised SGLT-2 therapy: background treatment was not randomised, duration and adherence were incompletely observed, and the manuscript does not show a treatment-by-SGLT-2 interaction.

The findings nevertheless triangulate with randomised evidence. SURPASS-CVOT reported a hazard ratio of 0.92 for tirzepatide versus dulaglutide,

narrowly missing superiority; dulaglutide had reduced events versus placebo in REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes).[9 10] The identical 0.92 estimate for the expanded atherosclerotic composite here is reassuring, while cautioning against treating the mortality inclusive 0.68 estimate as a definitive treatment effect.

Krüger and colleagues provide an important, transparent estimate of what initiating tirzepatide might achieve in routine care. The study strengthens confidence in cardiovascular safety and supports possible reduction in atherosclerotic events, but it does not establish a mortality indication or define the best sequence of cardiometabolic therapy. Longer follow-up, randomised and pragmatic comparisons, and more studies of additive benefit on contemporary background treatment are needed. Access deserves one final sentence: cardiovascular efficacy cannot benefit a population when cost, authorisation barriers, supply, and discontinuation prevent sustained treatment. The signal is compelling; the causal and clinical placement questions remain open.

Competing interests: The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: None. Further details of The BMJ policy on financial interests is here.

AI use: AI was not used to write the manuscript. MS Windows and Grammarly were used in the preparation of the manuscript and these may have integrated AI tools or features.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Nicholls SJ, Pavo I, Bhatt DL, etal. Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes. *N Engl J Med* 2025;393:-20. pmid: 41406444. doi: 10.1056/NEJMoa2505928

2 Krüger N, Schneeweiss S, Wang SV. Tirzepatide and the risk of atherosclerotic cardiovascular events: population based cohort study. *BMJ* . 2026;394:e100011.

3 Krüger N, Schneeweiss S, Desai RJ, etal. Cardiovascular outcomes of semaglutide and tirzepatide for patients with type 2 diabetes in clinical practice. *Nat Med* 2026;32:-52. pmid: 41207920. doi: 10.1038/s41591-025-04102-x

4 Wang SV, Schneeweiss SRCT-DUPLICATE Initiative, etal. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA* 2023;329:-85. pmid: 37097356. doi: 10.1001/jama.2023.4221

5 Hammoud R, Drucker DJ. Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. *Nat Rev Endocrinol* 2023;19:-16. pmid: 36509857. doi: 10.1038/s41574-022-00783-3

6 Packer M, Zile MR, Kramer CM, etal. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med* 2025;392:-37. pmid: 39555826. doi: 10.1056/NEJMoa2410027

7 Dani SS, Makwana B, Khadke S, etal. An Observational Study of Cardiovascular Outcomes of Tirzepatide vs Glucagon-Like Peptide-1 Receptor Agonists. *JACC Adv* 2025;4:. pmid: 40447342. doi: 10.1016/j.jacadv.2025.101740

8 Green JB, Bethel MA, Armstrong PW, etal. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015;373:-42. pmid: 26052984. doi: 10.1056/NEJMoa1501352

9 Nicholls SJ, Pavo I, Bhatt DL, etal. Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes. *N Engl J Med* 2025;393:-20. pmid: 41406444. doi: 10.1056/NEJMoa2505928

10 Gerstein HC, Colhoun HM, Dagenais GR, etal. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *The Lancet* 2019;394:-30. doi: 10.1016/S0140-6736(19)31149-3