SURPASS-CVOT – Tirzepatide demonstrates cardiovascular benefit in secondary prevention

Over a median of 4 years, tirzepatide at doses up to 15 mg was as effective at reducing a composite of cardiovascular events as dulaglutide 1.5 mg in this cardiovascular outcomes trial in people with type 2 diabetes aged ≥50 years with cardiovascular disease (CVD), published in the *New England Journal of Medicine*. In the REWIND cardiovascular outcomes trial, dulaglutide 1.5 mg had previously demonstrated significant reductions in major adverse cardiovascular events compared to placebo in people with type 2 diabetes, with no significant difference between those with and without CVD at baseline. Since GLP-1 receptor agonists are known to have beneficial impacts on cardiovascular events, it was deemed unethical to randomise people with type 2 diabetes and known CVD to placebo, and hence dulaglutide was chosen as an appropriate active comparator. In SURPASS-CVOT, the composite primary endpoint (cardiovascular death or non-fatal myocardial infarction or stroke) occurred in 12.2% of those treated with tirzepatide, compared to 13.1% in those treated with dulaglutide, confirming non-inferiority of tirzepatide and thus demonstrating cardiovascular benefit in this high-risk population with CVD at baseline.

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Although it was anticipated that the GIP/GLP-1 receptor agonist tirzepatide, similar to the GLP-1 RAs liraglutide, dulaglutide and semaglutide, would demonstrate cardiovascular benefit, this has not yet been confirmed in a cardiovascular outcomes trial. Since it was deemed unethical to treat people with established cardiovascular disease (CVD) and type 2 diabetes (who are at high risk of future cardiovascular events) with placebo, the present study, SURPASS-CVOT, was the first cardiovascular outcomes trial to use an active comparator: in this case, dulaglutide 1.5 mg weekly, which had previously been proven to have cardiovascular benefit in the REWIND trial (Gerstein et al, 2019).

In REWIND, one-third of participants had established CVD and the remainder had cardiovascular risk factors. Over a median follow-up of 5.4 years, the primary composite outcome of 3-point major adverse cardiovascular events (MACE; first occurrence of cardiovascular death, non-fatal stroke or non-fatal myocardial infarction) occurred in 12% of dulaglutide recipients (2.4 events per 100 person-years) and 13.4% of placebo recipients (2.7 events per 100 person-years, a hazard ratio of 0.88; 95% confidence interval 0.79–0.99).

Each of the three individual outcomes demonstrated benefit with dulaglutide, with possibly a greater effect on stroke than myocardial infarction. The hazard ratio was similar in those with and without established CVD at baseline, suggesting that dulaglutide may have benefit in both these groups. All-cause mortality risk was similar between dulaglutide and placebo.

The present study (Nicholls et al, 2025)

SURPASS-CVOT (Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes) was a double-blind, randomised, active-comparator study to determine non-inferiority of tirzepatide 15 mg (or highest tolerated dose) versus dulaglutide 1.5 mg in terms of 3-point MACE, in people aged ≥50 years with type 2 diabetes and established CVD. The 13 299 randomised participants had a mean BMI of 32.6 kg/m^2, mean HbA_{1c} of 68 mmol/mol (8.4%) and mean type 2 diabetes duration of nearly 15 years.

Citation: Brown P (2026) Diabetes Distilled: SURPASS-CVOT – Tirzepatide demonstrates cardiovascular benefit in secondary prevention. *Diabetes & Primary Care* **28**: [Early view publication]

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Over 97% of participants were taking glucose-lowering therapy at baseline, including almost one-third who were receiving an SGLT2 inhibitor and nearly 50% who were receiving insulin. Only 29% of participants were female, compared with 46.3% in the REWIND study.

Key secondary endpoints included the three individual MACE endpoints separately, all-cause mortality, 4-point MACE (3-point MACE plus coronary revascularisation), renal outcomes, and changes from baseline in HbA_{1c}, body weight, systolic blood pressure, triglycerides and LDL cholesterol.

Non-inferiority of tirzepatide to dulaglutide for the primary outcome was defined as an upper limit of less than 1.05 for the 95.3% confidence interval. If this was met, superiority would be defined as an upper limit of less than 1.0 for the 95.3% confidence limit.

Results

Over a median of 4 years, in the tirzepatide group versus the dulaglutide group:

- The primary composite endpoint occurred in 12.2% versus 13.1% (HR 0.92; 95.3% CI 0.83–1.01).
  - ➤ Non-inferiority was confirmed per the definitions above, but not superiority.
- Cardiovascular death occurred in 5.6% versus 6.2% (HR 0.89).
- Non-fatal myocardial infarction occurred in 4.7% versus 5.4% (HR 0.86).
- Non-fatal stroke occurred in 3.5% versus 3.8% (HR 0.91).

Mortality outcomes were prespecified secondary endpoints:

- Death from any cause occurred in 8.6% versus 10.2% (HR 0.84; 95% CI 0.75–0.94).
- Death from non-cardiovascular causes occurred in 3% versus 4% (HR 0.75; 95% CI 0.63–0.91).

The latter two findings suggest possible superiority of tirzepatide versus dulaglutide but should be considered exploratory; further analyses are required to confirm these findings.

The study confirmed the metabolic benefits of tirzepatide compared to dulaglutide, including a 9 mmol/mol difference in HbA_{1c} reduction, 6.8% greater weight loss, decreased triglycerides and a small 2 mm decrease in systolic blood pressure.

Around 20% of each group discontinued the trial drugs during the study, and around 75% of those randomised to tirzepatide were on the 15 mg dose at 36 months.

Limitations include the lack of a placebo group, the fact that more than 80% of participants were of White ethnicity, and that tirzepatide was only assessed in people with type 2 diabetes and CVD. There may also have been differences in SGLT2 inhibitor initiation between the groups during the study. A placebo-controlled cardiovascular outcomes trial of tirzepatide in people with obesity at high cardiovascular risk but without type 2 diabetes, SURMOUNT-MMO, is underway.

Implications for practice

SURPASS-CVOT is the first cardiovascular outcomes trial to use an active comparator, so it is important for clinicians to understand why this format was used. Since cardiovascular benefits had been demonstrated previously for liraglutide, dulaglutide and injectable semaglutide, it would not have been ethical to enrol people with type 2 diabetes and CVD, who are at high risk of further cardiovascular events, into a long-term study in which 50% would receive placebo.

It has been many years since REWIND, the cardiovascular outcomes study of dulaglutide, was published, and to fully appreciate the non-inferiority for MACE demonstrated here, clinicians need to understand the cardiovascular benefits achieved with 1.5 mg dulaglutide in REWIND, namely a significant 12% reduction in MACE compared with placebo. The effects did not differ in those with or without CVD at study entry.

SURPASS-CVOT, by confirming non-inferiority of tirzepatide to dulaglutide as used in the REWIND study, means that tirzepatide now has demonstrated cardiovascular benefits in people with type 2 diabetes and established CVD. Further *post hoc* analyses are underway, and the ongoing SURMOUNT-MMO trial will help clarify whether tirzepatide has cardiovascular benefits in people without CVD and in the wider population with obesity who have not developed type 2 diabetes.

Until now, many clinicians have preferred to "follow the evidence" and prescribe injectable semaglutide in preference to oral semaglutide

or tirzepatide for people with type 2 diabetes and established CVD. However, thanks to the present results, and the SOUL cardiovascular outcomes trial of oral semaglutide confirming cardiovascular benefits in people with type 2 diabetes and CVD (McGuire et al, 2025), we now have more evidence-based drug options for the people we support. Some people prefer an oral drug, and some will benefit from the weight loss and HbA_{1c}-lowering achievable with tirzepatide, and now we can prescribe these agents and be assured of the cardiovascular benefits for this highest-risk group. ■

Gerstein HC, Colhoun HM, Dagenais GR et al; REWIND investigators (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. *Lancet* **394**: 121–30

McGuire DK, Marx N, Mulvagh SL et al; SOUL Study Group (2025) Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. *N Engl J Med* **392**: 2001–12

Nicholls SJ, Pavo I, Bhatt DL et al; SURPASS-CVOT investigators (2025) Cardiovascular outcomes with tirzepatide versus dulaglutide in type 2 diabetes. *N Engl J Med* **393**: 2409–20

Cardiovascular outcomes with tirzepatide versus dulaglutide in type 2 diabetes

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Practice points

1. Evidence now confirms that tirzepatide has cardiovascular benefits in people with type 2 diabetes and established cardiovascular disease, as does oral semaglutide.
2. Some people prefer an oral drug, and some will benefit from the weight loss and HbA_{1c}-lowering achievable with tirzepatide, and now clinicians can prescribe these agents and be assured of the cardiovascular benefits for this highest-risk group.

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