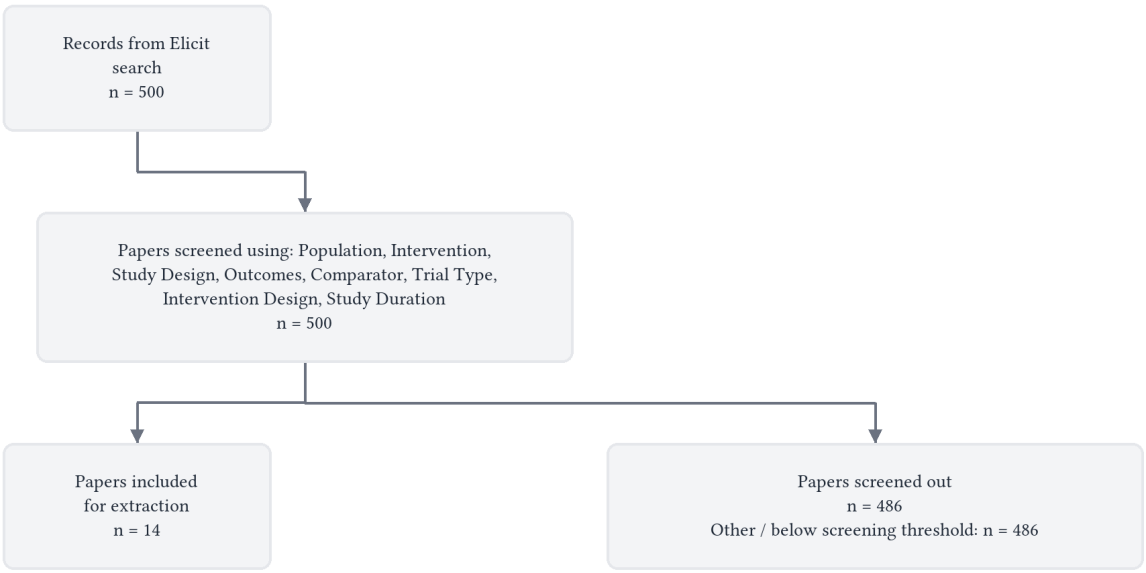
In adults with type 2 diabetes, does tirzepatide demonstrate a statistically significant reduction in major adverse cardiovascular events (MACE) compared to placebo in dedicated cardiovascular outcome trials, or is current data limited to exploratory endpoints from glycemic efficacy trials?

No dedicated cardiovascular outcome trial has yet demonstrated a statistically significant reduction in conventional MACE with tirzepatide versus placebo in a standard type 2 diabetes population; current evidence of cardiovascular benefit derives from pooled analyses of glycemic and obesity efficacy trials with exploratory cardiovascular endpoints, and from a dedicated trial in heart failure with preserved ejection fraction rather than atherothrombotic MACE, while the definitive trial in type 2 diabetes with established cardiovascular disease (SURPASS-CVOT) has not yet reported results.

Abstract

Current evidence does not include a completed dedicated cardiovascular outcome trial (CVOT) demonstrating a statistically significant reduction in conventional MACE (cardiovascular death, myocardial infarction, or stroke) with tirzepatide versus placebo in a standard type 2 diabetes population with established atherosclerotic cardiovascular disease. The pre-specified meta-analysis of the SURPASS glycemic efficacy program found a MACE-4 hazard ratio of 0.80 (95% CI: 0.57–1.11; p=0.089), consistent with cardiovascular safety but not reaching statistical significance [1]. More recent pooled analyses have yielded significant results: an individual participant data meta-analysis of 11 Phase 3 trials reported a 33% MACE reduction with tirzepatide 15 mg versus pooled comparators (HR 0.67; 95% CI: 0.51–0.87) [2], and a network meta-analysis found significant class-level cardiovascular benefit versus placebo [3]. However, these analyses pool data from glycemic and obesity trials with short follow-up (median 56 weeks) and exploratory cardiovascular endpoints [2, 4]. Separately, in patients with heart failure with preserved ejection fraction and obesity (the SUMMIT trial), tirzepatide significantly reduced cardiovascular death or worsening heart failure versus placebo (HR 0.62; 95% CI: 0.41–0.95; P=0.026), with consistent effects in the type 2 diabetes subgroup [5] —though this benefit was driven by heart failure events rather than atherothrombotic MACE [6]. The definitive trial, SURPASS-CVOT (n=13,299; 3-point MACE primary endpoint), compares tirzepatide to dulaglutide rather than placebo and has not yet reported results [7, 7]. In summary, tirzepatide's cardiovascular safety in type 2 diabetes is well established [8], and pooled analyses increasingly suggest cardiovascular efficacy, but the evidence base remains limited to exploratory endpoints from glycemic trials and a dedicated CVOT in a heart failure population; definitive evidence from a conventional T2D/ASCVD outcome trial is pending.

Flow Diagram



Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "In adults with type 2 diabetes, does tirzepatide demonstrate a statistically significant reduction in major adverse cardiovascular events (MACE) compared to placebo in dedicated cardiovascular outcome trials, or is current data limited to exploratory endpoints from glycemic efficacy trials?"

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population**: Does the study include adults (≥18 years) with type 2 diabetes mellitus?
- **Intervention**: Does the study investigate tirzepatide as the primary intervention?
- **Study Design**: Is the study a randomized controlled trial (RCT)?
- **Outcomes**: Does the study report MACE (major adverse cardiovascular events) or individual cardiovascular endpoints?
- **Comparator**: Does the study include a placebo control group?
- **Trial Type**: Is the study either a dedicated cardiovascular outcome trial (CVOT) or a glycemic efficacy trial?

- **Intervention Design**: Is tirzepatide studied as a single intervention (not combined with other novel antidiabetic agents in factorial designs)?
- **Study Duration**: Does the study have a follow-up duration of at least 12 weeks?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

At abstract screening, the number of papers excluded for each primary reason was:

- **Other / below screening threshold**: n = 486

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Trial Type**:

  Classify the trial design as one of the following for tirzepatide studies in adults with type 2 diabetes:

- Dedicated cardiovascular outcome trial (primary endpoint is MACE or CV outcomes)
- Glycemic efficacy trial with CV safety/exploratory endpoints
- Meta-analysis of dedicated CV outcome trials
- Meta-analysis of glycemic efficacy trials with CV endpoints
- Other (specify) Note whether CV outcomes were pre-specified primary, secondary, or exploratory endpoints.

- **Comparison Groups**:

  Extract the specific comparison groups for tirzepatide, focusing on:

- Placebo-controlled comparisons (extract all placebo vs tirzepatide data)
- Active comparator details (specify which GLP-1 RA or other antidiabetic agent)
- Whether the study allows for answering tirzepatide vs placebo questions (even if active comparator was used, some studies may have placebo arms or allow indirect comparison)

- **MACE Definition**:

  Extract the specific definition of Major Adverse Cardiovascular Events (MACE) used in each study involving tirzepatide in adults with type 2 diabetes:

- 3-point MACE (CV death, MI, stroke)
- 4-point MACE (+ hospitalized unstable angina)
- Other composite definitions
- Individual CV outcome components Note if different MACE definitions were used in subanalyses.

- **MACE Results**:

  Extract all MACE outcome data for tirzepatide vs placebo comparisons in adults with type 2 diabetes, including:

- Hazard ratio with 95% confidence intervals
- P-values for statistical significance
- Event rates in each group
- Number of participants and person-years of follow-up
- Whether results met statistical significance ($p<0.05$)

- Any superiority, non-inferiority, or safety findings If only tirzepatide vs active comparator data is available, note this limitation.
- **Study Population**:

  Extract baseline characteristics of the adult type 2 diabetes population studied:

- Mean age and diabetes duration
- Baseline cardiovascular risk level (established ASCVD, high CV risk, or other)
- Percentage with prior CV events
- Sample size for tirzepatide and control groups
- Key inclusion/exclusion criteria related to CV risk Focus on characteristics that affect generalizability of CV outcomes to broader T2D population.
- **Data Limitations**:

  Identify any limitations in the cardiovascular evidence for tirzepatide vs placebo in adults with type 2 diabetes:

- Whether dedicated CV outcome trial data is available or if evidence comes only from exploratory endpoints
- Post-hoc vs pre-specified analyses
- Follow-up duration adequacy for CV outcomes
- Statistical power limitations for MACE endpoints
- Availability of placebo-controlled data vs active-comparator only
- Any acknowledged limitations by study authors regarding CV outcome interpretation

Results

Characteristics of Included Studies

The 14 sources encompass a range of study designs, from individual randomized controlled trials and their sub-studies to meta-analyses and narrative reviews, addressing cardiovascular outcomes associated with tirzepatide in populations with type 2 diabetes (T2D) and related cardiometabolic conditions.

Study	Full Text Retrieved?	Study Type	CV Endpoint Status	Comparator(s)	Population
N. Sattar et al., 2022	Yes	Pre-specified meta-analysis of 7 RCTs from SURPASS program [1]	MACE-4 as pre-specified primary endpoint of meta-analysis [1]	Placebo (n=286), insulin degludec, insulin glargine, semaglutide 1 mg, dulaglutide [1]	n=7,215; mean age 58.8 y; 34.9% with CV disease history [1]
Stephen J. Nicholls et al., 2023	No	Dedicated CVOT (SURPASS-CVOT); design and baseline only [7]	3-point MACE as pre-specified primary endpoint [7]	Dulaglutide 1.5 mg (active comparator; no placebo arm) [7]	n=13,299; mean age 64.1 y; diabetes duration 14.7 y; established ASCVD [7]

Study	Full Text Retrieved?	Study Type	CV Endpoint Status	Comparator(s)	Population
Courtney L. Bradley et al., 2022	Yes	Narrative review of SURPASS program [9]	CV outcomes exploratory in glycemic trials; SURPASS-CVOT ongoing [9]	Placebo, semaglutide, insulin degludec, insulin glargine, dulaglutide [9]	Adults with uncontrolled T2DM and high CV risk [9]
Arya Aminorroaya et al., 2025	No	IPD meta-analysis of 11 Phase 3 RCTs [2]	MACE composite (ACS, CVA, HF hospitalization, CV death) [2]	Pooled comparators: placebo, insulin, GLP-1 RAs [2]	n=7,388; median age 55 y; 52% women [2]
M. Nauck & D. D'Alessio, 2022	Yes	Narrative review of SURPASS program [8]	MACE-4 explored; CV safety endpoint in glycemic trials [8]	Placebo (SURPASS-1, -5), semaglutide, dulaglutide, insulin degludec, insulin glargine [8]	Mean age 54.1–63.6 y; diabetes duration 4.7–13.3 y across trials [8]
M. Packer et al., 2025	No	Pre-specified subgroup analysis of SUMMIT trial (dedicated CVOT for HFpEF) [5]	CV death or worsening HF event as co-primary endpoint [5]	Placebo [5]	n=731; HFpEF with obesity (BMI ≥30); includes T2D subgroup [5]
Cardiovascular Diabetology et al., 2026	No	Systematic review and network meta-analysis [3]	CV events (specific MACE definition not stated) [3]	Placebo and individual GLP-1 RAs [3]	Adults with T2D and established ASCVD or high CV risk [3]
Maria-Ioanna Stefanou et al., 2024	Yes	Systematic review and meta-analysis of 13 RCTs (9 GLP-1 RA, 4 tirzepatide) [4]	MACE, stroke, and components (specific tirzepatide MACE definition not stated) [4]	Placebo (4 tirzepatide RCTs were placebo-controlled) [4]	65,878 T2DM patients total; tirzepatide trials not enriched for CV risk [4]
L. Sankaran & L. Curtis, 2023	Yes	Narrative review of SURPASS trials [10]	CV outcomes exploratory; SURPASS-4 reported no excess CV risk [10]	Placebo (SURPASS-1, -5), semaglutide, insulin degludec, insulin glargine [10]	SURPASS-4: 87% with prior CV event; diabetes duration 4.7–13.4 y across trials [10]

Study	Full Text Retrieved?	Study Type	CV Endpoint Status	Comparator(s)	Population
Iskandar Idris, 2024	Yes	Commentary on the SUMMIT trial (dedicated CVOT for HFpEF) [6]	CV death or worsening HF event as co-primary endpoint [6]	Placebo [6]	n=731; HFpEF with obesity (BMI ≥30) [6]
R. Wiese et al., 2023	No	Post-hoc ASCVD risk prediction analysis of SURPASS 1–5 [11]	Calculated ASCVD risk score (not adjudicated MACE) [11]	Placebo and active comparators (including semaglutide) [11]	T2D without CVD history; mean age 53.6–64.3 y [11]
Rachel Sinha et al., 2023	Yes	Narrative review of SURPASS and SURMOUNT programs [12]	CV outcomes exploratory; SURPASS-CVOT ongoing [12]	Placebo (SURPASS-1, -5), semaglutide, dulaglutide, insulin degludec, glargine [12]	Wide range of T2DM duration; SURPASS-4 enriched for high CV risk [12]
Hossein Hamid et al., 2024	No	Phase IV RCT design paper (T-PLAQUE trial) [13]	Coronary plaque progression by MDCTA (not MACE) [13]	Placebo [13]	T2DM aged 40–80 y; ≥20% coronary stenosis on CCTA [13]
Arya Aminorroaya et al., 2025a	No	IPD meta-analysis of 7 Phase 3 RCTs [14]	Cardiometabolic abnormalities and metabolic syndrome (not MACE) [14]	Placebo and standard antihyperglycemic agents [14]	n=7,805; weighted median age 59 y; 43.2% women [14]

The included sources span the evidence landscape from glycemic efficacy trials with exploratory CV endpoints (the SURPASS 1–5 program) through pooled analyses and meta-analyses of those trials, to dedicated cardiovascular outcome trials in specific populations (SUMMIT for HFpEF) and an ongoing definitive CVOT (SURPASS-CVOT). Full text was available for 7 of the 14 sources. Notably, several sources report on overlapping trial populations (e.g., SURPASS 1–5 data are used by Sattar et al., Nauck & D'Alessio, Wiese et al., Sinha et al., Sankaran & Curtis, and the Aminorroaya et al. meta-analyses), and none of the sources reports results from SURPASS-CVOT, which remains the only completed head-to-head dedicated CVOT in a conventional T2D population with established ASCVD.

Effects

MACE and Cardiovascular Composite Outcomes

Source	Outcome Definition	Tirzepatide vs. Comparator	HR (95% CI)	Statistical Significance	Key Context
N. Sattar et al., 2022	MACE-4 (CV death, MI, stroke, hospitalized unstable angina) [1]	Pooled tirzepatide vs. all controls (including placebo) [1]	0.80 (0.57–1.11) [1]	Not significant (p=0.089 for tirzepatide vs. placebo subset) [1]	142 events total; up to 24 months follow-up; pre-specified analysis [1]
Arya Aminorroaya et al., 2025	MACE composite (ACS, CVA, HF hospitalization, CV death) [2]	Tirzepatide 15 mg vs. pooled comparators (placebo, insulin, GLP-1 RAs) [2]	0.67 (0.51–0.87) [2]	Yes (CI excludes 1.0) [2]	119 events; median 56-week follow-up; IPW-weighted incidence 1.1% vs. 1.7% [2]
M. Packer et al., 2025 (SUMMIT)	CV death or worsening HF event [5]	Tirzepatide vs. placebo [5]	0.62 (0.41–0.95); P=0.026 [5]	Yes [5]	HFpEF with obesity population; consistent in T2D subgroup: HR 0.64 (0.35–1.15), P-interaction=0.95 [5]
Iskandar Idris, 2024 (SUMMIT commentary)	CV death or worsening HF event [6]	Tirzepatide vs. placebo [6]	0.62 (0.41–0.95); P=0.026 [6]	Yes; driven by worsening HF events (8.0% vs. 14.2%) [6]	n=731; mean 104-week follow-up; CV death alone numerically higher with tirzepatide (2.2% vs. 1.4%; HR 1.58, 0.52–4.83) [6]
Cardiovascular Diabetology et al., 2026	CV events (definition not specified) [3]	Tirzepatide vs. placebo (class-level); tirzepatide vs. GLP-1 RAs (agent-level) [3]	Not reported [3]	”Significantly reduced” vs. placebo; ”comparable efficacy” vs. GLP-1 RAs [3]	Network meta-analysis; adults with T2D and established ASCVD or high CV risk [3]
Maria-Ioanna Stefanou et al., 2024	MACE (pooled GLP-1 RA and GIP/GLP-1 RA analysis) [4]	Combined GLP-1/GIP-GLP-1 RAs vs. placebo [4]	OR 0.87 (0.81–0.94) for combined class [4]	Yes for combined class; no significant association for tirzepatide alone [4]	Tirzepatide-specific RCTs were underpowered and not designed as CVOTs [4]

Source	Outcome Definition	Tirzepatide vs. Comparator	HR (95% CI)	Statistical Significance	Key Context
M. Nauck & D. D'Alessio, 2022	MACE-4 [8]	Tirzepatide vs. pooled comparators [8]	HR <1.0; upper CI bound <1.3 [8]	Not statistically significant; interpreted as meeting CV safety threshold [8]	Low event numbers; short follow-up; ongoing SURPASS-CVOT noted [8]

Several sources did not report quantitative MACE data. The SURPASS-CVOT trial (Nicholls et al., 2023) reported only design and baseline characteristics, with no outcome results yet available [7]. The T-PLAQUE trial (Hamid et al., 2024) is designed to assess coronary plaque progression rather than clinical MACE endpoints [13]. Wiese et al. (2023) reported improvements in calculated ASCVD risk scores rather than adjudicated events [11]. Aminorroaya et al. (2025a) focused on metabolic syndrome resolution rather than MACE [14]. Bradley et al. (2022), Sankaran & Curtis (2023), and Sinha et al. (2023) provided narrative summaries without novel quantitative MACE data [9, 10, 12].

Cardiovascular Risk Factor Improvements

Beyond hard MACE endpoints, several sources documented tirzepatide's effects on surrogate cardiovascular markers. Wiese et al. (2023) found that 10.9–21.4% of tirzepatide-treated participants shifted to a lower ASCVD risk category versus 2.9–12.7% for placebo or comparators, and the improvements were qualitatively greater than those observed with semaglutide [11]. Aminorroaya et al. (2025a) reported that tirzepatide reduced the odds of metabolic syndrome by 72% (OR 0.28; 95% CI: 0.24–0.33) and the odds of elevated BMI by 96% (OR 0.04; 95% CI: 0.02–0.08) [14]. In the SUMMIT trial, tirzepatide produced reductions in left ventricular mass and paracardiac fat that were similar in patients with and without diabetes, despite attenuated weight loss in the diabetes subgroup (10.4% vs. 12.9%; P-interaction=0.04) [5]. Across the SURPASS program, tirzepatide consistently reduced blood pressure, lipids, liver fat, and inflammatory markers [10, 12].

Adverse Effects and Safety Signals

Gastrointestinal adverse events (nausea, vomiting, diarrhea, constipation) were the most commonly reported side effects across all tirzepatide studies, with frequency similar to that of selective GLP-1 receptor agonists and dose-dependent in nature [8]. In the SUMMIT trial, adverse events leading to discontinuation occurred in 6.3% of the tirzepatide group versus 1.4% in the placebo group [6]. Notably, cardiovascular death in the SUMMIT trial was numerically higher with tirzepatide than placebo (2.2% vs. 1.4%; HR 1.58; 95% CI: 0.52–4.83), though this was based on very few events (8 vs. 5 patients) and was not statistically significant [6]. Clinically significant hypoglycemia rates were below 1 per patient-year across treatment groups, with higher rates only when tirzepatide was combined with basal insulin [10].

Synthesis

The central question—whether tirzepatide produces a statistically significant reduction in MACE compared to placebo in a dedicated CVOT—can be addressed by carefully distinguishing the types of evidence available.

The apparent discrepancy in findings. The pre-specified meta-analysis of the SURPASS glycemic trials (Sattar et al., 2022) found a MACE-4 hazard ratio of 0.80 (95% CI: 0.57–1.11) that did not reach statistical significance [1]. In contrast, the IPD meta-analysis by Aminorroaya et al. (2025) reported a statistically significant 33% reduction in MACE (HR 0.67; 95% CI: 0.51–0.87) for tirzepatide 15 mg [2], and the SUMMIT trial demonstrated a significant 38% reduction in cardiovascular death or worsening heart failure (HR 0.62; 95% CI: 0.41–0.95; P=0.026) [5]. Meanwhile, Stefanou et al. (2024) found no statistically significant association between tirzepatide treatment alone and MACE reduction, while the broader class of GLP-1/GIP-GLP-1 RAs showed significant benefit [4].

Explaining heterogeneity through study design and analytic choices. The divergent findings are largely attributable to differences in MACE definitions, comparator pooling strategies, dose selection, and the number of included trials. Sattar et al. (2022) used a 4-point MACE definition and pooled all tirzepatide doses (5, 10, and 15 mg) against all comparators including active agents [1], while Aminorroaya et al. (2025) restricted to tirzepatide 15 mg only—the dose being evaluated in SURPASS-CVOT—and used an expanded composite including HF hospitalization [2]. The restriction to the highest dose may capture a dose-response relationship, as SURPASS data consistently showed dose-dependent improvements in glycemia, weight, and cardiometabolic risk factors [10]. Furthermore, Aminorroaya et al. pooled 11 Phase 3 RCTs (including SURMOUNT trials in obesity) rather than 7 [2], substantially expanding the event base beyond the 142 events in Sattar et al. [1].

Population context and generalizability. The SUMMIT trial, which produced the most clearly significant result, enrolled patients with HFpEF and obesity rather than a conventional T2D population with established ASCVD [6]. Its composite endpoint of cardiovascular death or worsening heart failure is distinct from the atherothrombotic 3-point MACE typically assessed in diabetes CVOTs [5]. The significant result was driven by reductions in worsening heart failure events (HR 0.54; 95% CI: 0.34–0.85), not by cardiovascular death, which was numerically unfavorable (HR 1.58; 95% CI: 0.52–4.83) [6]. These findings may therefore reflect tirzepatide's hemodynamic and adiposity-reducing benefits in HFpEF rather than anti-atherothrombotic effects directly applicable to conventional MACE reduction in T2D.

Statistical power and evidence maturity. Multiple sources explicitly acknowledge that the SURPASS glycemic trials were not powered for cardiovascular efficacy [4, 8, 12]. Follow-up durations were generally short—up to 24 months in Sattar et al. [1] and a median of 56 weeks in Aminorroaya et al. (2025) [2] —which may be insufficient to capture the full trajectory of cardiovascular benefit, particularly for atherosclerosis-mediated endpoints. By comparison, the landmark GLP-1 RA CVOTs that established cardiovascular benefit (e.g., LEADER, SUSTAIN-6) typically had median follow-up of 2–3.5 years in populations enriched for established ASCVD.

The role of SURPASS-CVOT. The single definitive placebo-referenced CVOT for tirzepatide in a T2D/ASCVD population is SURPASS-CVOT, which randomized 13,299 participants with established atherosclerotic cardiovascular disease to tirzepatide or dulaglutide (an active comparator with established CV benefit) [7]. This trial uses 3-point MACE as its primary endpoint and is event-driven, targeting 1,615 adjudicated MACE events [7]. Crucially, it does not include a placebo arm; instead, it will assess non-inferiority and superiority against dulaglutide, with an additional analysis to confirm superiority versus a putative placebo [7]. Results are not yet available [7, 7]. Multiple sources identify this trial as the critical piece of evidence needed to definitively establish tirzepatide's cardiovascular efficacy [4, 8–10, 12].

What can be concluded. In the T2D population specifically, tirzepatide has demonstrated cardiovascular safety—the upper bound of the 95% CI for MACE-4 was consistently below 1.3 across the SURPASS program [1, 8] —but has not achieved a statistically significant reduction in conventional 3- or 4-point MACE in any single dedicated CVOT enrolling a standard T2D/ASCVD population. The statistically significant findings from the Aminorroaya et al. (2025) IPD meta-analysis (HR 0.67; 0.51–0.87) [2] and the 2026 network meta-analysis showing significant class-level benefit versus placebo [3] provide increasingly suggestive evidence of cardiovascular efficacy, but these derive

from pooled analyses of glycemic/obesity trials with short follow-up and exploratory CV endpoints [2, 4]. In the HFpEF-with-obesity population, tirzepatide has demonstrated a statistically significant reduction in the composite of cardiovascular death or worsening heart failure versus placebo (SUMMIT trial), with consistent effects regardless of diabetes status [5, 6]. The forthcoming SURPASS-CVOT results will provide the definitive test of whether tirzepatide reduces atherothrombotic MACE in T2D patients with established cardiovascular disease—and whether it does so to a degree that exceeds the benefit of an established GLP-1 RA [7].

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