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Editor Summary:
As presented at AHA Scientific Sessions 2025, in a trial emulation analysis including benchmarking to data from randomized clinical trials, treatment with semaglutide and tirzepatide showed similar levels of benefit on cardiovascular outcomes in individuals at elevated cardiovascular risk with obesity and diabetes.

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1. **Supplementary Information:**

A. **PDF Files**

Item	Present?	Filename Whole original file name including extension. i.e.: Smith_SI.pdf. The extension must be .pdf	A brief, numerical description of file contents. i.e.: *Supplementary Figures 1-4, Supplementary Discussion, and Supplementary Tables 1-4.*
Supplementary Information	Yes	TIRZSEMA-CVOT_appendix_final_revision.pdf	All supplementary figures (1-3) and tables (1-30)
Reporting Summary	Yes	NMED-FT145221B_Kruger_RS.pdf	
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Cardiovascular outcomes of semaglutide and tirzepatide for patients with type 2 diabetes in clinical practice

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Competing interests:
Dr Schneeweiss reported personal fees from Aetion Inc, a software-enabled analytics company, and grants from Bayer, UCB, and Boehringer Ingelheim to Brigham and Women's Hospital outside the submitted work. Dr Schunkert reported personal fees from AstraZeneca, Bayer Vital GmbH, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, MSD, Novartis, Pharmacosmos, Sanofi, Servier, Synlab, Amgen, and Amarin outside the submitted work. Dr

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Abstract

Cardiovascular outcome trials of the incretin-based medicines tirzepatide and semaglutide have shown benefits in populations with varying levels of cardiovascular risk. However, without direct head-to-head comparisons, treatment decisions rely on indirect evidence from heterogeneous trial populations, leaving optimal treatment choices uncertain. We therefore conducted five cohort studies to assess the effectiveness of tirzepatide and semaglutide in patients with elevated cardiovascular risk, including obesity and type 2 diabetes, enrolled in insurance programs in United States between 2018 and 2025. First, we emulated two cardiovascular outcome trials, SUSTAIN-6 (semaglutide versus sitagliptin as placebo proxy) and SURPASS-CVOT (tirzepatide versus dulaglutide), to benchmark and critically evaluate our design, data, and analytic framework. Second, we assessed each drug in expanded populations reflective of patients routinely seen in clinical practice. Third, we directly compared tirzepatide versus semaglutide. Baseline confounders were balanced using propensity score matching. For the primary composite end point of myocardial infarction, stroke, or all-cause mortality, benchmarking identified high agreement between the reference trials and their emulations for all individual end points except for all-cause mortality in SUSTAIN-6, informing subsequent analyses. In expanded populations, comparing semaglutide versus sitagliptin for the composite outcome of myocardial infarction or stroke yielded a hazard ratio of 0.82 (95% CI, 0.74 to 0.91), and comparing tirzepatide versus dulaglutide for the composite outcome including mortality yielded a hazard ratio of 0.87 (0.75 to 1.01). In the head-to-head comparison of tirzepatide versus semaglutide, the hazard ratio was 1.06 (0.95 to 1.18). These findings support a comparable cardiovascular benefit of tirzepatide and semaglutide in clinical practice and demonstrate how rigorously designed real-world evidence can complement randomized clinical trials.

Introduction

Cardiovascular disease remains the leading cause of mortality worldwide, with obesity and type 2 diabetes as major modifiable risk factors.[1] In the United States, more than 40% of adults are obese, with projections indicating 1 in 2 will be affected by 2030.[2–4] When present alongside other cardiovascular risk factors, obesity and type 2 diabetes compound the risk of myocardial infarction, stroke, and premature death, escalating both individual and public health burden.[5,6]

Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as key therapies for the treatment of obesity and type 2 diabetes, with several agents demonstrating cardiovascular benefits.[7–12] Among these, semaglutide has demonstrated reduced risk of major adverse cardiovascular events in trial participants with moderate or high cardiovascular risk. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist with rapidly growing use, has demonstrated even greater effects on glycemic control and weight loss.[13–15] However, evidence on the cardiovascular benefits of tirzepatide is only emerging, and no randomized study has directly compared it with semaglutide.[16,17] In the absence of head-to-head comparisons, indirect evidence across heterogeneous trial populations with placebo or inferior active comparators provides limited guidance for clinical decision making.

To provide timely, complementary evidence, we conducted a comparison of tirzepatide and semaglutide in patients at low, moderate, and high cardiovascular risk who were diagnosed with obesity and type 2 diabetes and subgroups with specific cardiovascular conditions. Our study proceeded in three steps. First, we emulated the two cardiovascular outcome trials SUSTAIN-6 (semaglutide versus placebo) and SURPASS-CVOT (tirzepatide versus dulaglutide) using the RCT-DUPLICATE approach to benchmark findings and inform the study design and analytic approach for expanded questions; second, we evaluated the effectiveness of each agent in populations expanded to those treated in routine care; and third, we directly compared tirzepatide and semaglutide in contemporary patient populations reflective of clinical practice.[18–21]

Results

Emulating Pivotal Cardiovascular Outcome Trials and Expanding Populations

To validate our analytical framework, we emulated the cardiovascular outcome trials SUSTAIN-6 and SURPASS-CVOT using three national claims databases from the United States. Protocol components, including eligibility criteria, treatment strategies, and follow-up definitions, were closely aligned with the original trials (see Methods). At the time the protocols were finalized, trial results for SURPASS-CVOT were not yet available, findings were released during the conduct of this study.[16] A total of 158,310 patients met the eligibility criteria for the emulation of SUSTAIN-6 and 44,671 patients for the emulation of SURPASS-CVOT emulation.

When expanding trial eligibility criteria to reflect broader patient populations typically encountered in clinical practice, we identified 453,201 individuals initiating semaglutide or sitagliptin (expanding SUSTAIN-6 eligibility) and 136,089 initiating tirzepatide or dulaglutide (expanding SURPASS-CVOT eligibility). For the head-to-head comparison of tirzepatide versus semaglutide, 297,842 initiators were included (**Figure 1**).

Before matching, patients in the trial eligible and expanded populations initiating semaglutide or tirzepatide were younger, more likely to be White, and were more frequently prescribed sulfonylureas compared to sitagliptin or dulaglutide users. After 1:1 propensity score matching, measured baseline characteristics were well-balanced across treatment groups. In the matched expanded populations, the mean age ranged from 59.2 to 69.2 years, 50.4% to 55.8% were female, and the mean body mass index ranged from 34.5 to 38.7 kg/m^2. A history of prior myocardial infarction or stroke was present in 2.9% to 9.3%, and chronic kidney disease was observed in 18.9% to 36.7% of patients (**Table 1***, Supplementary Tables 1-18 in the Supplementary Information*).

Benchmarking against SUSTAIN-6 and SURPASS-CVOT

In the emulation of SUSTAIN-6 comparing semaglutide to sitagliptin, a proxy for placebo, in patients at moderate and high cardiovascular risk (**Table 2,** ***Supplementary Table 19 in the Supplementary Information***), the hazard ratio (HR) for the primary end point was HR = 0.68 (95% confidence interval (CI), 0.60 to 0.77) compared to the trial estimate of HR = 0.74 (95% CI, 0.58 to 0.95). The four agreement metrics were met (**Table 2**). When examining the individual components of the primary end point, we observed closely concordant results for myocardial infarction and stroke, but divergent results for all-cause mortality suggestive of residual confounding. Secondary end points in the trial emulations as well as in their respective reference trials were not powered sufficiently to assess statistical agreement.

In the emulation of SURPASS-CVOT comparing tirzepatide to dulaglutide in patients at high cardiovascular risk (**Table 2,** ***Supplementary Table 19 in the Supplementary Information***), the estimated hazard ratio was HR = 0.83 (95% CI, 0.69 to 1.01) compared to the trial estimates of HR = 0.92 (95% CI, 0.83 to 1.01). This benchmarking confirmed all agreement metrics, for both the primary composite outcome and all-cause mortality, supporting the validity of our approach.

	End point	Trial emulation estimate	Trial estimate	SA	DA	EA	SD
SUSTAIN-6	Major adverse cardiovascular events	0.68 (0.60 to 0.77)	0.74 (0.58 to 0.95)	Yes	Yes	Yes	Yes
	Myocardial infarction	0.70 (0.57 to 0.86)	0.74 (0.51–1.08)	N/A*	Yes	Yes	Yes
	Stroke	0.82 (0.65 to 1.03)	0.61 (0.38–0.99)	N/A*	Yes	Yes	Yes
	All-cause mortality	*0.58 (0.48 to 0.71)*	*1.05 (0.74 to 1.50)*	N/A*	No	No	No
	Major adverse cardiovascular events	0.83 (0.69 to 1.01)	0.92 (0.83 to 1.01)	Yes	Yes	Yes	Yes

SURPASS-CVOT	Myocardial infarction	0.81 (0.61 to 1.06)	0.86 (0.74 to 1.00)	N/A*	Yes	Yes	Yes
	Stroke	0.92 (0.65 to 1.29)	0.91 (0.76 to 1.09)	N/A*	Yes	Yes	Yes
	All-cause mortality	0.76 (0.52 to 1.11)	0.84 (0.75 to 0.94)	N/A*	Yes	Yes	Yes

Tab. 2 | Benchmarking of results from trial emulations against reference trials to inform analyses in expanded populations. *Statistical agreement was assessed only for the primary end points. See details in the main text. Abbreviations: DA = directional agreement; EA = estimate agreement; N/A = not applicable; SA = statistical agreement; SD = standardized difference agreement.

Applying learnings from benchmarks to expanded populations

Informed by the database study that benchmarked against SUSTAIN-6, we amended the protocol of the expansion study comparing semaglutide versus sitagliptin to focus on end points that did not include death of any cause. Specifically, we added a composite end point of myocardial infarction or stroke without death of any cause. Similarly, a version of the composite end point of hospitalization for heart failure or urgent care visit requiring intravenous diuretics was added that did not include death. Amendments were documented in updated study protocols available on ClinicalTrials.gov. No changes were made to the end points for the comparison of tirzepatide versus dulaglutide in the expanded population because we observed high concordance with SURPASS-CVOT estimates in the primary composite end point as well as mortality in the benchmarking study. Because the confounding structure for the head-to-head comparison of tirzepatide versus semaglutide was expected to be more similar to the tirzepatide versus dulaglutide benchmarking study, we proceeded with the pre-specified analysis plan that included death in the primary composite MACE outcome.

Primary end point in expanded populations and high-risk subgroups

Semaglutide versus sitagliptin

Among patients with obesity and type 2 diabetes at low, moderate, or high cardiovascular risk in clinical practice, the 1-year risk of the composite end point of myocardial infarction or stroke was 1.5% (95% CI, 1.4 to 1.6%) with semaglutide compared to 1.7% (95% CI, 1.6 to 1.9%) with sitagliptin. This corresponded to a risk difference of -0.3% (95% CI, -0.4 to -0.1%), and a hazard ratio of 0.82 (95% CI, 0.74 to 0.91) (**Figure 2,** ***Supplementary Table 19 in the Supplementary Information***). Pooled mean follow-up on-treatment for semaglutide users was 193 days (median = 157 days; interquartile range [IQR] = 85 to 331 days) and for sitagliptin users 195 days (median = 160; 95 to 322). Treatment discontinuation (46%) was the most common reason for censoring (***Supplementary Table 20 in the Supplementary Information***). In the subgroup at high cardiovascular risk, effect estimates were similar (HR, 0.80; 95% CI, 0.71 to 0.91).

Tirzepatide versus dulaglutide

Among patients in the expanded population who initiated tirzepatide or dulaglutide, the 1-year risk for the primary end point including all-cause mortality in the tirzepatide group was 1.4% (95% CI 1.3 to 1.6%) versus 1.8% (95% CI, 1.5 to 2.0%) for dulaglutide. This yielded a risk difference of -0.3% (95% CI, -0.6 to 0.04%), and HR = 0.87 (95% CI, 0.75 to 1.01) (**Figure 2,** ***Supplementary Table 19 in the Supplementary Information***). Among tirzepatide users, the pooled mean on-treatment follow-up was 189 days (median = 162; 72 to 321). For dulaglutide users, the corresponding follow-up was on average 173 days (median = 139; 73 to 257). Discontinuation of treatment (37%) was the most common reason for censoring (***Supplementary Table 20 in the Supplementary Information***). Among patients at high cardiovascular risk, the effect estimate was HR = 0.88 (95% CI, 0.73 to 1.07).

Tirzepatide versus semaglutide

In the direct head-to-head comparison, the 1-year risk of the primary end point including all-cause mortality was 1.3% (95% CI, 1.2 to 1.5%) for tirzepatide and 1.3% (95% CI, 1.2 to 1.5%) for semaglutide, resulting in a risk difference of 0.0% (95% CI, -0.2 to 0.2%) and HR = 1.06 (95% CI, 0.95 to 1.18) (**Figure 2,** ***Supplementary Table 19 in the Supplementary Information***). The mean follow-up on-treatment was 181 days (median = 155; 71 to 290) for tirzepatide initiators and 174 days (108) (median = 148; 82 to 254) for semaglutide initiators. Treatment discontinuation (34%) was the most common censoring reason (***Supplementary Table 20 in the Supplementary Information***). Among individuals at high cardiovascular risk, the hazard ratio was HR = 1.11 (95% CI, 0.96 to 1.27).

Secondary, safety, and negative control end points

For individual components of the primary end point, semaglutide vs sitagliptin reduced myocardial infarction (HR 0.81, 95% CI 0.70 to 0.92), and stroke (HR 0.84, 95% CI 0.71 to 0.99) in the expanded populations at low, moderate and high cardiovascular risk. Tirzepatide showed a non-inferior reduction in all-cause mortality (HR 0.88, 95% CI 0.68 to 1.16), myocardial infarction (HR 0.91, 95% CI 0.73 to 1.12), and stroke (HR 0.78, 95% CI 0.59 to 1.03) compared to dulaglutide, although confidence intervals remained compatible with no difference. In the head-to-head comparison between tirzepatide and semaglutide, the two drugs yielded similar risks for component end points all-cause mortality (HR 1.03, 95% CI 0.84 to 1.27), myocardial infarction (HR 1.03, 95% CI 0.88 to 1.21), and stroke (HR 1.15, 95% CI 0.92 to 1.45) (**Figure 3,** ***Supplementary Table 21 in the Supplementary Information***).

Semaglutide showed a lower risk of the secondary composite end point of heart failure hospitalization or urgent heart failure visit compared to sitagliptin in the expanded populations, (HR = 0.61 (95% CI, 0.57 to 0.66). Tirzepatide demonstrated a lower risk of the secondary composite end point in heart failure hospitalization, urgent heart failure visit, or all-cause mortality compared against dulaglutide HR = 0.75 (95% CI, 0.65 to 0.86). For tirzepatide versus semaglutide, contrary to the primary end point in the head-to-head comparison, there was some supporting evidence for tirzepatide to have a modest benefit, although the 95% CI overlapped the null, HR = 0.91 (95% CI, 0.81 to 1.01) (**Figure 3,** ***Supplementary Table 21 in the Supplementary Information***).

For safety outcomes, semaglutide and tirzepatide showed lower risks for serious bacterial infections compared to sitagliptin and dulaglutide, respectively. No meaningful differences in the risk of urinary tract infections or gastrointestinal adverse events between treatment groups were observed (***Supplementary Table 22 in the Supplementary Information***).

No associations were observed for the two negative control outcomes, lumbar radiculopathy and abdominal hernia, supporting the validity of the analyses (**Figure 3,** ***Supplementary Table 23 in the Supplementary Information***).

Subgroups and sensitivity analyses

Prespecified subgroup analyses in the expanded populations for age showed no meaningful treatment effect heterogeneity (**Figure 4,** ***Supplementary Table 24 in the Supplementary Information***). Across sex subgroups, effects were similar for semaglutide versus sitagliptin and for tirzepatide versus semaglutide whereas for tirzepatide versus dulaglutide, estimates suggested male patients to benefit more from tirzepatide than female patients. Among patients

receiving concomitant sodium-glucose cotransporter-2 (SGLT2) inhibitors at baseline, no meaningful difference to those patients without concomitant SGLT2 inhibitor use was observed.

Sensitivity analyses using an as-started causal contrast led to modestly attenuated estimates. Effect estimates remained robust when restricting to patients with available hemoglobin A1c and including it in the propensity score (***Supplementary Table 23 in the Supplementary Information***). In *post-hoc* analyses, we further evaluated the comparative effectiveness of semaglutide versus dulaglutide in the expanded population to contextualize whether a reduction in the primary end point, relative to the comparisons including tirzepatide, was similar or greater. Effect estimates confirmed an increased risk (HR = 1.24, 1.15 to 1.34), which further supported the robustness of our findings. The comparative effectiveness of an expanded 2-year on-treatment analysis that followed patients who stay on the exposure or comparator therapies for a prolonged time showed concordant results with the 1-year on-treatment analysis (***Supplementary Table 25 in the Supplementary Information***).

Discussion

In this database study, treatment with semaglutide (against sitagliptin, a placebo proxy) led to a reduced risk of major adverse cardiovascular events, and tirzepatide (against dulaglutide) demonstrated similar risk reduction in patients at elevated cardiovascular risk with obesity and type 2 diabetes. These findings align closely with prior cardiovascular outcome trials and solidify the evidence base by demonstrating consistent benefits in broader patient populations treated in clinical practice.

In the direct comparison of tirzepatide versus semaglutide, we observed confidence intervals compatible with no difference and point estimates indicating a modest numeric advantage of semaglutide, if any, for reducing major adverse cardiovascular events, particularly among patients at high cardiovascular risk. Conversely, point estimates for tirzepatide showed a potential modest advantage for heart failure end points, with confidence intervals compatible with no difference, consistent with recent data supporting protective effects of semaglutide and tirzepatide on heart failure outcomes and a potential incremental benefit with the latter.[25] Potential explanations include the dual receptor agonism of tirzepatide.[22] Current insight into the cardiovascular biology of GIP is limited, and findings in preclinical and clinical studies point in different directions, ranging from potentially cardioprotective effects to heightened vascular inflammation and artherogenesis.[23,24] This aligns with findings from SURPASS-CVOT, which showed no meaningful additive effect on major adverse cardiovascular events compared with an older GLP-1 receptor agonist, and with findings of a potential greater protection in heart failure that could be compatible with more pronounced weight loss mediated by GIP.[16,25] In contrast, GLP-1 receptor activation has consistently reduced major adverse cardiovascular events in randomized trials.[26,27] Tirzepatide binds the GLP-1 receptor with lower affinity than semaglutide and exhibits distinct signaling bias, which may result in comparatively different downstream GLP-1 receptor signaling dynamics.[28] Furthermore, tirzepatide has shown longer titration periods in clinical practice, delaying attainment of full maintenance doses and potentially dampening early cardiovascular benefits.[29] These hypotheses require further confirmation.

Our findings offer comprehensive real-world evidence for the cardiovascular effectiveness of tirzepatide in clinical practice in the absence of studies with direct comparisons to semaglutide and ahead of further evidence from the SURPASS-CVOT randomized controlled trial that compared tirzepatide against an older GLP-1 receptor agonist that is not frequently used in routine care.[14,17] As cardiovascular risk remains high among adults with type 2 diabetes and excess weight, timely evaluation of new therapies is a public health priority. While randomized trials are the reference methodology for establishing treatment effectiveness, they leave many clinically relevant questions unanswered, which may delay access for new indications.[30–32] Non-randomized database studies have inherent limitations; however, when rigorously designed using proven analytic approaches to emulate reference trials, real-world evidence of several glucose-lowering drug classes have demonstrated strong concordance with trial estimates.[20,25,33] As dozens of novel agents currently under study seek new indications, the question arises whether the traditional practice of two confirmatory trials for every indication expansion remains justified, especially when database study emulations that benchmark against previously conducted, closely related reference trials have yielded aligned results.[34,35]

This study demonstrates how database studies rooted in benchmarks against previously conducted randomized trials for the drugs of interest can produce complementary evidence to

support expanded cardiovascular indications. By preregistering detailed protocols with contemporaneously documented amendments, we ensured methodological transparency. By aligning key protocol components and analytic frameworks with those of SUSTAIN-6 and SURPASS-CVOT, we produced self-critical evidence that allowed us to directly benchmark results against reference trials to inform subsequent analyses in expanded populations. Close agreement observed between trials and estimates from the database analyses for all end points except one supported the fitness of the design and data for assessing cardiovascular effectiveness and safety. However, benchmarking against SUSTAIN-6 flagged disagreement for the effect on all-cause mortality, highlighting potential residual confounding for this secondary end point that could reflect preferential prescribing in patients for whom clinicians anticipated limited life expectancy. The observed divergence in mortality results when comparing injectable semaglutide to sitagliptin (a placebo-proxy) in benchmarking analyses led us to view the results for outcomes containing mortality with skepticism and focused our interpretation on the non-mortality clinical endpoints. For transparency we still reported the mortality findings. In contrast, the concordance of benchmarking results for all outcomes, including mortality, in the SURPASS-CVOT emulation study comparing tirzepatide to dulaglutide provided support for the validity of evaluating these outcomes in expanded study populations. As the landscape of cardiometabolic therapeutics evolves rapidly, real-world evidence may serve as a critical tool to generate comparative insights beyond trials that is essential for clinical decision-making and regulatory evaluation.

This study has several limitations. First, treatment allocation was not randomized, raising the potential for residual confounding despite extensive pre-treatment covariate adjustment through propensity score matching. The resulting concordance between the emulated and actual SUSTAIN-6 and SURPASS-CVOT trial estimates strengthen confidence in the internal validity of our findings for the successfully assessed end points. When differences in results for endpoints were observed, this informed subsequent analyses. Second, information on outcomes, comorbidities, and cardiovascular risk factors was derived from administrative claims, which may be less reliable than trial-based assessments. We addressed this by incorporating a range of algorithms based on diagnosis, procedure, and prescription claims, as well as frailty indicators and health service utilization. The end point algorithms were validated and showed a sensitivity of over 99% for mortality in the National Death Index, a positive predictive value of 94% for myocardial infarction, 95% for stroke, and 98% for heart failure hospitalization.[34,36–41] Third, medication exposure was identified from pharmacy dispensing records, which is more accurate than prescribing information. Given the modest treatment persistence observed in clinical practice our results may not capture long-term cardiovascular outcomes. The divergence in event rates between treatment groups observed within one year across both randomized trials and equally in our analyses suggests that meaningful effects may emerge within a short time frame. Forth, although our data represent a diverse population, findings may best apply to the United States and have more limited applicability to international settings. Lastly, we assumed neutral effects on cardiovascular end points for sitagliptin as a comparator in the semaglutide analysis. This assumption is supported by a prior outcome trial and observational data.[20,42]

Relevant for clinical practice, our findings show that treatment with semaglutide lowered the risk of major adverse cardiovascular events compared to sitagliptin, while tirzepatide showed at least comparable benefit to dulaglutide, an older GLP-1 receptor agonist with established cardiovascular efficacy. In a direct head-to-head comparison, tirzepatide demonstrated similar benefits in reducing major adverse cardiovascular events as semaglutide. These findings provide timely insights into the cardiovascular effectiveness of modern GLP-1 receptor agonist-based

therapies that can inform clinical decision-making in the absence of a head-to-head randomized trial.

Methods

Data Sources

The five cohort studies were conducted using three nationwide claims databases, including Medicare Parts A, B, and D (2018 through 2020), Optum Clinformatics Data Mart (2018 through Feburary 2025), and Merative MarketScan (2018 through 2023). Medicare claims data includes beneficiaries aged 65 years and older enrolled in traditional fee-for-service. Optum and MarketScan databases capture commercially insured individuals across the United States. All three databases capture deidentified, longitudinal patient-level information on demographics; diagnoses and procedures from inpatient, outpatient, and emergency department encounters; and prescription medications dispensed to outpatients. Each database permits tracking of healthcare utilization and medication exposure over time, and patients may contribute to more than one database if they meet the respective eligibility criteria.

Specification and emulation of the studies

To inform our study design and analytic approach for the head-to-head tirzepatide versus semaglutide comparison of interest, we sought to conduct studies that allowed us to benchmark results of similarly designed database studies against results from randomized trials asking closely related questions. Insights from benchmarking can inform and lead to changes in subsequent analyses for the expanded questions of interest. We emulated and benchmarked against two cardiovascular outcome trials (reference trials), SUSTAIN-6 (semaglutide versus placebo) and SURPASS-CVOT (tirzepatide versus dulaglutide) in a pair of cohort studies. Key protocol components, including eligibility criteria, treatment strategies, assignment procedures, follow-up, outcome definitions, causal contrast, identifying assumptions, and the data analysis plan, were translated into operational definitions using validated claims-based algorithms and observational analogs of key study design choices.

SUSTAIN-6 evaluated once-weekly semaglutide versus placebo in patients at moderate and high cardiovascular risk with type 2 diabetes, showing a 26% relative risk reduction in major adverse cardiovascular events (HR 0.74; 95% CI 0.58–0.95). SURPASS-CVOT compared once-weekly tirzepatide with dulaglutide in adults with type 2 diabetes and high cardiovascular risk, showing a 9% relative risk reduction in major adverse cardiovascular events (HR 0.92; 95% CI 0.83–1.01).

Building on these reference trials, we specified two protocols that expanded eligibility to assess the effectiveness of semaglutide versus sitagliptin and tirzepatide versus dulaglutide in populations reflective of patients routinely seen in clinical practice, spanning low, moderate, or high cardiovascular risk (***Supplementary Table 26 in the Supplementary Information***).

Finally, we specified a protocol for a direct head-to-head comparison of tirzepatide versus semaglutide. These three protocols were emulated using the same analytic approach applied in the trial emulations used for benchmarking. Specification and emulation of the reference trial including our expansion studies are stated in the Supplementary Information, following the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guideline (***Supplementary Tables 27-29 in the Supplementary Information***).[43]

Data availability

The study was approved by the Mass General Brigham Institutional Review Board. The use of deidentified secondary data qualified for a waiver of informed consent by United States federal

regulations. Data use agreements and licensing agreements do not allow sharing of patient-level claims data with third parties. However, data can be requested at the vendors directly (Optum Clinformatics, connected@optum.com; Medicare, resdac@umn.edu; Merative MarketScan, marketscan.support@merative.com). The analytical code with which to create the tables, figures and analysis results for this study is available at https://github.com/nilskruger/Major-Adverse-Cardiovascular-Outcomes-for-Semaglutide-and-Tirzepatide-in-Clinical-Practice/.

Transparency statement

We prespecified and registered the study protocols for the five cohort studies before outcome analyses were conducted to enhance transparency and minimize analytical bias. Protocols and their amendments are publicly accessible in ClinicalTrials.gov under the National Clinical Trial (NCT) identifiers NCT06659744, NCT07088718, NCT07096063, and in the Open Science Framework (osf.io/38rw9).[44] Each protocol outlines the study rationale and design following the HARmonized Protocol Template to Enhance Reproducibility (HARPER), a structured framework for transparent and reproducible observational study design.[45] The study was conducted between October 2024 to August 2025 and reported following the Reporting of Studies Conducted Using Observational Routinely Collected Health Data for Pharmacoepidemiology (RECORD-PE) statement and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidance.[46]

Study cohorts

We designed five active-comparator, new-user cohort studies including patients with obesity and type 2 diabetes at elevated cardiovascular risk.[47] All patients were required to have continuous enrollment of at least 12 months before cohort entry and meet eligibility criteria for one of the five cohort studies defined below (study design diagrams depicted in ***Supplementary Figures 1-3 in the Supplementary Information***).

Semaglutide versus sitagliptin: In one set of analyses, we compared initiators of semaglutide with initiators of sitagliptin in patients at elevated cardiovascular risk with type 2 diabetes and obesity. Sitagliptin, a dipeptidyl peptidase-4 inhibitor, was selected as an active-comparator placebo proxy because it was recommended in clinical guidelines as a second-line glucose-lowering therapy, had a similar high cost to the study drugs, showed no effect on cardiovascular outcomes in a large randomized controlled trial, and has been validated as a placebo proxy in prior claims-based research.[20,42] This choice was intended to avoid potential confounding associated with non-user comparisons and other active comparators which have been linked to a possible excess risk or decrease in risk of major adverse cardiovascular outcomes.[27,48]
To benchmark our findings against randomized evidence, we first applied eligibility criteria after SUSTAIN-6 that required patients to be at moderate or high cardiovascular risk.[11] Moderate risk was defined as age ≥60 years with subclinical cardiovascular disease, such as microalbuminuria or proteinuria, left ventricular hypertrophy or dysfunction, or an ankle–brachial index <0.9. High risk was defined as age ≥50 years with established cardiovascular disease, including prior major atherosclerotic events, revascularization, significant arterial stenosis, ischemia, NYHA class II–III heart failure, or chronic kidney disease.
We then expanded the cohort by relaxing the trial eligibility criteria to reflect populations typically encountered in practice at low, moderate, or high cardiovascular risk, including patients on lipid-lowering therapy or antihypertensive treatment (**Figure 1** and in the ***Supplementary Information***).

Tirzepatide versus dulaglutide: Using the same framework, we compared initiators of tirzepatide with initiators of dulaglutide to emulate the design and rationale of the SURPASS-CVOT trial.[17]

Patients enrolled were at high cardiovascular risk. At the time the protocol was finalized, trial results were not yet available; the study therefore aimed at predicting eventual trial readouts, countering the potential criticism of tailoring the design toward known results. While conducting the analysis, primary results became available and allowed us to benchmark against known outcomes.[16] After benchmarking, we expanded the cohort to evaluate effects in broader patient populations at low, moderate, or high cardiovascular risk (**Figure 1**).

Tirzepatide versus semaglutide: Upon establishing agreement with the trial benchmarks, we conducted a direct comparison of new initiators of tirzepatide and semaglutide to assess differences in cardiovascular and select safety outcomes in clinical practice (**Figure 1**).

Outcomes

The primary end point was major adverse cardiovascular events, a composite of all-cause mortality, myocardial infarction, or stroke. Secondary outcomes included the individual components of the primary end point. For the expanded populations, we further assessed a composite of hospitalization for heart failure, all-cause mortality, or an urgent visit for heart failure requiring intravenous diuretics as well as select safety end points including gastrointestinal adverse events, serious bacterial infections, and urinary tract infections.[49] End points were ascertained during 52 weeks of follow-up in an as-treated approach, with censoring at the first occurrence of an end point, treatment discontinuation (plus 45-day grace period), treatment switching, start of another agent within the same class, disenrollment, or study end.

Insights from the benchmarking studies prompted an amendment to the protocol for the comparison of semaglutide versus sitagliptin in expanded populations. Due to the observed divergence in the results for the mortality endpoint between the SUSTAIN-6 benchmarking study and the SUSTAIN-6 trial findings, results of the all-cause mortality endpoint was viewed skeptically. Additional composite endpoints with the mortality component removed were added to the protocol comparing semaglutide to sitagliptin in the expanded population in amendments documented on clinicaltrials.gov. Given the observed concordance in results for the SURPASS-CVOT benchmarking study and SURPASS-CVOT trial findings, no amendments were made to the protocol for the study that expanded the population for comparisons of tirzepatide versus dulaglutide. With the expectation that the confounding structure for the head-to-head comparison would more closely resemble that of the SURPASS-CVOT benchmarking study, no amendments were made to the protocol for the head-to-head comparison of tirzepatide and semaglutide.

Subgroups, sensitivity, and *post-hoc* analyses

Subgroups of interest in the expanded populations included stratifying by age (<65 or ≥65 years), sex, concomitant use of sodium-glucose cotransporter-2 (SGLT2) inhibitors (yes, no), and patients at high cardiovascular risk. In addition, we assessed the effectiveness in patients with certain cardiovascular conditions, such as coronary heart disease, cardiomyopathies, valve disorders, heart failure, as well as patients under high-intensive lipid-lowering therapy.

Sensitivity analyses included as-started follow-up emulating a per-protocol analysis, restricting analyses to patients with hemoglobin A1c measurement in the last 120 days before initiating the study drugs and adjusting for the most recent readout. We included two negative control outcome analyses to evaluate potential residual confounding, defined as new diagnosis of lumbar radiculopathy and abdominal hernia, which have no biologically plausible association with the study drugs.

To contextualize whether the reduction in the primary composite end point, relative to comparisons involving tirzepatide, was similar or greater, we conducted a *post-hoc* analysis evaluating the comparative effectiveness of semaglutide versus dulaglutide in the expanded population. Another *post-hoc* analysis examined extending the on-treatment follow-up to two years among patients who remained on therapy to assess potential changes in effectiveness beyond the first year.

Covariates

We evaluated a broad set of covariates to capture potential confounding. These included demographics (e.g., age, sex, race, and claims-based proxies for socioeconomic status such as geographic location and copayments), as well as detailed cardiovascular risk profiles. The latter encompassed both traditional risk factors (e.g., smoking status, obesity severity, hypertension, hyperlipidemia) and established cardiovascular disease (e.g., prior myocardial infarction, unstable or stable angina, ischemic stroke or transient ischemic attack, peripheral artery disease, prior coronary or peripheral revascularization, atrial fibrillation, cardiomyopathy, valvular heart disease, chronic heart failure, and device implantation such as pacemakers or implantable cardioverter-defibrillators). We also captured subclinical indicators of elevated risk, such as microalbuminuria, edema, or obstructive sleep apnea. Additional covariates included markers of cardiometabolic burden and diabetes-related complications (e.g., nephropathy, neuropathy, retinopathy, diabetic foot ulcers, episodes of hypo- or hyperglycemia), renal disease (acute or chronic kidney disease, hypertensive nephropathy), coexisting comorbidities (e.g., chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, depression, dementia), and infection history (e.g., pneumonia, urinary tract infection, COVID-19, influenza). Medication history covered glucose-lowering therapies, cardiovascular drugs, and other commonly prescribed agents. Health care utilization was described by hospitalizations (including heart failure–related admissions), emergency visits, specialist encounters, diagnostic testing, and preventive care services. Where available, laboratory values and vitals were reported (e.g., B-type natriuretic peptide, hemoglobin A1c, serum creatinine, estimated glomerular filtration rate, lipid profile, systolic blood pressure, and body mass index). Full definitions and assessment windows are provided in the ***Supplementary Information***.

Benchmarking against Randomized Trials and Predefined Binary Agreement Metrics

To assess concordance between our database emulations and their randomized trial counterparts, we compared the primary endpoint results with the published findings from SUSTAIN-6 and, once results became available, from SURPASS-CVOT.[18,19,21] Agreement between the trial and real-world evidence estimates was evaluated using three prespecified binary metrics defined by the RCT-DUPLICATE initiative:

1. Statistical agreement, defined as both the database study and trial estimates and their 95% confidence intervals lying on the same side of the null (assessed for primary end points only, secondary end points were not powered for statistical agreement);
2. Directional agreement, defined as both the database study and trial estimates lying on the same side of the null;
3. Estimate agreement, defined as the estimate of the database study falling within the 95% confidence interval of the trial;
4. Standardized difference agreement, defined as an absolute standardized difference $|Z| < 1.96$, with $Z = \frac{\hat{\theta}_{RCT} - \hat{\theta}_{RWE}}{\sqrt{\hat{\sigma}^2_{RCT} + \hat{\sigma}^2_{RWE}}}$) where $\hat{\theta}_{RCT}$ and $\hat{\theta}_{RWE}$ are the treatment effect estimates with associated variances $\hat{\sigma}^2$.

Statistical Analysis

We summarized baseline covariates using appropriate descriptive statistics and assessed balance between groups with standardized mean differences, considering values below 0.10 indicative of adequate balance. Propensity scores for each pairwise comparison were estimated with logistic regression, using the variables described in the covariate section. To mimic randomization in the database studies, we matched eligible patients who initiated each study drug in a 1:1 ratio to initiators of the comparator drug based on the propensity score, using a caliper width of 0.01 on the propensity score scale. Absolute risks at 52 weeks were derived from Kaplan-Meier estimates on the combined patient-level data from the databases as well as individually (results for the primary end points before and after propensity score matching are found in ***Supplementary Table 30 in the Supplementary information***). For individual components of the primary end point other than death, absolute risks were calculated using the Aalen–Johansen estimator to account for competing risks. Risk differences at 52 weeks were obtained as contrasts of these estimates. Pointwise 95% confidence intervals were derived via a nonparametric patient-level bootstrap with 1,000 replicates, resampling patients with replacement from the analytic cohort. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with Cox proportional hazards models. Database-specific estimates were pooled using fixed-effects inverse variance meta-analysis.

Under the assumptions made in the power calculations (***Supplementary Table 31 in the Supplementary Information***), analyses of the primary end points in the emulation of SUSTAIN-6 and the comparison of semaglutide versus sitagliptin in expanded populations was estimated to have >99% power for superiority. For the benchmarking emulation of SURPASS-CVOT and the comparison of tirzepatide versus dulaglutide in expanded populations, the estimated power to detect non-inferiority was >80%. For the comparison of tirzepatide versus semaglutide in expanded populations, the estimated power to detect non-inferiority was >90%. Analyses were performed with Python, R, and the Aetion Evidence Platform, a validated system extensively used for reproducible real-world evidence studies and trial emulations, benchmarked against US Food and Drug Administration Sentinel Initiative workflows.

Fig. 1 | **Overview of the study design to assess the comparative effects of semaglutide and tirzepatide in patients at cardiovascular risk**. The study proceeded in three sequential steps. (**a**) We emulated the design of the SUSTAIN-6 and SURPASS-CVOT trials using three United States claims databases to benchmark the trial emulations against the the reference trials and predict results. (**b**) We expanded the patient populations within this framework to assess the effectiveness of each agent in clinical practice. (**c**) We compared tirzepatide versus semaglutide in a head-to-head comparison to inform clinical decision-making. Abbreviations: CV = cardiovascular; MACE = major adverse cardiovascular events; S = selection of patients initiating semaglutide, tirzepatide, dulaglutide, or sitagliptin (as a placebo proxy) via propensity score 1:1 nearest neighbor matching to mimic randomization; T2D = type 2 diabetes.

Fig. 2 | **Cumulative incidence curves for the composite end point of major adverse cardiovascular events in expanded populations. (a-c)** The composite end point of myocardial infarction or stroke in patients initiating semaglutide versus sitagliptin **(a)**, the composite end point of myocardial infarction, stroke, or all-cause mortality in patients initiating tirzepatide versus dulaglutide **(b)**, and the composite end point of myocardial infarction, stroke, or all-cause mortality in patients initiating tirzepatide versus semaglutide **(c)**. Shaded bands represent 95% confidence intervals around the Kaplan–Meier estimate.

Fig. 3 | **Effectiveness and safety end points in expanded populations. (a-c)** 1-year risks and hazard ratios for effectiveness and safety endpoints, together with negative controls, are shown for 159,002 patients initiating semaglutide versus sitagliptin **(a)**, 78,304 patients initiating tirzepatide versus dulaglutide **(b)**, and 172,382 patients initiating tirzepatide versus semaglutide **(c)**. *For the expanded population of patients initiating semaglutide versus sitagliptin in **a** our analysis focused on end points that did not include all-cause mortality. See main text for details. Abbreviations: HHF = hospitalization for heart failure; HR = hazard ratio; CI = confidence interval.

Fig. 4 | **Major adverse cardiovascular events in subgroups. (a-c)** 1-year risks and hazard ratios for the composite end point of myocardial infarction or stroke in 159,002 patients initiating semaglutide versus sitagliptin **(a)**, the composite end point of myocardial infarction, stroke, or all-cause mortality in 78,304 patients initiating tirzepatide vs dulaglutide **(b)**, and and the composite end point of myocardial infarction, stroke or all-cause mortality in 172,382 patients initiating tirzepatide vs semaglutide **(c)**. Abbreviations: SGLT2i = sodium glucose cotransporter 2 inhibitor; HR = hazard ratio; CI = confidence interval.

Tab 1 | Baseline characteristics of patients initiating semaglutide versus sitagliptin, tirzepatide versus dulaglutide, and tirzepatide versus semaglutide after 1:1 propensity score matching.

	n (%)								
	Semaglutide versus sitagliptin			Tirzepatide versus dulaglutide			Tirzepatide versus semaglutide		
	Semaglutide (n = 79,501)	Sitagliptin (n = 79,501)	SMD	Tirzepatide (n = 39,152)	Dulaglutide (n = 39,152)	SMD	Tirzepatide (n = 86,191)	Semaglutide (n = 86,191)	SMD
Demographics									
Age; mean (SD)	63.28 (11.18)	63.32 (11.89)	0.003	60.38 (11.45)	60.38 (11.72)	0.00	59.24 (11.59)	59.26 (11.72)	0.002
Gender									
Female; n (%)	42,525 (53,5%)	42,657 (53,7 %)	0.003	21,157 (54,0%)	21,181 (54,1%)	0.001	48,025 (55,7%)	48,074 (55,8%)	0.001
Male; n (%)	36,976 (46.5%)	36,844 (46.3%)	0.003	17,995 (46.0%)	17,971 (45.9%)	0.001	38,166 (44.3%)	38,117 (44.2%)	0.001
Race									
White; n (%)	25,746 (55.6%)	25,740 (55.6%)	0.000	10,954 (28.0%)	10,940 (27.9%)	0.001	27,648 (32.1%)	27,589 (32.0%)	0.001
Black; n (%)	6,321 (13.6%)	6,254 (13.5%)	0.003	3,483 (8.9%)	3,471 (8.9%)	0.001	7,551 (8.8%)	7,535 (8.7%)	0.001
Unknown / Missing; n (%)	13,038 (28.2%)	13,114 (28.3%)	0.003	9,991 (25.5%)	10,009 (25.6%)	0.001	24,779 (28.7%)	24,866 (28.8%)	0.002
Others; n (%)	1,207 (2.6%)	1,204 (2.6%)	0.000	367 (0.9%)	375 (1.0%)	0.002	868 (1.0%)	856 (1.0%)	0.001
Region / State									
Northeast; n (%)	10,455 (13.2%)	10,520 (13.2%)	0.002	3,689 (9.4%)	3,703 (9.5%)	0.001	6,789 (7.9%)	6,688 (7.8%)	0.004
Midwest / North central; n (%)	15,841 (19.9%)	15,989 (20.1%)	0.005	9,574 (24.5%)	9,609 (24.5%)	0.002	18,664 (21.7%)	18,693 (21.7%)	0.001
South; n (%)	43,242 (54.4%)	43,187 (54.3%)	0.001	20,441 (52.2%)	20,342 (52.0%)	0.005	50,849 (59.0%)	50,808 (58.9%)	0.001
West; n (%)	9,901 (12.5%)	9,742 (12.3%)	0.006	5,430 (13.9%)	5,477 (14.0%)	0.003	9,831 (11.4%)	9,944 (11.5%)	0.004
BMI class									
25.0-29.9; n (%)	13,016 (16.4%)	12,821 (16.1%)	0.007	3,601 (9.2%)	3,610 (9.2%)	0.001	5,712 (6.6%)	5,723 (6.6%)	0.001
30.0-34.9; n (%)	9,831 (12.4%)	9,751 (12.3%)	0.003	6,388 (16.3%)	6,401 (16.3%)	0.001	12,744 (14.8%)	12,713 (14.7%)	0.001
35.0-39.9; n (%)	5,791 (7.3%)	5,829 (7.3%)	0.002	8,502 (21.7%)	8,501 (21.7%)	0.000	20,622 (23.9%)	20,589 (23.9%)	0.001
40.0 and above; n (%)	22,425 (28.2%)	22,492 (28.3%)	0.002	9,925 (25.3%)	9,921 (25.3%)	0.000	24,374 (28.3%)	24,478 (28.4%)	0.003
Unspecified obesity; n (%)	28,438 (35.7%)	28,608 (36.0%)	0.004	10,736 (27.4%)	10,719 (27.4%)	0.001	22,739 (26.4%)	22,688 (26.3%)	0.001
Cardiovascular risk factors									
Smoking/Tobacco use; n (%)	15,188 (19.1%)	15,201 (19.1%)	0.000	6,039 (15.4%)	6,003 (15.3%)	0.003	16,213 (18.8%)	16,255 (18.9%)	0.001
Hypertension; n (%)	68,720 (86.4%)	68,763 (86.5%)	0.002	33,542 (85.7%)	33,459 (85.5%)	0.006	73,529 (85.3%)	73,475 (85.2%)	0.002
Hyperlipidemia; n (%)	65,752 (82.7%)	65,555 (82.5%)	0.007	32,542 (83.1%)	32,485 (83.0%)	0.004	71,467 (82.9%)	71,458 (82.9%)	0.000
Cardiovascular comorbidities									
Coronary atherosclerosis; n (%)	16,317 (20.5%)	16,130 (20.3%)	0.006	7,030 (18.0%)	6,973 (17.8%)	0.004	14,415 (16.7%)	14,483 (16.8%)	0.002
Stable angina; n (%)	3,301 (4.2%)	3,251 (4.1%)	0.003	1,464 (3.7%)	1,472 (3.8%)	0.001	3,052 (3.5%)	3,071 (3.6%)	0.001
Unstable angina; n (%)	2,046 (2.6%)	2,033 (2.6%)	0.001	809 (2.1%)	796 (2.0%)	0.002	1,610 (1.9%)	1,617 (1.9%)	0.001
Acute myocardial infarction; n (%)	1,008 (1.3%)	990 (1.2%)	0.002	390 (1.0%)	396 (1.0%)	0.002	671 (0.8%)	692 (0.8%)	0.003
Old myocardial infarction; n (%)	3,238 (4.1%)	3,192 (4.0%)	0.003	1,296 (3.3%)	1,288 (3.3%)	0.001	2,513 (2.9%)	2,506 (2.9%)	0.000
Cardiac conduction disorder; n (%)	4,154 (5.2%)	4,115 (5.2%)	0.002	1,862 (4.8%)	1,863 (4.8%)	0.000	3,779 (4.4%)	3,772 (4.4%)	0.000
Previous cardiac procedure; n (%)	1,537 (1.9%)	1,467 (1.8%)	0.006	555 (1.4%)	544 (1.4%)	0.002	1,029 (1.2%)	1,065 (1.2%)	0.004
Ischemic stroke; n (%)	821 (1.0%)	822 (1.0%)	0.000	263 (0.7%)	274 (0.7%)	0.003	408 (0.5%)	400 (0.5%)	0.001
TIA; n (%)	1,331 (1.7%)	1,349 (1.7%)	0.002	572 (1.5%)	577 (1.5%)	0.001	1,109 (1.3%)	1,132 (1.3%)	0.002
Peripheral vascular disease or surgery; n (%)	7,128 (9.0%)	7,027 (8.8%)	0.004	3,097 (7.9%)	3,099 (7.9%)	0.000	5,935 (6.9%)	5,900 (6.8%)	0.002
Atrial fibrillation; n (%)	7,657 (9.6%)	7,722 (9.7%)	0.003	3,167 (8.1%)	3,160 (8.1%)	0.001	6,667 (7.7%)	6,755 (7.8%)	0.004
Other cardiac dysrhythmia; n (%)	14,397 (18.1%)	14,437 (18.2%)	0.001	6,857 (17.5%)	6,842 (17.5%)	0.001	15,194 (17.6%)	15,379 (17.8%)	0.006
Edema; n (%)	9,313 (11.7%)	9,315 (11.7%)	0.000	4,542 (11.6%)	4,452 (11.4%)	0.007	10,018 (11.6%)	10,029 (11.6%)	0.000
Heart failure; n (%)	9,656 (12.1%)	9,516 (12.0%)	0.005	4,405 (11.3%)	4,289 (11.0%)	0.009	8,641 (10.0%)	8,761 (10.2%)	0.005
Cardiomyopathy; n (%)	3,661 (4.6%)	3,619 (4.6%)	0.003	1,674 (4.3%)	1,671 (4.3%)	0.000	3,290 (3.8%)	3,346 (3.9%)	0.003
Valve disorders; n (%)	7,803 (9.8%)	7,812 (9.8%)	0.000	3,444 (8.8%)	3,444 (8.8%)	0.000	7,338 (8.5%)	7,343 (8.5%)	0.000

Valve replacement; n (%)	915 (1.2%)	925 (1.2%)	0.001	341 (0.9%)	347 (0.9%)	0.002	690 (0.8%)	675 (0.8%)	0.002
Implantable cardioverter defibrillator; n (%)	234 (0.3%)	225 (0.3%)	0.002	100 (0.3%)	94 (0.2%)	0.003	184 (0.2%)	203 (0.2%)	0.005
Pulmonary hypertension; n (%)	1,977 (2.5%)	2,009 (2.5%)	0.003	911 (2.3%)	906 (2.3%)	0.001	1,972 (2.3%)	1,962 (2.3%)	0.001
Venous or pulmonary embolism; n (%)	2,405 (3.0%)	2,434 (3.1%)	0.002	1,159 (3.0%)	1,143 (2.9%)	0.002	2,417 (2.8%)	2,411 (2.8%)	0.000
Diabetes complications									
Diabetic retinopathy; n (%)	7,018 (8.8%)	6,895 (8.7%)	0.005	3,520 (9.0%)	3,540 (9.0%)	0.002	5,979 (6.9%)	5,944 (6.9%)	0.002
Diabetic neuropathy; n (%)	20,103 (25.3%)	19,893 (25.0%)	0.006	9,816 (25.1%)	9,731 (24.9%)	0.005	17,753 (20.6%)	17,886 (20.8%)	0.004
Diabetic nephropathy; n (%)	16,382 (20.6%)	16,090 (20.2%)	0.009	7,859 (20.1%)	7,673 (19.6%)	0.012	14,167 (16.4%)	14,227 (16.5%)	0.002
Diabetes with peripheral circulatory disorders; n (%)	9,605 (12.1%)	9,583 (12.1%)	0.001	5,044 (12.9%)	4,988 (12.7%)	0.004	9,627 (11.2%)	9,683 (11.2%)	0.002
Diabetic foot; n (%)	2,096 (2.6%)	2,073 (2.6%)	0.002	1,106 (2.8%)	1,077 (2.8%)	0.004	1,978 (2.3%)	1,957 (2.3%)	0.002
Erectile dysfunction; n (%)	3,153 (4.0%)	3,084 (3.9%)	0.004	1,811 (4.6%)	1,827 (4.7%)	0.002	3,900 (4.5%)	3,988 (4.6%)	0.005
Hypoglycemia; n (%)	15,124 (19.0%)	15,177 (19.1%)	0.002	9,112 (23.3%)	9,024 (23.0%)	0.005	19,509 (22.6%)	19,400 (22.5%)	0.003
Hyperglycemia/DKA/HONK; n (%)	42,188 (53.1%)	41,857 (52.6%)	0.008	21,187 (54.1%)	21,055 (53.8%)	0.007	42,600 (49.4%)	42,539 (49.4%)	0.001
Skin infections; n (%)	8,090 (10.2%)	8,056 (10.1%)	0.001	4,104 (10.5%)	3,990 (10.2%)	0.010	8,541 (9.9%)	8,566 (9.9%)	0.001
Other comorbidities									
Microalbuminuria or proteinuria; n (%)	3,911 (4.9%)	3,842 (4.8%)	0.004	2,342 (6.0%)	2,317 (5.9%)	0.003	4,556 (5.3%)	4,452 (5.2%)	0.005
Acute kidney injury; n (%)	5,238 (6.6%)	5,236 (6.6%)	0.000	2,165 (5.5%)	2,087 (5.3%)	0.009	3,729 (4.3%)	3,762 (4.4%)	0.002
CKD Stage 1-2; n (%)	3,603 (4.5%)	3,549 (4.5%)	0.003	1,410 (3.6%)	1,409 (3.6%)	0.000	3,521 (4.1%)	3,583 (4.2%)	0.004
CKD Stage 3-4; n (%)	11,173 (14.1%)	11,117 (14.0%)	0.002	4,366 (11.2%)	4,287 (10.9%)	0.006	9,317 (10.8%)	9,238 (10.7%)	0.003
Unspecified CKD; n (%)	4,472 (5.6%)	4,462 (5.6%)	0.001	1,953 (5.0%)	1,912 (4.9%)	0.005	3,491 (4.1%)	3,479 (4.0%)	0.001
Urinary tract infections; n (%)	10,771 (13.5%)	10,818 (13.6%)	0.002	4,630 (11.8%)	4,625 (11.8%)	0.000	10,137 (11.8%)	10,058 (11.7%)	0.003
COPD; n (%)	8,914 (11.2%)	8,911 (11.2%)	0.000	3,906 (10.0%)	3,846 (9.8%)	0.005	7,860 (9.1%)	7,909 (9.2%)	0.002
Asthma; n (%)	8,083 (10.2%)	8,050 (10.1%)	0.001	4,357 (11.1%)	4,290 (11.0%)	0.005	10,140 (11.8%)	10,145 (11.8%)	0.000
Obstructive sleep apnea; n (%)	20,290 (25.5%)	20,293 (25.5%)	0.000	11,636 (29.7%)	11,597 (29.6%)	0.002	28,394 (32.9%)	28,358 (32.9%)	0.001
Serious bacterial infections; n (%)	2,798 (3.5%)	2,804 (3.5%)	0.000	1,140 (2.9%)	1,106 (2.8%)	0.005	1,983 (2.3%)	1,973 (2.3%)	0.001
Pneumonia; n (%)	4,006 (5.0%)	4,048 (5.1%)	0.002	1,604 (4.1%)	1,576 (4.0%)	0.004	3,133 (3.6%)	3,114 (3.6%)	0.001
Liver disease; n (%)	11,550 (14.5%)	11,473 (14.4%)	0.003	6,351 (16.2%)	6,236 (15.9%)	0.008	14,548 (16.9%)	14,477 (16.8%)	0.002
MASH/MASLD; n (%)	6,375 (8.0%)	6,278 (7.9%)	0.005	3,692 (9.4%)	3,630 (9.3%)	0.005	9,214 (10.7%)	9,152 (10.6%)	0.002
Osteoarthritis; n (%)	21,376 (26.9%)	21,391 (26.9%)	0.000	10,325 (26.4%)	10,334 (26.4%)	0.001	23,274 (27.0%)	23,372 (27.1%)	0.003
Depression; n (%)	15,261 (19.2%)	15,175 (19.1%)	0.003	7,749 (19.8%)	7,679 (19.6%)	0.004	17,010 (19.7%)	17,046 (19.8%)	0.001
Dementia; n (%)	2,955 (3.7%)	2,909 (3.7%)	0.003	1,053 (2.7%)	1,041 (2.7%)	0.002	1,661 (1.9%)	1,662 (1.9%)	0.000
Delirium or psychosis; n (%)	1,218 (1.5%)	1,205 (1.5%)	0.001	531 (1.4%)	510 (1.3%)	0.005	883 (1.0%)	875 (1.0%)	0.001
Anxiety; n (%)	13,744 (17.3%)	13,792 (17.3%)	0.002	8,427 (21.5%)	8,179 (20.9%)	0.015	19,929 (23.1%)	19,771 (22.9%)	0.004
Sleep disorders; n (%)	24,589 (30.9%)	24,449 (30.8%)	0.004	11,988 (30.6%)	11,931 (30.5%)	0.003	28,221 (32.7%)	28,233 (32.8%)	0.000
Anemia; n (%)	14,705 (18.5%)	14,618 (18.4%)	0.003	6,526 (16.7%)	6,466 (16.5%)	0.004	14,226 (16.5%)	14,207 (16.5%)	0.001
COVID; n (%)	4,830 (6.1%)	5,015 (6.3%)	0.010	4,697 (12.0%)	4,693 (12.0%)	0.000	9,847 (11.4%)	9,944 (11.5%)	0.004
Hyperthyroidism/other thyroid disorders; n (%)	19,154 (24.1%)	19,121 (24.1%)	0.001	9,209 (23.5%)	9,094 (23.2%)	0.007	21,679 (25.2%)	21,772 (25.3%)	0.002
Hypothyroidism; n (%)	15,441 (19.4%)	15,392 (19.4%)	0.002	7,418 (18.9%)	7,277 (18.6%)	0.009	17,371 (20.2%)	17,404 (20.2%)	0.001
Urinary incontinence; n (%)	3,890 (4.9%)	3,811 (4.8%)	0.005	1,823 (4.7%)	1,821 (4.7%)	0.000	3,909 (4.5%)	3,867 (4.5%)	0.002
Use of other medications									
Metformin; n (%)	47,654 (59.9%)	47,488 (59.7%)	0.004	20,297 (51.8%)	20,367 (52.0%)	0.004	42,087 (48.8%)	42,204 (49.0%)	0.003
Insulins; n (%)	14,450 (18.2%)	14,038 (17.7%)	0.014	8,197 (20.9%)	8,115 (20.7%)	0.005	13,932 (16.2%)	13,906 (16.1%)	0.001
Sulfonylureas; n (%)	18,417 (23.2%)	18,366 (23.1%)	0.002	6,974 (17.8%)	6,911 (17.7%)	0.004	11,495 (13.3%)	11,418 (13.2%)	0.003
SGLT2 inhibitors; n (%)	12,234 (15.4%)	11,864 (14.9%)	0.013	8,143 (20.8%)	8,161 (20.8%)	0.001	15,897 (18.4%)	15,928 (18.5%)	0.001
Any other glucose-lowering drugs; n (%)	4,865 (6.1%)	4,835 (6.1%)	0.002	2,316 (5.9%)	2,307 (5.9%)	0.001	4,370 (5.1%)	4,384 (5.1%)	0.001
ACE or ARB; n (%)	59,870 (75.3%)	59,907 (75.4%)	0.001	28,583 (73.0%)	28,472 (72.7%)	0.006	61,304 (71.1%)	61,148 (70.9%)	0.004
ARNI; n (%)	864 (1.1%)	861 (1.1%)	0.000	627 (1.6%)	624 (1.6%)	0.001	1,347 (1.6%)	1,378 (1.6%)	0.003
Beta-blockers; n (%)	33,255 (41.8%)	33,333 (41.9%)	0.002	15,200 (38.8%)	15,182 (38.8%)	0.001	32,384 (37.6%)	32,591 (37.8%)	0.005
Calcium channel blockers; n (%)	26,321 (33.1%)	26,403 (33.2%)	0.002	12,321 (31.5%)	12,286 (31.4%)	0.002	26,196 (30.4%)	26,243 (30.4%)	0.001

Loop diuretics; n (%)	13,878 (17.5%)	13,927 (17.5%)	0.002	6,147 (15.7%)	6,040 (15.4%)	0.008	12,882 (14.9%)	12,893 (15.0%)	0.000
Thiazides; n (%)	27,881 (35.1%)	27,961 (35.2%)	0.002	13,220 (33.8%)	13,261 (33.9%)	0.002	30,433 (35.3%)	30,394 (35.3%)	0.001
Other diuretics; n (%)	6,442 (8.1%)	6,421 (8.1%)	0.001	3,347 (8.5%)	3,342 (8.5%)	0.000	7,464 (8.7%)	7,526 (8.7%)	0.003
Nitrates; n (%)	5,322 (6.7%)	5,234 (6.6%)	0.004	2,199 (5.6%)	2,202 (5.6%)	0.000	4,173 (4.8%)	4,135 (4.8%)	0.002
Statins; n (%)	63,368 (79.7%)	63,301 (79.6%)	0.002	31,016 (79.2%)	31,109 (79.5%)	0.006	64,885 (75.3%)	64,817 (75.2%)	0.002
PCSK9 inhibitors/other lipid-lowering drugs; n (%)	10,492 (13.2%)	10,370 (13.0%)	0.005	5,262 (13.4%)	5,154 (13.2%)	0.008	11,539 (13.4%)	11,571 (13.4%)	0.001
Antiplatelet medications; n (%)	8,847 (11.1%)	8,786 (11.1%)	0.002	3,764 (9.6%)	3,723 (9.5%)	0.004	7,159 (8.3%)	7,239 (8.4%)	0.003
Oral anticoagulants; n (%)	8,007 (10.1%)	8,055 (10.1%)	0.002	3,538 (9.0%)	3,540 (9.0%)	0.000	7,402 (8.6%)	7,426 (8.6%)	0.001
NSAIDS; n (%)	26,168 (32.9%)	26,171 (32.9%)	0.000	12,818 (32.7%)	12,802 (32.7%)	0.001	29,544 (34.3%)	29,645 (34.4%)	0.002
COPD/Asthma medications; n (%)	26,536 (33.4%)	26,463 (33.3%)	0.002	13,489 (34.5%)	13,344 (34.1%)	0.008	30,956 (35.9%)	30,907 (35.9%)	0.001
Urinary tract infections antibiotics; n (%)	36,563 (46.0%)	36,475 (45.9%)	0.002	17,746 (45.3%)	17,734 (45.3%)	0.001	40,944 (47.5%)	40,896 (47.4%)	0.001
Healthcare utilization									
Number of endocrinologist visits; mean (SD)	0.43 (1.20)	0.41 (1.54)	0.016	0.44 (1.31)	0.44 (1.43)	0.005	0.42 (1.34)	0.42 (1.37)	0.00
Number of cardiologist visits; mean (SD)	1.46 (3.37)	1.45 (3.31)	0.005	1.29 (2.97)	1.30 (3.16)	0.002	1.28 (2.99)	1.29 (3.07)	0.004
Number of Hospitalizations; mean (SD)	2.54 (21.95)	2.42 (17.31)	0.006	1.81 (13.73)	1.75 (14.13)	0.004	1.22 (10.95)	1.26 (16.98)	0.003
Emergency department visit; n (%)	26,726 (33.6%)	26,693 (33.6%)	0.001	11,738 (30.0%)	11,570 (29.6%)	0.009	22,894 (26.6%)	23,039 (26.7%)	0.004
Burden of comorbidities									
Combined comorbidity index; mean (SD)	1.85 (2.39)	1.84 (2.37)	0.007	1.70 (2.26)	1.68 (2.22)	0.011	1.53 (2.13)	1.54 (2.13)	0.005
Claims frailty index; mean (SD)	0.17 (0.06)	0.17 (0.06)	0.000	0.16 (0.06)	0.16 (0.06)	0.000	0.15 (0.05)	0.15 (0.05)	0.000
Healthy behavior markers									
Colonoscopy / Sigmoidoscopy; n (%)	7,905 (9.9%)	7,919 (10.0%)	0.001	4,034 (10.3%)	4,047 (10.3%)	0.001	9,377 (10.9%)	9,251 (10.7%)	0.005
Flu/Pneumococcal vaccine; n (%)	23,902 (30.1%)	23,969 (30.1%)	0.002	12,399 (31.7%)	12,410 (31.7%)	0.001	24,895 (28.9%)	24,898 (28.9%)	0.000
Pap smear; n (%)	5,817 (7.3%)	5,878 (7.4%)	0.003	3,016 (7.7%)	3,061 (7.8%)	0.004	8,081 (9.4%)	8,064 (9.4%)	0.001
Mammograms; n (%)	19,056 (24.0%)	19,162 (24.1%)	0.003	9,746 (24.9%)	9,830 (25.1%)	0.005	23,658 (27.4%)	23,538 (27.3%)	0.003
Telemedicine; n (%)	17,215 (21.7%)	17,097 (21.5%)	0.004	9,743 (24.9%)	9,719 (24.8%)	0.001	21,862 (25.4%)	21,958 (25.5%)	0.003
Laboratory and diagnostic tests									
HbA1c tests; mean (SD)	2.39 (1.50)	2.38 (1.84)	0.004	2.41 (1.38)	2.41 (1.32)	0.000	2.27 (1.35)	2.26 (1.35)	0.007
Lipid panels; mean (SD)	1.66 (1.32)	1.66 (1.54)	0.005	1.57 (1.15)	1.57 (1.18)	0.001	1.63 (1.15)	1.63 (1.20)	0.000

Abbreviations: ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DKA = diabetic ketoacidosis; ED = emergency department; HbA1c = hemoglobin A1c; HONK = hyperglycemic hyperosmolar nonketotic state; MASH = metabolic dysfunction–associated steatohepatitis; MASLD = metabolic dysfunction–associated steatotic liver disease; MI = myocardial infarction; n = number of individuals; NSAIDs = non-steroidal anti-inflammatory drugs; PCSK9 = proprotein convertase subtilisin/kexin type 9; SD = standard deviation; SGLT2 = sodium–glucose cotransporter 2; SMD = standardized mean difference; TIA = transient ischemic attack.

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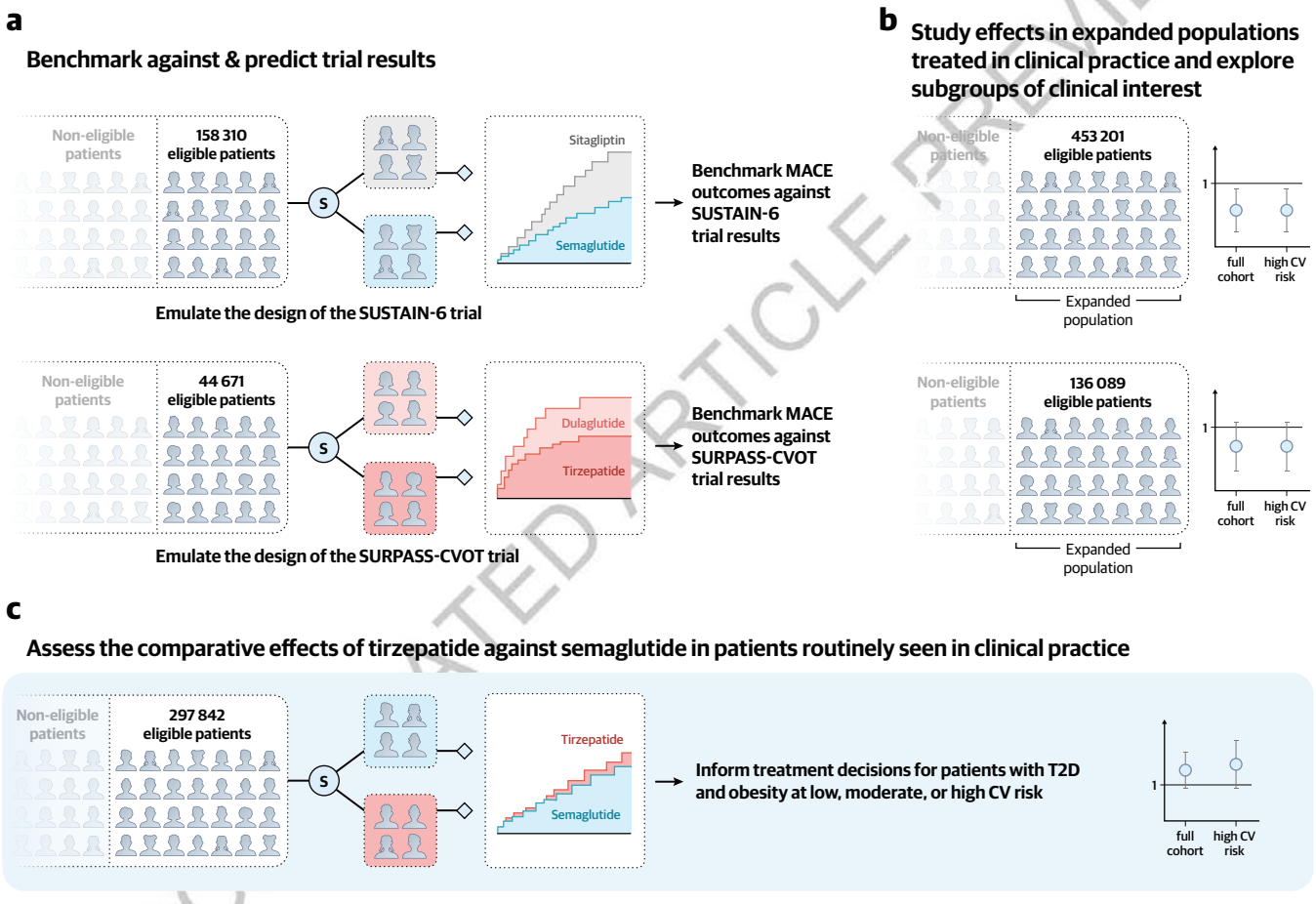

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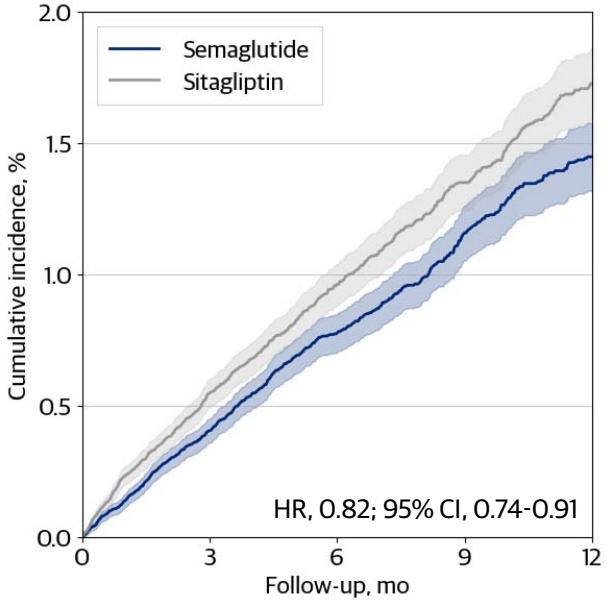
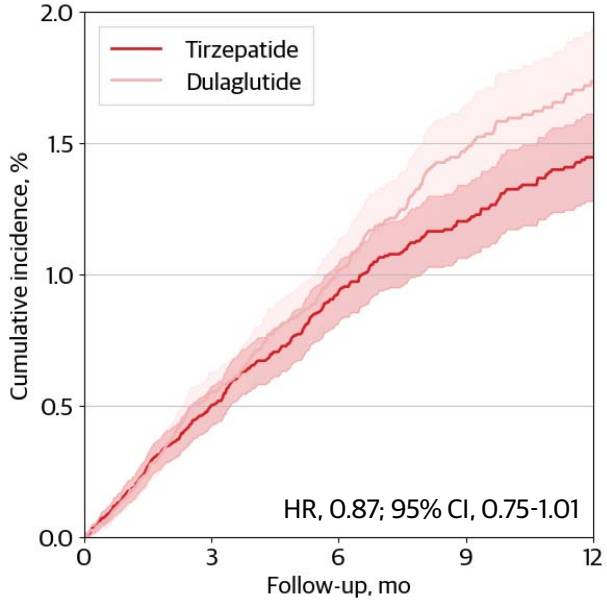


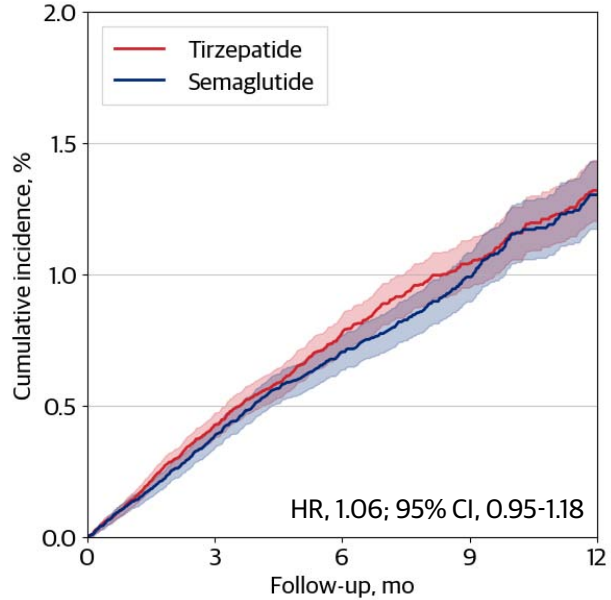
No. at risk					
Semaglutide	79.501	58.742	35.342	24.354	17.802
Sitagliptin	79.501	60.066	36.808	24.276	16.822

b



No. at risk					
Tirzepatide	39.152	27.630	17.574	11.890	8.129
Dulaglutide	39.152	27.922	15.286	8.832	4.764

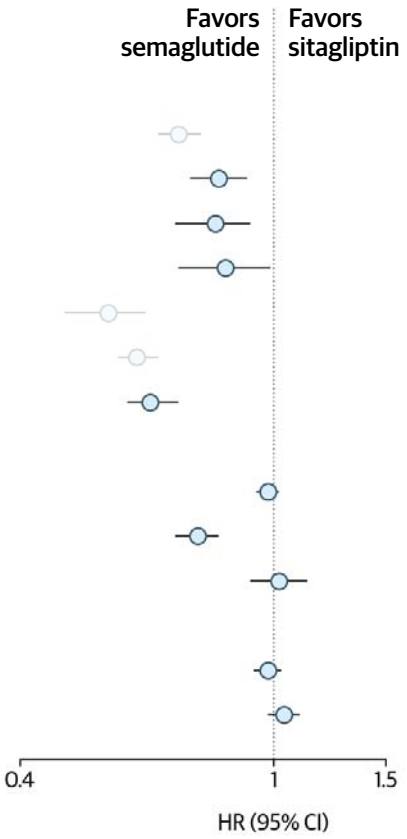
c



No. at risk					
Tirzepatide	86.191	59.937	36.612	23.320	14.014
Semaglutide	86.191	61.933	34.701	18.793	10.248

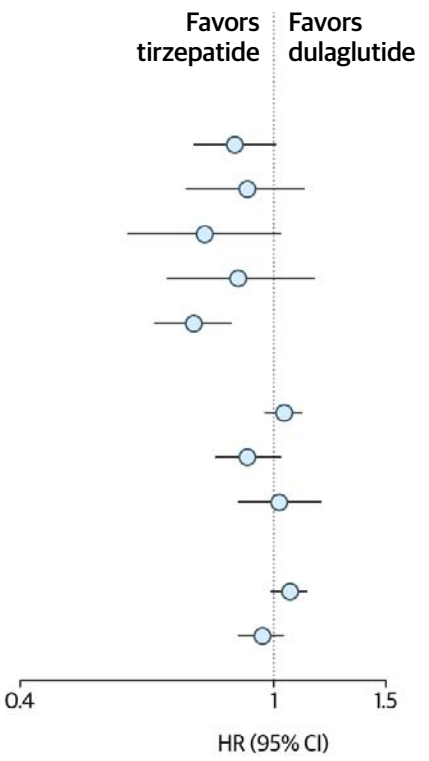
a

Effectiveness end points	1-year risk, % (95% CI)		HR (95% CI)
	Semaglutide	Sitagliptin	
*Myocardial infarction, stroke, or all-cause mortality**	*3.22 (2.43 to 3.55)*	*4.20 (3.80 to 4.51)*	*0.71 (0.65 to 0.77)*
Myocardial infarction, stroke	1.49 (1.36 to 1.62)	1.74 (1.60 to 1.88)	0.82 (0.74 to 0.91)
Myocardial infarction	0.89 (0.78 to 0.98)	1.08 (0.98 to 1.19)	0.81 (0.70 to 0.92)
Stroke	0.63 (0.55 to 0.73)	0.70 (0.63 to 0.79)	0.84 (0.71 to 0.99)
*All-cause mortality**	*0.77 (0.67 to 0.87)*	*1.32 (1.20 to 1.44)*	*0.55 (0.47 to 0.63)*
*HHF, urgent visit, or all-cause mortality**	*2.19 (2.03 to 2.35)*	*3.50 (3.30 to 3.69)*	*0.61 (0.57 to 0.66)*
HHF, urgent visit	0.63 (0.55 to 0.73)	0.70 (0.63 to 0.79)	0.64 (0.59 to 0.71)
Safety end points			
Urinary tract infection	8.74 (8.44 to 9.04)	8.81 (8.51 to 9.10)	0.98 (0.94 to 1.02)
Serious bacterial infection	2.63 (2.45 to 2.80)	3.40 (3.21 to 3.59)	0.76 (0.70 to 0.82)
Gastrointestinal adverse events	1.46 (1.33 to 1.58)	1.44 (1.32 to 1.56)	1.02 (0.92 to 1.13)
Negative controls			
Lumbar radiculopathy	6.44 (6.18 to 6.69)	6.48 (6.23 to 6.73)	0.98 (0.93 to 1.03)
Abdominal hernia	5.02 (4.79 to 5.25)	4.97 (4.74 to 5.20)	1.04 (0.98 to 1.10)



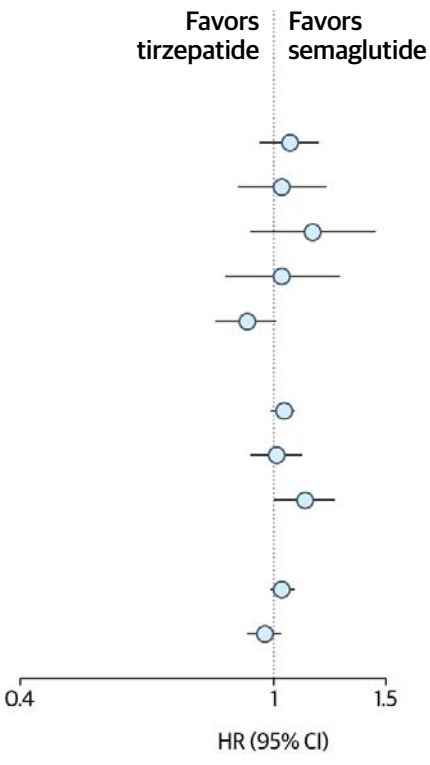
b

Effectiveness end points	1-year risk, % (95% CI)		HR (95% CI)
	Tirzepatide	Dulaglutide	
Myocardial infarction, stroke, or all-cause mortality	1.44 (1.28 to 1.61)	1.75 (1.54 to 1.96)	0.87 (0.75 to 1.01)
Myocardial infarction	0.69 (0.58 to 0.80)	0.88 (0.74 to 1.04)	0.91 (0.73 to 1.12)
Stroke	0.36 (0.28 to 0.43)	0.48 (0.39 to 0.58)	0.78 (0.59 to 1.03)
All-cause mortality	0.48 (0.38 to 0.59)	0.48 (0.38 to 0.59)	0.88 (0.68 to 1.16)
HHF, urgent visit, or all-cause mortality	1.64 (1.45 to 1.83)	2.07 (1.84 to 2.30)	0.75 (0.65 to 0.86)
Safety end points			
Urinary tract infection	8.37 (7.96 to 8.78)	8.02 (7.56 to 8.48)	1.04 (0.97 to 1.11)
Serious bacterial infection	2.28 (2.06 to 2.50)	2.51 (2.26 to 2.77)	0.91 (0.81 to 1.03)
Gastrointestinal adverse events	1.52 (1.34 to 1.70)	1.45 (1.26 to 1.64)	1.02 (0.88 to 1.19)
Negative controls			
Lumbar radiculopathy	7.24 (6.86 to 7.62)	7.23 (6.79 to 7.67)	1.06 (0.99 to 1.13)
Abdominal hernia	4.65 (4.33 to 4.97)	4.78 (4.42 to 5.14)	0.96 (0.88 to 1.04)



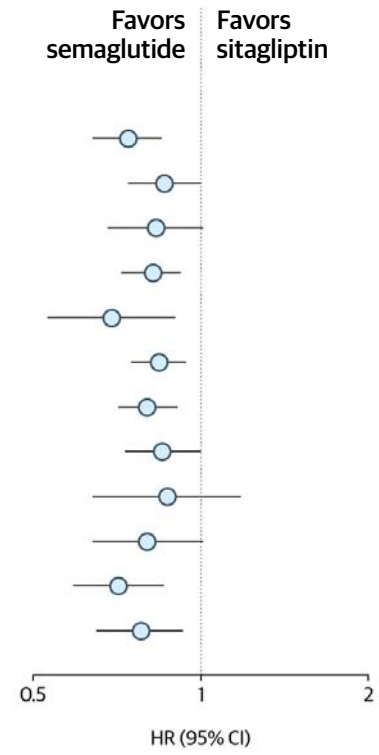
c

Effectiveness end points	1-year risk, % (95% CI)		HR (95% CI)
	Tirzepatide	Semaglutide	
Myocardial infarction, stroke, or all-cause mortality	1.33 (1.21 to 1.45)	1.32 (1.19 to 1.46)	1.06 (0.95 to 1.18)
Myocardial infarction	0.63 (0.55 to 0.71)	0.69 (0.60 to 0.79)	1.03 (0.88 to 1.21)
Stroke	0.31 (0.26 to 0.36)	0.29 (0.23 to 0.35)	1.15 (0.92 to 1.45)
All-cause mortality	0.45 (0.38 to 0.53)	0.41 (0.34 to 0.49)	1.03 (0.84 to 1.27)
HHF, urgent visit, or all-cause mortality	1.45 (1.32 to 1.58)	1.51 (1.38 to 1.65)	0.91 (0.81 to 1.01)
Safety end points			
Urinary tract infection	8.30 (8.00 to 8.60)	7.92 (7.61 to 8.23)	1.04 (0.99 to 1.08)
Serious bacterial infection	1.85 (1.71 to 1.99)	1.92 (1.76 to 2.08)	1.01 (0.92 to 1.11)
Gastrointestinal adverse events	1.44 (1.31 to 1.56)	1.38 (1.24 to 1.52)	1.12 (1.00 to 1.25)
Negative controls			
Lumbar radiculopathy	7.45 (7.18 to 7.72)	7.23 (6.93 to 7.52)	1.03 (0.99 to 1.08)
Abdominal hernia	4.63 (4.40 to 4.86)	4.70 (4.45 to 4.95)	0.97 (0.91 to 1.03)



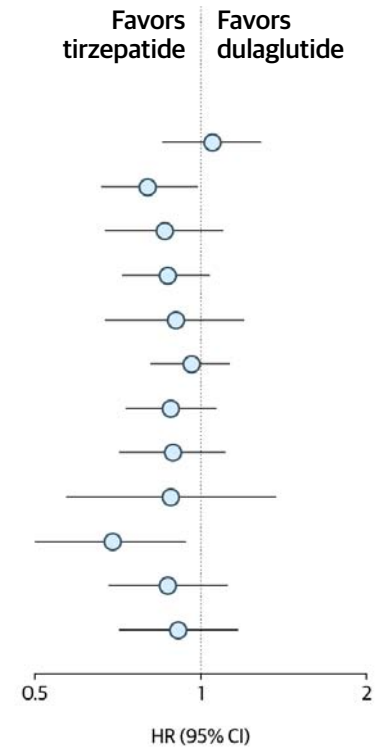
a

Subgroup	1-year risk, % (95% CI)		HR (95% CI)
	Semaglutide	Sitagliptin	
Female	1.41 (1.22 to 1.59)	1.79 (1.60 to 1.99)	0.74 (0.64 to 0.85)
Male	1.63 (1.43 to 1.83)	1.76 (1.56 to 1.96)	0.86 (0.74 to 1.00)
Stroke	0.78 (0.66 to 0.91)	0.93 (0.78 to 1.07)	0.83 (0.68 to 1.01)
Age below 65	2.20 (1.96 to 2.44)	2.46 (2.24 to 2.68)	0.82 (0.72 to 0.92)
Age 65 or older	1.24 (0.96 to 1.53)	1.84 (1.48 to 2.20)	0.69 (0.53 to 0.90)
Concomitant SGLT2i use	1.54 (1.39 to 1.69)	1.74 (1.59 to 1.89)	0.84 (0.75 to 0.94)
At high cardiovascular risk	3.10 (2.76 to 3.45)	3.57 (3.24 to 3.91)	0.80 (0.71 to 0.91)
Coronary heart disease	3.53 (3.05 to 4.01)	3.69 (3.25 to 4.12)	0.85 (0.73 to 1.00)
Cardiomyopathy	3.96 (2.94 to 4.97)	4.37 (3.34 to 5.39)	0.87 (0.64 to 1.18)
Valve disorders	3.46 (2.77 to 4.15)	3.75 (3.14 to 4.36)	0.80 (0.64 to 1.01)
Heart failure	4.10 (3.42 to 4.77)	5.12 (4.44 to 5.80)	0.71 (0.59 to 0.86)
High-intensive lipid-lowering therapy	1.96 (1.66 to 2.27)	2.38 (2.07 to 2.69)	0.78 (0.65 to 0.93)



b

Subgroup	1-year risk, % (95% CI)		HR (95% CI)
	Tirzepatide	Dulaglutide	
Female	1.47 (1.24 to 1.71)	1.51 (1.23 to 1.78)	1.05 (0.85 to 1.29)
Male	1.56 (1.31 to 1.82)	1.99 (1.68 to 2.31)	0.80 (0.66 to 0.99)
Stroke	0.80 (0.64 to 0.95)	1.04 (0.82 to 1.25)	0.86 (0.67 to 1.10)
Age below 65	2.50 (2.13 to 2.86)	2.88 (2.44 to 3.32)	0.87 (0.72 to 1.04)
Age 65 or older	1.57 (1.21 to 1.93)	2.07 (1.58 to 2.56)	0.90 (0.67 to 1.20)
Concomitant SGLT2i use	1.63 (1.42 to 1.83)	1.67 (1.44 to 1.90)	0.96 (0.81 to 1.13)
At high cardiovascular risk	3.16 (2.70 to 3.62)	3.94 (3.33 to 4.55)	0.88 (0.73 to 1.07)
Coronary heart disease	3.53 (2.91 to 4.16)	4.45 (3.63 to 5.27)	0.89 (0.71 to 1.11)
Cardiomyopathy	4.01 (2.62 to 5.37)	4.56 (2.95 to 6.13)	0.88 (0.57 to 1.37)
Valve disorders	3.46 (2.60 to 4.31)	5.68 (4.34 to 7.01)	0.69 (0.50 to 0.94)
Heart failure	5.01 (3.99 to 6.03)	5.86 (4.62 to 7.09)	0.87 (0.68 to 1.12)
High-intensive lipid-lowering therapy	1.99 (1.61 to 2.37)	2.25 (1.80 to 2.70)	0.91 (0.71 to 1.17)



c

Subgroup	1-year risk, % (95% CI)		HR (95% CI)
	Tirzepatide	Semaglutide	
Female	1.22 (1.07 to 1.37)	1.11 (0.96 to 1.27)	1.13 (0.96 to 1.32)
Male	1.48 (1.29 to 1.66)	1.54 (1.32 to 1.76)	1.06 (0.90 to 1.25)
Stroke	0.87 (0.75 to 0.99)	0.79 (0.67 to 0.92)	1.17 (0.98 to 1.40)
Age below 65	2.22 (1.95 to 2.48)	2.10 (1.80 to 2.40)	1.12 (0.96 to 1.30)
Age 65 or older	1.53 (1.24 to 1.82)	1.37 (1.08 to 1.67)	1.22 (0.95 to 1.56)
Concomitant SGLT2i use	1.29 (1.16 to 1.41)	1.16 (1.02 to 1.29)	1.15 (1.01 to 1.30)
At high cardiovascular risk	3.11 (2.76 to 3.46)	3.09 (2.67 to 3.51)	1.11 (0.96 to 1.27)
Coronary heart disease	3.23 (2.78 to 3.69	3.23 (2.72 to 3.73)	1.05 (0.88 to 1.25)
Cardiomyopathy	3.93 (2.91 to 4.95)	4.69 (3.34 to 6.03)	0.98 (0.71 to 1.36)
Valve disorders	3.01 (2.43 to 3.60)	3.35 (2.60 to 4.09)	1.04 (0.81 to 1.34)
Heart failure	4.54 (3.78 to 5.29)	4.38 (3.59 to 5.16)	1.01 (0.82 to 1.24)
High-intensive lipid-lowering therapy	1.91 (1.62 to 2.20)	1.99 (1.65 to 2.32)	1.04 (0.86 to 1.26)