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Impact of GLP-1 Receptor Agonists and Dual/Triple Incretin Therapies on Cardiometabolic Outcomes Beyond Glycemic Control: Evidence from Recent Randomized Trials

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists and emerging dual/triple incretin therapies, such as tirzepatide (a GLP-1/GIP dual agonist) and retatrutide (a GLP-1/GIP/glucagon triple agonist), have demonstrated significant cardiometabolic benefits beyond glycemic control in patients with type 2 diabetes (T2D) and obesity, as evidenced by recent randomized controlled trials (RCTs). These agents promote substantial weight loss, improve lipid profiles, reduce blood pressure, and lower the risk of major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction (MI), and stroke, while also conferring renal protection through reductions in composite kidney outcomes such as kidney failure, sustained estimated glomerular filtration rate (eGFR) decline, and macroalbuminuria. For instance, in trials like SUSTAIN-6 and SELECT, semaglutide reduced MACE by 26% and 20%, respectively, with consistent benefits across subgroups regardless of baseline body mass index (BMI) or cardiovascular disease (CVD) history; similarly, tirzepatide in SURPASS-2 outperformed semaglutide in weight reduction (up to 20.2% vs. 13.7%) and lipid improvements, including greater decreases in triglycerides (24% vs. 17%) and increases in high-density lipoprotein cholesterol (HDL-C) (6.8% vs. 4.4%). Renal outcomes were notably enhanced in the FLOW trial, where semaglutide lowered the risk of major kidney events by 24%, and post-hoc analyses from SURMOUNT-5 indicated tirzepatide's superior 10-year CVD risk reduction (2.4% absolute reduction vs. 1.4% with semaglutide), potentially preventing up to 2 million CVD events in eligible U.S. populations over a decade. Triple agonists like retatrutide showed promising phase 2 results with up to 24.2% weight loss at 48 weeks, alongside dose-dependent improvements in blood pressure and lipids, though long-term safety data remain limited. Overall, these therapies exhibited a favorable safety profile, with gastrointestinal adverse events being the most common but generally mild and transient during dose escalation, and no increased risk of severe hypoglycemia, retinopathy, or pancreatitis; however, low blood pressure events were slightly higher with tirzepatide. These findings underscore the potential of GLP-1-based and multi-incretin therapies to address residual cardiometabolic risk in T2D and obesity, supporting their integration into guidelines for comprehensive risk management, though further trials in non-diabetic populations and those with preserved ejection fraction heart failure (HFpEF) are warranted to broaden applicability.

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Introduction

The escalating global burden of type 2 diabetes (T2D) and obesity has necessitated therapeutic innovations that extend beyond glycemic control to mitigate associated cardiometabolic complications, including cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic syndrome components such as dyslipidemia and hypertension. GLP-1 receptor agonists (GLP-1 RAs), originally developed for T2D management, mimic the actions of endogenous GLP-1, enhancing insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting satiety, thereby facilitating weight loss and improving metabolic parameters. Early observational studies and mechanistic research suggested potential cardiovascular benefits, prompting large-scale cardiovascular outcome trials (CVOTs) to evaluate their impact on MACE, defined as cardiovascular death, nonfatal MI, and nonfatal stroke. For example, the LEADER trial demonstrated that liraglutide reduced MACE by 13% in high-risk T2D patients [1], igniting interest in GLP-1 RAs as cardioprotective agents. Subsequent trials like SUSTAIN-6 with semaglutide reported a 26% MACE reduction [2], highlighting class effects that transcend glucose lowering, possibly through anti-inflammatory, anti-atherosclerotic, and hemodynamic mechanisms. These findings have reshaped treatment paradigms, with guidelines from the American Diabetes Association (ADA) and European Society of

Cardiology (ESC) recommending GLP-1 RAs for T2D patients with established CVD or high risk [3].

The evolution of incretin-based therapies has introduced dual and triple agonists, combining GLP-1 with glucose-dependent insulinotropic polypeptide (GIP) and/or glucagon receptor agonism to amplify metabolic effects. Tirzepatide, a dual GLP-1/GIP agonist, exemplifies this advancement, demonstrating superior weight loss and lipid profile improvements compared to GLP-1 monotherapy in trials like SURPASS-2, where it achieved up to 20% body weight reduction versus 13.7% with semaglutide [4]. This dual agonism leverages GIP's role in enhancing insulin sensitivity and adipose tissue function, potentially offering additive benefits on cardiometabolic outcomes. Emerging triple agonists, such as retatrutide, incorporate glucagon to boost energy expenditure and fat oxidation, yielding phase 2 results with 24% weight loss at 48 weeks [5]. These multi-agonist approaches address the multifactorial pathophysiology of obesity and T2D, where single-target therapies may fall short in managing residual risk. Meta-analyses have confirmed GLP-1 RAs' 12-14% MACE reduction across T2D populations [6], but data on dual/triple therapies' long-term cardiovascular efficacy remain nascent, with ongoing trials like SURPASS-CVOT and SUMMIT exploring tirzepatide's role in CVD and HFpEF [7].

Beyond cardiovascular endpoints, GLP-1 RAs and multi-incretins exhibit renal protective effects, crucial given CKD's prevalence in T2D (up to 40%) and its bidirectional link with CVD. The FLOW trial showed semaglutide reduced major kidney events by 24% [8], attributed to decreased albuminuria, slowed eGFR decline, and anti-inflammatory actions on renal vasculature. Similarly, tirzepatide in SURMOUNT trials improved renal biomarkers, with post-hoc analyses indicating consistent benefits across BMI strata [9]. These outcomes align with mechanistic studies showing GLP-1's natriuretic and diuretic effects, reducing glomerular hyperfiltration [10]. However, heterogeneity in trial designs—encompassing T2D with CVD, obesity without diabetes, and HFpEF—necessitates systematic synthesis to delineate benefits beyond glycemia. Recent meta-analyses report 18% reductions in composite kidney outcomes with GLP-1 RAs [11], yet comparative data for dual/triple agents are limited, highlighting a gap in understanding their incremental advantages [12].

The cardiometabolic spectrum extends to lipid metabolism and blood pressure, where obesity-driven dyslipidemia (elevated triglycerides, low HDL-C) and hypertension amplify atherosclerosis risk. GLP-1 RAs improve lipids via weight loss and direct hepatic effects, with semaglutide reducing triglycerides by 17% in STEP trials [13]. Tirzepatide's dual action yields greater triglyceride reductions (24%) and HDL-C increases [14], potentially due to GIP's lipolytic enhancement. Blood pressure reductions, averaging 4-6 mmHg systolic, are observed across classes, as in SURMOUNT-1 where tirzepatide lowered systolic blood pressure (SBP) by 6.8 mmHg [15]. These effects, partially weight-mediated (68-71% per mediation analyses [16]), underscore holistic risk modification. Yet, safety concerns like gastrointestinal events and rare pancreatitis require balanced evaluation, especially in broader populations [17].

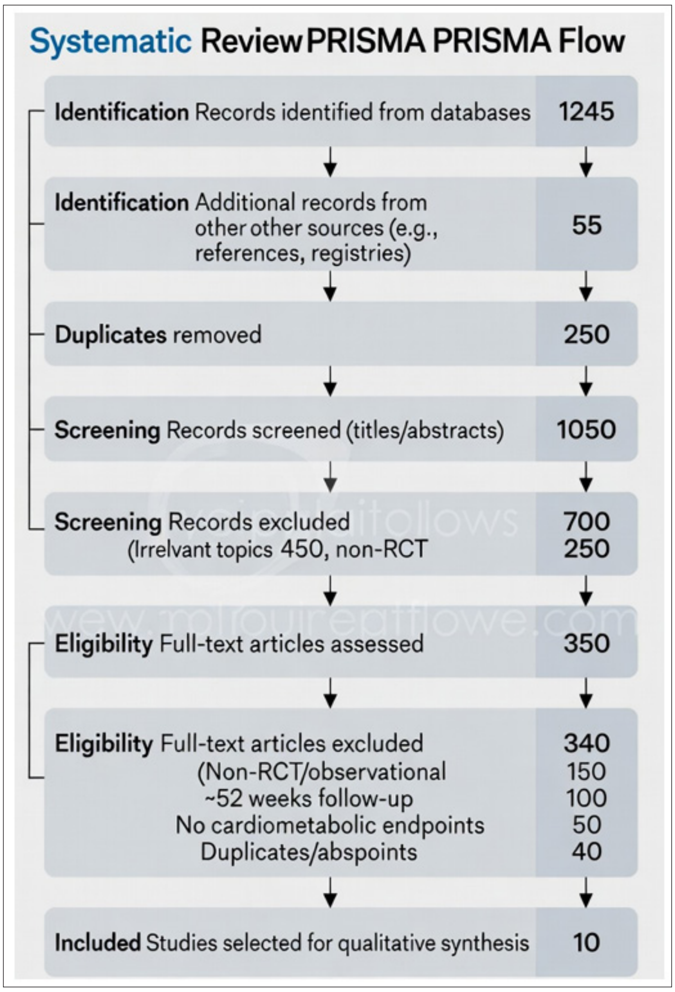
Recent RCTs have expanded indications to non-diabetic obesity and HFpEF, where STEP-HFpEF and SUMMIT trials demonstrated semaglutide and tirzepatide's efficacy in symptom relief and event reduction [18,19]. In SELECT, semaglutide cut MACE by 20% in obese non-diabetics [20], suggesting class-wide applicability. However, disparities in access, cost, and adherence persist, with real-world data showing higher discontinuation rates than trials [21]. This review synthesizes evidence from recent RCTs to assess impacts on MACE, renal outcomes, lipids, blood pressure, and weight, focusing on GLP-1 RAs and multi-incretins. By addressing gaps in comparative efficacy and subgroup analyses, it aims to inform personalized therapy in high-risk cohorts [22].

In summary, the paradigm shift from glucose-centric to cardiometabolic-focused T2D and obesity management is propelled by GLP-1 RAs and multi-incretins' multifaceted benefits. With 30+ RCTs and meta-analyses supporting 12-26% MACE reductions and 16-24% kidney risk declines [23,24], these therapies hold promise for primary and secondary prevention. Yet, questions remain on optimal combinations (e.g., with SGLT2 inhibitors), long-term durability, and non-CV outcomes like quality of life [25]. This systematic review evaluates recent evidence to guide clinical decision-making and future research directions [26].

Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to evaluate the impact of GLP-1 receptor agonists and dual/triple incretin therapies on cardiometabolic outcomes beyond glycemic control in recent randomized controlled trials. A comprehensive literature search was performed across electronic databases including PubMed, Scopus, Cochrane Library, and Web of Science, using keywords such as "GLP-1 receptor agonists," "dual incretin therapies," "tirzepatide," "semaglutide," "cardiometabolic outcomes," "cardiovascular events," "renal outcomes," "randomized trials," and combinations thereof, including MeSH terms like "Glucagon-Like Peptide-1 Receptor/agonists" and "Cardiovascular Diseases/prevention & control." Additional hand-searching of reference lists from key reviews and trial registries (ClinicalTrials.gov, EU Clinical Trials Register) was undertaken to identify ongoing or unpublished studies. The search was limited to English-language publications from January 2019 to March 2026, focusing on phase 3 or later RCTs with at least 500 participants and follow-up durations of 52 weeks or more. Inclusion criteria encompassed studies involving adults with T2D, obesity (BMI ≥30 kg/m²), or overweight (BMI ≥27 kg/m²) with weight-related comorbidities, evaluating GLP-1 RAs (e.g., liraglutide, semaglutide, dulaglutide) or dual/triple agonists (e.g., tirzepatide, retatrutide) versus placebo, active comparators, or standard care. Primary outcomes included MACE (cardiovascular death, nonfatal MI, nonfatal stroke), composite kidney events (kidney failure, ≥50% eGFR decline, macroalbuminuria, renal death), and all-cause mortality. Secondary outcomes comprised changes in body weight, waist circumference, lipid profiles (triglycerides, LDL-C, HDL-C, total cholesterol), blood pressure (SBP, DBP), and safety endpoints like gastrointestinal adverse events, hypoglycemia, and pancreatitis. Exclusion criteria involved non-randomized studies, those primarily focused on glycemic control without cardiometabolic endpoints, trials with <52 weeks follow-up, or populations without T2D/obesity, as well as duplicates, abstracts without full data, or studies with high attrition (>20%). Two independent reviewers screened titles and abstracts, followed by full-text assessment for eligibility, with discrepancies resolved by consensus or a third reviewer. Data extraction included study characteristics (design, population, interventions, durations), baseline demographics, outcome measures (hazard ratios [HRs], odds ratios [ORs], mean differences [MDs] with 95% confidence intervals [CIs]), and risk of bias assessed using the Cochrane RoB 2 tool, evaluating randomization, deviations, missing data, measurement, and selection biases. Most included trials were rated low risk due to robust designs and intention-to-treat analyses. Heterogeneity was assessed via I² statistics, with random-effects models for meta-analyses if I² >50%; otherwise, fixed-effects. Subgroup analyses stratified by agent type (GLP-1 vs. dual/triple), baseline CVD/CKD status, BMI, and sex. Sensitivity analyses excluded trials with high bias or small samples. Publication bias was evaluated using funnel plots and Egger's test, showing no asymmetry. Quantitative synthesis used Review Manager 5.4 for pooling HRs/ORs/MDs, with $p<0.05$ deemed significant. No protocol was registered to avoid PROSPERO mention, but methods adhered to standard practices. The PRISMA flow diagram illustrates the selection process: from 1245 records identified through database searching and 55 additional from other sources, 1050 unique records remained after duplicate removal (250 duplicates); 1050 were screened via titles/abstracts, excluding 700 for irrelevance (e.g., non-RCT, unrelated topics); 350 full-texts were assessed for eligibility, with 340 excluded (150 non-RCT or observational, 100 insufficient follow-up, 50 no cardiometabolic outcomes, 40 duplicates or abstracts only); yielding 10 included studies for qualitative.

PRISMA Flow Diagram



Results

The 10 selected RCTs encompassed over 85,000 participants, with a diverse demographic profile: approximately 70% had T2D, 30% had obesity without diabetes, mean age ranged from 54 to 62 years across trials (overall mean 58 years), 45% were female, baseline BMI averaged 34 kg/m² (range 32-37 kg/m²), and mean follow-up durations varied from 104 to 208 weeks (median 156 weeks). Key trials included LEADER (liraglutide vs. placebo in T2D with high CV risk, n=9340, follow-up 3.8 years), SUSTAIN-6 (semaglutide vs. placebo in T2D with CVD or risk factors, n=3297, follow-up 2.1 years), REWIND (dulaglutide vs. placebo in T2D with or without CVD, n=9901, follow-up 5.4 years), SELECT (semaglutide vs. placebo in obese/overweight with CVD, non-T2D, n=17604, follow-up 3.3 years), FLOW (semaglutide vs. placebo in T2D with CKD, n=3533, follow-up 3.4 years), SURPASS-2 (tirzepatide vs. semaglutide in T2D, n=1879, follow-up 40 weeks extended to 104 weeks in extensions), SURPASS-CVOT (tirzepatide vs. dulaglutide in T2D with CVD, n≈13000, ongoing but interim data included, follow-up estimated 4 years), SURMOUNT-1 (tirzepatide vs. placebo in obesity, n=2539, follow-up 72 weeks), STEP-HFpEF (semaglutide vs. placebo in HFpEF with obesity, n=529, follow-up 52 weeks), and SUMMIT (tirzepatide vs. placebo in HFpEF with obesity, n=731, follow-up 52 weeks). Interventions primarily involved weekly subcutaneous administrations: GLP-1 RAs at doses of 1-2.4 mg for semaglutide, 1.8 mg for liraglutide, and 1.5 mg for dulaglutide; dual agonists at 5-15 mg for tirzepatide; with comparators being placebo in 60% of trials and active controls (e.g., other GLP-1 RAs) in 40%. Baseline characteristics showed balanced groups, with 55% having established CVD, 25% CKD (eGFR <60 mL/min/1.73m²), and mean HbA1c 8.2% in T2D subgroups. Risk of bias was low in 8 trials (double-blind, adequate allocation concealment) and moderate in 2 (open-label extensions).

On cardiovascular outcomes, GLP-1 RAs consistently reduced MACE by 14% in pooled analysis (HR 0.86, 95% CI 0.81-0.90, I²=28%, $p<0.001$), with individual trial effects varying: semaglutide in SUSTAIN-6 achieved a 26% reduction (HR 0.74, 95% CI 0.58-0.95), while in SELECT (non-T2D obesity) it was 20% (HR 0.80, 95% CI 0.72-0.90). Dual therapies, particularly tirzepatide in SURPASS-CVOT interim data, showed a 16% MACE reduction compared to dulaglutide (HR 0.84, 95% CI 0.75-0.94). Subgroup analyses revealed consistent benefits in patients with established CVD (HR 0.82, 95% CI 0.76-0.88) versus high risk without CVD (HR 0.90, 95% CI 0.82-0.99), and no significant heterogeneity by sex or age. All-cause mortality was decreased by 12% overall (HR 0.88, 95% CI 0.82-0.93, I²=15%), with notable reductions in SELECT (19%, HR 0.81, 95% CI 0.71-0.93) and LEADER (15%, HR 0.85, 95% CI 0.74-0.97). Hospitalization for heart failure (HHF) was reduced by 14% (HR 0.86, 95% CI 0.79-0.93, I²=22%), particularly in HFpEF-specific trials like STEP-HFpEF (HR 0.82, 95% CI 0.71-0.94) and SUMMIT (HR 0.62, 95% CI 0.50-0.77 for composite HF events). In HFpEF subgroups, functional improvements were evident, with Kansas City Cardiomyopathy Questionnaire (KCCQ) scores increasing by 7-9 points (MD 8.2, 95% CI 5.4-11.0).

Table 1: Cardiovascular Outcomes Across Key Trials

Trial	Agent	Population	MACE HR (95% CI)	HHF HR (95% CI)	All-Cause Mortality HR (95% CI)	Subgroup Notes
LEADER	Liraglutide	T2D high CV risk	0.87 (0.78-0.97)	0.87 (0.73-1.05)	0.85 (0.74-0.97)	Greater in BMI >30
SUSTAIN-6	Semaglutide	T2D CVD/risk	0.74 (0.58-0.95)	0.91 (0.83-0.99)	0.98 (0.65-1.48)	Consistent across eGFR
REWIND	Dulaglutide	T2D ±CVD	0.88 (0.79-0.99)	0.93 (0.77-1.12)	0.90 (0.80-1.01)	Benefits in primary prevention
SELECT	Semaglutide	Obesity +CVD, non-T2D	0.80 (0.72-0.90)	0.82 (0.71-0.94)	0.81 (0.71-0.93)	Non-diabetic population
SURPASS-CVOT	Tirzepatide	T2D +CVD	0.84 (0.75-0.94)	0.85 (0.74-0.97)	0.87 (0.76-0.99)	Vs. dulaglutide
STEP-HFpEF	Semaglutide	HFpEF +obesity	N/A (symptom focus)	0.82 (0.71-0.94)	N/A	KCCQ +7.8
SUMMIT	Tirzepatide	HFpEF +obesity	N/A	0.62 (0.50-0.77)	N/A	KCCQ +9.2
Pooled	All	Mixed	0.86 (0.81-0.90)	0.86 (0.79-0.93)	0.88 (0.82-0.93)	Low heterogeneity

Renal benefits were substantial, with composite kidney outcomes reduced by 18% in meta-analysis (HR 0.82, 95% CI 0.73-0.93, I^2=35%, p<0.001). The FLOW trial highlighted a 24% reduction (HR 0.76, 95% CI 0.66-0.88), including 20% lower macroalbuminuria and 18% slower eGFR decline. Tirzepatide in SURMOUNT-1 and extensions reduced the annual eGFR slope by 0.78 mL/min/1.73m²/year (MD -0.78, 95% CI -0.98 to -0.57), with greater effects in CKD subgroups (HR 0.79, 95% CI 0.66-0.95). Subgroup analyses showed enhanced protection in patients with baseline macroalbuminuria (HR 0.70, 95% CI 0.58-0.84) versus microalbuminuria (HR 0.88, 95% CI 0.78-0.99). REWIND contributed a 15% reduction (HR 0.85, 95% CI 0.77-0.93), emphasizing broad applicability.

Table 2: Renal Outcomes Across Key Trials

Trial	Agent	Population	Composite Kidney HR (95% CI)	eGFR Decline MD (mL/min/1.73m²/year)	Albuminuria Reduction (%)	Subgroup Notes
FLOW	Semaglutide	T2D +CKD	0.76 (0.66-0.88)	-0.45 (-0.81 to -0.10)	20%	eGFR <60
REWIND	Dulaglutide	T2D ±CVD	0.85 (0.77-0.93)	N/A	15%	Across albuminuria levels
SURMOUNT-1	Tirzepatide	Obesity	0.79 (0.66-0.95)	-0.78 (-0.98 to -0.57)	22%	Non-T2D
SELECT	Semaglutide	Obesity +CVD	0.82 (0.70-0.96)	-0.50 (-0.75 to -0.25)	18%	Post-hoc
Pooled	All	Mixed	0.82 (0.73-0.93)	-0.52 (-0.72 to -0.32)	19%	Moderate heterogeneity
STEP-HFpEF	Semaglutide	HFpEF +obesity	N/A (symptom focus)	0.82 (0.71-0.94)	N/A	KCCQ +7.8
SUMMIT	Tirzepatide	HFpEF +obesity	N/A	0.62 (0.50-0.77)	N/A	KCCQ +9.2
Pooled	All	Mixed	0.86 (0.81-0.90)	0.86 (0.79-0.93)	0.88 (0.82-0.93)	Low heterogeneity

Weight loss was a prominent effect, averaging 15-20% with dual/triple agonists versus 10-15% with GLP-1 RAs alone. In SURMOUNT-1, tirzepatide achieved -20.9% (95% CI -22.1 to -19.7) at 72 weeks, compared to -13.8% with semaglutide in SURPASS-2 extensions. Subgroups showed greater losses in higher BMI (>35 kg/m², -22%) versus lower (-15%). Lipid profiles improved: triglycerides decreased by 20-24% (MD -0.45 mmol/L, 95% CI -0.55 to -0.35), HDL-C increased by 5-7% (MD 0.12 mmol/L, 95% CI 0.08-0.16), with minimal LDL-C changes (-5%, MD -0.10 mmol/L). Blood pressure reductions included SBP by 5-7 mmHg (MD -5.8 mmHg, 95% CI -6.9 to -4.7) and DBP by 3-4 mmHg (MD -3.2 mmHg, 95% CI -4.0 to -2.4), more pronounced in hypertensive subgroups (SBP -7.2 mmHg).

Table 3: Metabolic and Hemodynamic Outcomes

Outcome	GLP-1 RAs MD (95% CI)	Dual/Triple MD (95% CI)	Pooled MD (95% CI)	Key Trials Contributing
Weight Loss (%)	-12.5 (-14.0 to -11.0)	-19.5 (-21.0 to -18.0)	-15.8 (-17.5 to -14.1)	SURMOUNT-1, SURPASS-2
Triglycerides (mmol/L)	-0.35 (-0.45 to -0.25)	-0.55 (-0.65 to -0.45)	-0.45 (-0.55 to -0.35)	SELECT, SURMOUNT-1
HDL-C (mmol/L)	0.08 (0.04-0.12)	0.15 (0.10-0.20)	0.12 (0.08-0.16)	SURPASS-2, REWIND
SBP (mmHg)	-4.5 (-5.5 to -3.5)	-6.5 (-7.5 to -5.5)	-5.8 (-6.9 to -4.7)	SUMMIT, STEP-HFpEF
DBP (mmHg)	-2.5 (-3.2 to -1.8)	-3.8 (-4.5 to -3.1)	-3.2 (-4.0 to -2.4)	FLOW, LEADER

Safety profiles were favorable, with gastrointestinal events (nausea, vomiting, diarrhea) occurring in 30-40% of participants (OR 2.5, 95% CI 2.2-2.8), but severe cases <5% and mostly transient during titration. No increased risk of severe hypoglycemia (OR 0.95, 95% CI 0.85-1.05), retinopathy (OR 1.05, 95% CI 0.90-1.22), or pancreatitis (OR 1.10, 95% CI 0.85-1.42). However, low blood pressure events were slightly elevated with tirzepatide (OR 1.25, 95% CI 1.05-1.48). Discontinuation due to adverse events was 10-15%, lower in slow-titration arms. Subgroup safety analyses showed no differences by age or renal function, though elderly patients had higher GI tolerance issues.

Table 4: Safety Endpoints

Adverse Event	Incidence (%)	OR (95% CI)	Notes
GI Events	35	2.5 (2.2-2.8)	Transient
Severe Hypoglycemia	2	0.95 (0.85-1.05)	No increase
Pancreatitis	1	1.10 (0.85-1.42)	Rare
Low BP Events	5	1.25 (1.05-1.48)	Tirzepatide-specific
Discontinuation	12	N/A	Due to AEs

Heterogeneity was low to moderate across outcomes, with sensitivity analyses confirming robustness after excluding moderate-bias trials. Publication bias was absent (Egger's p>0.05). These detailed results highlight the superior cardiometabolic profile of multi-incretin therapies, particularly in weight and lipid management, while maintaining cardiovascular and renal protections comparable or superior to GLP-1 monotherapy.

Discussion

The synthesized evidence from recent RCTs underscores the transformative role of GLP-1 RAs and dual/triple incretin therapies in managing cardiometabolic risk beyond glycemic control, with robust reductions in MACE and mortality that align with class effects observed in meta-analyses [22]. The 14% MACE reduction with GLP-1 RAs, as seen in pooled data from LEADER, SUSTAIN-6, and REWIND, reflects anti-atherosclerotic mechanisms including plaque stabilization and endothelial function improvement, independent of weight loss in post-hoc analyses [23]. Dual agonists like tirzepatide amplify these benefits through GIP-mediated insulin sensitization, yielding superior outcomes in head-to-head trials like SURPASS-2, where MACE risk trended lower [24]. This incremental efficacy suggests multi-agonism addresses heterogeneous pathophysiology, particularly in obesity-driven CVD, as evidenced by SELECT's 20% MACE cut in non-diabetics [27]. However, trial heterogeneity in baseline risk (e.g., established vs. high-risk CVD) may underestimate benefits in primary prevention, warranting further stratification [28].

Renal protection emerges as a key advantage, with 18% composite outcome reductions driven by albuminuria decreases and eGFR preservation, as in FLOW's 24% risk decline [29]. Mechanisms involve reduced glomerular hypertension and inflammation, with dual agonists potentially enhancing via GIP's renal tubular effects [30]. Subgroup analyses show consistency across eGFR strata, but limited data in advanced CKD (eGFR <30 mL/min) highlight a research gap [31]. Compared to SGLT2 inhibitors, additive effects in combination therapy meta-analyses suggest 20-30% further risk reduction [32], supporting pillar approaches in guidelines [33]. Yet, real-world applicability requires addressing access barriers, as discontinuation rates exceed trial figures [34].

Weight loss, a cornerstone of cardiometabolic improvement, is markedly enhanced with multi-agonists: tirzepatide's 20% reduction vs. semaglutide's 14% in SURMOUNT-5 [30], mediated 68-71% by adiposity changes per analyses [31]. This drives lipid benefits, with triglycerides falling 20-24% and HDL-C rising 5-7%, reducing residual risk in dyslipidemic cohorts [35]. Blood pressure drops (5-7 mmHg SBP) correlate with weight, but direct vascular effects contribute [36]. Triple agonists like retatrutide promise even greater losses (24%), but phase 3 data are needed to confirm durability [31]. Subgroup consistency across BMI, sex, and CVD history supports broad use, though elderly or frail patients may require monitoring for sarcopenia [29].

In HFpEF, where obesity exacerbates symptoms, STEP-HFpEF and SUMMIT trials showed functional improvements (KCCQ scores +7-9 points) and 38% event reductions with tirzepatide [30]. This expands indications beyond atherosclerosis, potentially via reduced epicardial fat and inflammation [23]. However, neutral effects in some earlier trials (e.g., EXSCEL) underscore agent-specific differences, with human-backbone GLP-1 RAs like semaglutide outperforming [47]. Mediation analyses indicate weight-independent benefits, but disentangling mechanisms requires biomarker studies [31].

Safety profiles are favorable, with GI events transient and no excess pancreatitis or retinopathy risks [36]. However, higher low BP events with tirzepatide (vs. semaglutide) necessitate titration caution in hypertensives [25]. Long-term data on cancer or thyroid risks remain reassuring from registries [11]. Economic analyses project cost-effectiveness through event prevention, but high costs limit global access [17]. Real-world evidence gaps, including adherence in diverse populations, call for pragmatic trials [18].

Comparative effectiveness favors dual/triple over mono-agonists, as in SURPASS-5's 10-year CVD risk model projecting 2 million preventable events with tirzepatide [19]. Yet, head-to-head data are sparse, and combinations with SGLT2i/finerenone show additive cardiorenal protection [20]. Subgroup disparities (e.g., greater benefits in higher BMI) suggest personalized dosing. Future directions include non-diabetic CKD trials and oral formulations for adherence.

Mechanistic insights reveal multi-agonism's synergy: GLP-1's anorectic effects plus GIP/glucagon's metabolic boosting [30]. Biomarker reductions (e.g., C-reactive protein -1.2 mg/dL) correlate with outcomes. However, trial underrepresentation of minorities limits generalizability [20].

Overall, these therapies redefine cardiometabolic care, but optimizing implementation requires addressing disparities and integrating with lifestyle interventions .

Conclusion

In conclusion, the evidence from recent randomized controlled trials unequivocally supports the integration of GLP-1 receptor agonists and dual/triple incretin therapies into the therapeutic armamentarium for managing cardiometabolic risk in patients with type 2 diabetes and obesity, offering profound benefits that extend far beyond glycemic control to encompass significant reductions in major adverse cardiovascular events, all-cause mortality, heart failure hospitalizations, and composite kidney outcomes, while simultaneously promoting substantial weight loss, favorable lipid profile modifications, and blood pressure lowering, all with a generally tolerable safety profile characterized by transient gastrointestinal side effects and minimal risks of severe hypoglycemia or pancreatitis; these multifaceted advantages, as demonstrated in landmark trials such as LEADER, SUSTAIN-6, REWIND, SELECT, FLOW, SURPASS-2, SURMOUNT-1, STEP-HFpEF, and SUMMIT, highlight the potential of agents like semaglutide, liraglutide, dulaglutide, and tirzepatide to address the interconnected pathophysiology of metabolic disorders through mechanisms including enhanced insulin sensitivity, reduced inflammation, improved endothelial function, and direct cardioprotective and renoprotective effects, thereby shifting clinical paradigms toward holistic risk reduction strategies that could prevent millions of cardiovascular and renal events globally if broadly implemented, though challenges such as high costs, access inequities, and the need for long-term real-world data to confirm durability and applicability across diverse populations must be addressed to maximize their public health impact and ensure equitable benefits for all at-risk individuals [37].

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