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Systematic review

PERSONALIZING INCRETIN THERAPY FOR OBESITY: A FOCUSED SYSTEMATIC REVIEW

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ABSTRACT

Background: Incretin treatment selection should consider comorbidity, expected weight loss, durability, route, tolerability, body composition, and access. This review evaluated phenotype-oriented evidence for semaglutide, tirzepatide, and emerging oral or multi-agonist therapies.

Methods: PRISMA 2020 and PRISMA-S informed a focused narrative review. PubMed/MEDLINE, Embase, Scopus, Web of Science, CENTRAL, trial registries and citation sources were searched with bibliographic coverage from 1 January 2024 to a final search date of 8 January 2026, and supplementary searches without a lower date limit. Two reviewers screened records and extracted data independently. Risk of bias and certainty of evidence were appraised descriptively rather than through formal RoB 2, ROBINS-I or GRADE procedures.

Results: Twenty-eight report-level sources were included (22 primary analyses and 6 contextual sources). Tirzepatide produced greater weight loss than semaglutide in SURMOUNT-5; semaglutide reduced major cardiovascular events in SELECT. Both improved outcomes in obesity-related heart failure with preserved ejection fraction, while tirzepatide improved obstructive sleep apnea outcomes and reduced diabetes onset in prediabetes. Semaglutide and tirzepatide showed phase 3 and phase 2 metabolic dysfunction-associated steatohepatitis (MASH) results, respectively. Discontinuation in routine care was common.

Conclusions: Treatment should follow phenotype and a sustainable plan rather than an average weight-loss hierarchy. Cost, route, adverse effects, reproductive plans, persistence, and muscle function should inform selection. Biomarker-guided algorithms remain investigational.

Keywords: Obesity; Glucagon-Like Peptide-1 Receptor Agonists; Weight Loss; Cardiovascular Diseases; Precision Medicine.

INTRODUCTION

Obesity is a chronic, relapsing, and biologically heterogeneous disease that requires long-term management. The 2025 World Health Organization guideline placed GLP-1-based medicines within comprehensive chronic obesity care (1), while the U.S. Food and Drug Administration expanded the indication for semaglutide 2.4 mg to reduction of major cardiovascular events in adults with established cardiovascular disease and overweight or obesity (2). These developments make drug selection a clinical outcome question rather than a choice based solely on the percentage of weight lost.

Semaglutide produced substantial weight reduction in STEP 1 (3), but withdrawal was followed by marked regain and partial reversal of cardiometabolic improvement (4). Tirzepatide produced substantial reductions in SURMOUNT-1 (5), supported maintenance when continued in SURMOUNT-4 (6), and was superior to semaglutide in the head-to-head SURMOUNT-5 trial (7). Oral semaglutide (8), oral orforglipron in phase 2 and phase 3 trials (9, 10), and the triple agonist retatrutide (11) have expanded the range of administration routes and expected efficacy.

Comorbidity changes the hierarchy of evidence. Semaglutide has cardiovascular outcome data from SELECT and its long-term weight analysis (12, 13). In obesity-related heart failure with preserved ejection fraction (HFpEF), semaglutide improved symptoms, physical limitations, and exercise function in patients without and with type 2 diabetes (14, 15), whereas tirzepatide reduced a composite of cardiovascular death or worsening heart failure in SUMMIT (16). Tirzepatide also has direct randomized evidence in obstructive sleep apnea (OSA) (17). Hepatic evidence includes phase 2 and phase 3 semaglutide trials (18, 19) and the phase 2

SYNERGY-NASH trial of tirzepatide (20). Long-term follow-up from SURMOUNT-1 further supports tirzepatide in people with prediabetes (21).

The clinical value observed in trials is modified by access, dose escalation, tolerability, and persistence. Real-world comparisons and discontinuation studies show that many patients do not remain on treatment long enough to reproduce trial efficacy (22, 23). Substantial weight reduction also includes loss of lean mass, although available body-composition studies indicate that most lost tissue is fat mass and do not establish that lean-mass reduction necessarily causes functional decline (24, 25).

This review examines how selected contemporary incretin trials inform treatment choice by dominant comorbidity, sustained access, route compatibility, and functional vulnerability. Its objective is to distinguish direct clinical-outcome evidence from cross-trial comparisons and interpretive monitoring recommendations.

METHODS

Review design and reporting standard

This focused systematic review uses a structured narrative synthesis. Reporting follows PRISMA 2020 and PRISMA-S (26–28). A protocol defining eligibility, extraction fields and the synthesis plan was prepared before extraction; it was not prospectively registered or publicly deposited.

PICO and eligibility criteria

The primary population was adults with obesity or overweight and a clinically relevant comorbidity or treatment-pathway concern. Adolescent studies were excluded from the main synthesis. The PICO framework is shown in Table 1.

Table 1. PICO framework of the review

Component	Definition
Population	Adults with obesity or overweight. Prespecified phenotypes included prediabetes, established atherosclerotic cardiovascular disease (ASCVD), HFpEF, OSA, metabolic dysfunction-associated steatohepatitis (MASH), risk of sarcopenia or functional vulnerability, reproductive age or preconception, and barriers to injectable therapy.
Intervention	Semaglutide, tirzepatide, oral semaglutide, orforglipron, retatrutide, and related contemporary GLP-1, GIP/GLP-1, or triple GIP/GLP-1/glucagon strategies. Liraglutide was not part of the primary comparative synthesis because the review focused on contemporary higher-efficacy therapies.
Comparator	Placebo, lifestyle intervention, active comparator, continuation versus withdrawal, injectable versus oral strategy, or real-world treatment trajectories.
Outcomes	Weight reduction and maintenance; incident type 2 diabetes; major adverse cardiovascular events; HFpEF outcomes; OSA metrics; MASH histology; body composition and physical function; adverse events; discontinuation and reinitiation; quality of life.

Inclusion and exclusion criteria

Eligible primary sources were randomized controlled trials, randomized withdrawal trials, head-to-head trials, extension and maintenance analyses, body-composition substudies, outcome trials, and large observational cohorts. Minimum follow-up for primary clinical studies was 12 weeks, except where a shorter report provided unique safety or treatment-pathway information. Systematic reviews, network meta-analyses, guidelines, regulatory documents, and professional statements were used for context and citation searching but were not used as primary evidence of comparative effect.

Studies were excluded when they involved a non-target population, an intervention outside the contemporary scope, follow-up too short for a clinically relevant outcome, a duplicate or secondary report without new data, or outcomes that could not inform phenotype, maintenance, persistence, route, body composition, or comorbidity-related selection.

Information sources and search strategy

Sources comprised MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection, CENTRAL, ClinicalTrials.gov, WHO ICTRP and citation searching. Bibliographic coverage began on 1 January 2024; supplementary searching had no lower date limit and retained earlier studies. The final search date was 8 January 2026.

The core strategy combined obesity or overweight terms with drug-class and individual-drug terms. Outcome terms were reserved for supplementary searches and screening. Supplementary Section S1 reproduces the search strings for each platform; per-source yields are reported in aggregate within the selection flow.

The search design and source coverage are summarized in Table 2.

Table 2. Search design and source coverage

Search component	Sources	Coverage	Purpose
Contemporary bibliographic search	PubMed, Embase, Scopus, Web of Science Core Collection, CENTRAL	From 1 January 2024; final search date 8 January 2026	Recent phase 3, outcome, extension, comparative, body-composition, and observational evidence.

Search component	Sources	Coverage	Purpose
Trial-register search	ClinicalTrials.gov, WHO ICTRP	Registry status searched through 8 January 2026; no publication-date restriction	Completed and ongoing adult obesity studies; verification of trial programs and outcomes.
Supplementary evidence search	PubMed, citation indexes, reference lists, and journal websites	Citation and topic searches through 8 January 2026; earlier studies retained	Earlier and phenotype-specific randomized, outcome, withdrawal, body-composition, and persistence evidence.
Targeted website and citation search	WHO, FDA, EASO, journal websites, backward and forward citation searching	Web and citation checks through 8 January 2026	Regulatory, policy, reproductive-context, online-first, and citation-linked evidence.

Study selection and data extraction

Two reviewers independently screened titles, abstracts and full texts, resolving disagreements by consensus or by a third reviewer. Extraction fields included design, sample size, population, intervention, comparator, dose, duration, weight, glycemia, cardiovascular and HFpEF outcomes, sleep apnea, MASH histology, body composition, adverse events, discontinuation and reinitiation. Supplementary Tables S4A and S4B present the extraction template and the principal study-level summaries.

Risk of bias and confidence in the evidence

RoB 2 (29) and ROBINS-I (30) provided the frameworks for randomized and non-randomized evidence, applied descriptively rather than through completed signaling-question forms. Tables S3A and S3B accordingly present domain-relevant considerations rather than formal domain and overall ratings. Bias is distinguished throughout from imprecision, surrogate endpoints and restricted applicability. Table 8 gives a narrative interpretation of certainty rather than formal GRADE ratings.

Risk of bias due to missing results was considered qualitatively; outcome-to-protocol comparisons were not carried out for every study, so selective reporting cannot be excluded. Funnel plots and tests for small-study effects were not applied, because too few comparable studies were available within any single outcome domain. No sensitivity analyses were conducted.

Data synthesis

Meta-analysis was not performed because drugs, doses, follow-up, populations, estimands, and outcomes differed substantially. Narrative synthesis grouped weight reduction, prediabetes, ASCVD, HFpEF, OSA, MASH, oral routes, body composition, functional vulnerability, and persistence. Reported numerical results are not interchangeable across trials or estimands. Linked analyses from the same trial were interpreted together without summing overlapping participants. Treatment-selection and monitoring suggestions are interpretive; a phenotype-based prescribing algorithm was not tested.

RESULTS

Study selection

The selection flow identified 426 database/register records: 112 duplicates and 18 further records were removed before screening, leaving 296 records, of which 232 were excluded. Of the 64 reports sought, 2 were not retrieved, 62 were assessed and 45 were excluded, leaving 17. Other methods yielded 43 assessed reports, of which 32 were excluded and 11 retained. The resulting 28 sources comprise 22 primary reports or analyses listed in Table 5 and six contextual sources identified in Table 4; they do not represent 28 independent trials. The 18 pre-screening removals comprise protocols, insufficient abstracts, corrections and non-primary publications, reported here by category rather than by citation. Figure 1 presents the flow, and Table 3 gives database/register exclusion categories.

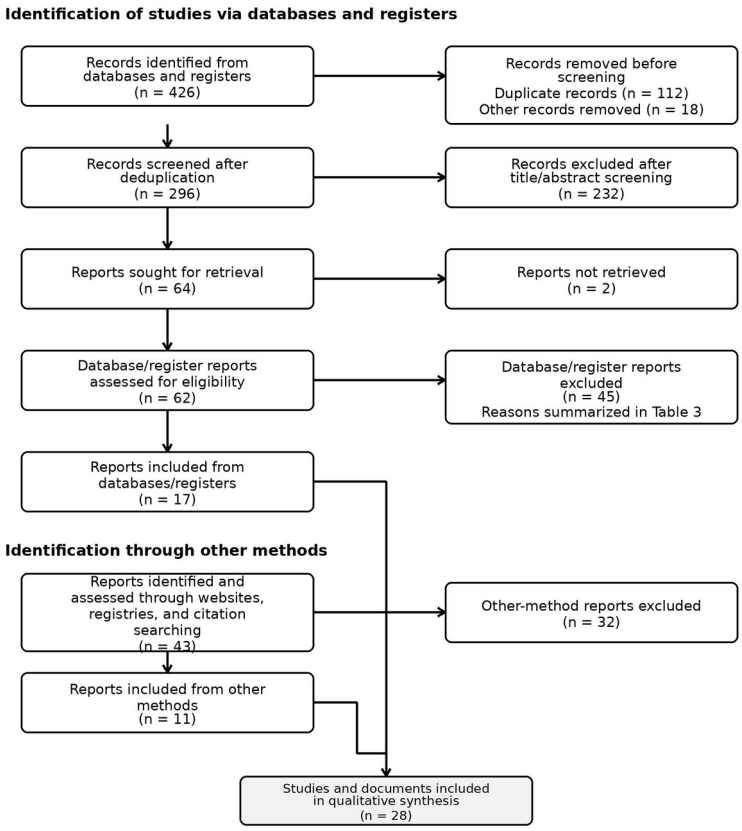

Figure 1. Study selection flow. Contextual sources are distinguished from primary reports.

Table 3. Reasons for exclusion of database or register full-text reports

Reason for exclusion	n	Explanation
Short follow-up or no clinically relevant outcome	16	Reports limited to early surrogate changes without maintenance, comorbidity, safety-trajectory, or clinically interpretable outcome data.
Wrong population or intervention	10	Predominantly diabetes-only studies without obesity-oriented outcomes or interventions outside the contemporary prespecified scope.
Duplicate or secondary report without new data	11	Comments, letters, conference-only summaries, or secondary publications without an independent dataset or new eligible analysis.
No data relevant to personalization or treatment trajectory	8	Treatment effects could not be linked to phenotype, body composition, persistence, route, or a clinically relevant pathway.

Characteristics of the included evidence

The 22 primary reports in Table 5 informed clinical effects. WHO guidance (1), FDA material (2), body-composition and comparative reviews (25, 31), and reproductive-context sources (32, 33) informed interpretation. Methodological references (26–30) are not part of the 28-source evidence set. Related analyses may share participants and must not be counted as independent trials.

Table 4. Structure of the evidence base

Evidence group	Included sources	Role in synthesis
Randomized efficacy, comparative, outcome, and withdrawal studies	STEP 1, SURMOUNT-1, SURMOUNT-4, SURMOUNT-5, OASIS 1, orforglipron phase 2 and ATTAIN-1, retatrutide phase 2, SELECT, STEP-HFpEF, STEP-HFpEF DM, SUMMIT, SURMOUNT-OSA, semaglutide NASH, ESSENCE, and SYNERGY-NASH (3, 5–12, 14–20).	Primary estimates of efficacy, comparative effects, clinical outcomes, maintenance, and safety.
Extensions and secondary randomized analyses	STEP 1 extension, SELECT long-term weight analysis, SURMOUNT-1 diabetes-prevention analysis (4, 13, 21).	Withdrawal, long-term weight maintenance, and transition to type 2 diabetes.
Body-composition evidence	SURMOUNT-1 DXA substudy and systematic review/network meta-analysis (24, 25).	DXA primary data (24); secondary synthesis (25) provides context and is not an independent participant cohort.

Evidence group	Included sources	Role in synthesis
Real-world cohorts	Semaglutide versus tirzepatide and discontinuation/reinitiation cohorts (22, 23).	Applicability under routine dosing, access, discontinuation, and reinitiation.
Contextual sources	WHO, FDA, body-composition and comparative meta-analyses, and reproductive-context sources (1, 2, 25, 31–33).	Guideline, regulatory, comparative, and reproductive interpretation; not primary comparative evidence.

Note: Categories overlap. Reference 25 contributes to body-composition context and the contextual-source group; it is counted once in the total of 28 sources.

Weight reduction, comparative efficacy, and maintenance

In STEP 1, mean weight change at 68 weeks was -14.9% with semaglutide 2.4 mg and -2.4% with placebo, for an estimated treatment difference of -12.4 percentage points (95% CI -13.4 to -11.5) (3). One year after withdrawal, participants previously assigned semaglutide regained 11.6 percentage points, leaving a net change of -5.6% from baseline at week 120 (4). In SURMOUNT-1, mean weight change at 72 weeks was -15.0%, -19.5%, and -20.9% with tirzepatide 5, 10, and 15 mg, respectively, versus -3.1% with placebo (5).

SURMOUNT-4 showed that after an open-label lead-in, continued tirzepatide produced a further mean change of approximately -5.5% from randomization to week 88, whereas switching to placebo produced 14.0% regain; 89.5% versus 16.6% maintained at least 80% of the initial weight loss (6). In SURMOUNT-5, mean weight change at 72 weeks was -20.2% with tirzepatide and -13.7% with semaglutide, a between-group difference of -6.5 percentage points; waist circumference changed by -18.4 and -13.0 cm, respectively (7). These results support tirzepatide when maximal weight reduction is the dominant goal, while the withdrawal studies support planning for chronic therapy or a structured maintenance strategy.

Cardiovascular disease and HFpEF

In SELECT, major adverse cardiovascular events occurred in 6.5% of participants receiving semaglutide and 8.0% receiving placebo (hazard ratio 0.80, 95% CI 0.72-0.90) (12). At 208 weeks, mean weight change was -10.2% with semaglutide and -1.5% with placebo, and waist circumference changed by -7.7 versus -1.3 cm (13). This provides the strongest direct basis for semaglutide in patients with established ASCVD without diabetes.

HFpEF evidence is not confined to one molecule. In STEP-HFpEF, semaglutide improved the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) by 16.6 points versus 8.7 with placebo and reduced weight by 13.3% versus 2.6%; the between-group improvement in six-minute walk distance (6MWD) was 20.3 m (14). In STEP-HFpEF DM, the KCCQ-CSS treatment difference was 7.3 points (95% CI 4.1-10.4), the weight difference was -6.4 percentage points (95% CI -7.6 to -5.2), and the 6MWD difference was 14.3 m (15). In SUMMIT, cardiovascular death or worsening heart failure occurred in 9.9% with tirzepatide and 15.3% with placebo (hazard ratio 0.62, 95% CI 0.41-0.95), with a KCCQ-CSS treatment difference of 6.9 points (95% CI 3.3-10.6) (16). The SUMMIT composite was driven mainly by fewer worsening-HF events; a reduction in cardiovascular mortality alone was not demonstrated (16). No direct semaglutide-tirzepatide HFpEF comparison was included; selection should therefore reflect the outcome priority, diabetes status, tolerability, and access rather than an unsupported class hierarchy.

Obstructive sleep apnea

SURMOUNT-OSA included two 52-week randomized trials with 469 participants. Tirzepatide reduced apnea-hypopnea index by approximately 20.0 events per hour more than placebo in participants not using positive airway pressure and by 23.8 events per hour more than placebo in participants using positive airway pressure; corresponding between-group weight differences were approximately -16.1 and -17.3 percentage points (17). These direct data support tirzepatide in moderate-to-severe OSA with obesity, while positive airway pressure adherence and sleep symptoms remain clinically relevant monitoring targets.

MASH and related liver outcomes

In the phase 2 semaglutide NASH trial, resolution of steatohepatitis without worsening fibrosis occurred in 59% with semaglutide 0.4 mg daily and 17% with placebo, while improvement in fibrosis stage without worsening steatohepatitis did not differ significantly (43% vs 33%) (18). In the phase 3 ESSENCE trial, 1,197 participants were randomized; the 72-week interim analysis covered the first 800. In this analysis, MASH resolution without worsening fibrosis occurred in 62.9% with semaglutide 2.4 mg and 34.3% with placebo; fibrosis improvement without worsening MASH occurred in 36.8% and 22.4%, respectively (19). In SYNERGY-NASH, MASH resolution without worsening fibrosis occurred in 44%, 56%, and 62% with tirzepatide 5, 10, and 15 mg versus 10% with placebo; at least one-stage fibrosis improvement without worsening MASH occurred in 55%, 51%, and 51% versus 30% (20). Semaglutide has the more mature phase 3 hepatic evidence, while tirzepatide has promising phase 2 histological data. These findings apply to biopsy-confirmed MASH populations and should not be automatically extrapolated to all patients with MASLD.

Prediabetes and diabetes prevention

Among 1,032 participants with prediabetes in the long-term SURMOUNT-1 analysis, mean weight change at 176 weeks was -12.3%, -18.7%, and -19.7% with tirzepatide 5, 10, and 15 mg versus -1.3% with placebo. Type 2 diabetes developed in 1.3% versus 13.3%, corresponding to a hazard ratio of 0.07 (21). This supports tirzepatide when diabetes prevention is a dominant clinical priority, while recognizing that risk may change after treatment withdrawal.

Oral strategies and route preference

In OASIS 1, oral semaglutide 50 mg produced a mean 68-week weight change of -15.1% versus -2.4% with placebo, and 170/317 (54%) versus 17/295 (6%) achieved at least 15% weight loss (8). In the phase 2 orforglipron trial, mean weight change at 36 weeks reached -14.7% at the most effective dose versus -2.3% with placebo (9). In the phase 3 ATTAIN-1 trial, treatment-regimen estimates at 72 weeks were -7.5%, -8.4%, and -11.2% with orforglipron 6, 12, and 36 mg versus -2.1% with placebo (10). Oral delivery can address injection aversion or logistical barriers, but no direct evidence establishes superior long-term persistence compared with injectables. Oral agents should therefore be selected for route compatibility rather than assumed adherence advantage.

Triple agonism, body composition, and persistence

In the phase 2 retatrutide trial, mean weight reduction reached 24.2% at 48 weeks at the highest dose, but long-term safety, maintenance, and clinical outcome data remain limited (11). In the SURMOUNT-1 DXA substudy, tirzepatide reduced body weight by 21.3%, fat mass by 33.9%, and lean mass by 10.9%, compared with 5.3%, 8.2%, and 2.6% with placebo; approximately three quarters of lost weight was fat mass (24). Across GLP-1-based therapies, body-composition evidence indicates a consistent reduction in lean mass but sparse evidence for falls, disability, strength, or independence (25).

In a large real-world comparison, tirzepatide was associated with greater probabilities of achieving at least 5%, 10%, and 15% weight loss than semaglutide, but discontinuation was common in both groups (22). In a US cohort of 125,474 adults initiating liraglutide, semaglutide, or tirzepatide, one-year discontinuation reached 46.5% among patients with type 2 diabetes and 64.8% among those without diabetes; among 41,792 discontinuers eligible for the reinitiation analysis, estimated restart rates within one year of stopping were 47.3% and 36.3%, respectively (23). These findings support explicit discussion of cost, access, adverse effects, and a maintenance plan before treatment begins.

Safety and tolerability

Across the included randomized trials, gastrointestinal adverse events - primarily nausea, diarrhea, vomiting, and constipation - were the most common treatment-related events. They were usually mild to moderate, occurred mainly during dose escalation, and were a principal reason for treatment discontinuation in obesity trials (5, 7, 9, 10). Gastrointestinal events were also reported in MASH trials (18–20). In SURMOUNT-1, discontinuation due to adverse events occurred in 4.3%, 7.1%, and 6.2% of participants receiving tirzepatide 5, 10, and 15 mg, respectively, compared with 2.6% receiving placebo (5). In SURMOUNT-5, treatment was discontinued because of adverse events in 6.1% of participants receiving tirzepatide and 8.0% receiving semaglutide (7). In ATTAIN-1, adverse events led to discontinuation in 5.3%-10.3% across the orforglipron groups versus 2.7% with placebo; serious adverse events occurred in 3.8%-5.5% and 4.9%, respectively (10).

Serious adverse events were not consistently more frequent with incretin-based therapy than with comparators. In SELECT, permanent discontinuation due to adverse events occurred in 16.6% with semaglutide and 8.2% with placebo, mainly because of gastrointestinal disorders; gallbladder-related disorders occurred in 2.8% and 2.3%, respectively (12). Gallbladder-related events were uncommon but were also reported in obesity and MASH trials (18–20). Acute pancreatitis was rare across the included studies and was generally reported as isolated adjudicated cases, which precluded reliable between-drug comparisons (11, 17–20). Overall, tolerability was influenced more by gastrointestinal symptoms and dose escalation than by serious or rare events, although individual risk assessment remains necessary. The characteristics and principal numerical findings of the key included primary studies are summarized in Table 5.

Table 5. Key included primary studies and numerical findings

Study	Design and population	Intervention/ comparator	Follow-up	Key numerical finding	Personalization implication
STEP 1 (3)	RCT; n=1,961; adults without diabetes	Semaglutide 2.4 mg vs placebo	68 weeks	Weight -14.9% vs -2.4%; difference -12.4 pp (95% CI -13.4 to -11.5).	High-efficacy semaglutide; maintenance planning required.
STEP 1 extension (4)	Off-treatment extension of trial subset	Prior semaglutide vs prior placebo	1 year off treatment	Regain 11.6 pp after semaglutide; net change -5.6% from baseline at week 120.	Withdrawal commonly reverses part of benefit.
SURMOUNT-1 (5)	RCT; n=2,539; obesity without diabetes	Tirzepatide 5/10/15 mg vs placebo	72 weeks	Weight -15.0%, -19.5%, -20.9% vs -3.1%.	Strong option when magnitude of weight loss dominates.
SURMOUNT-4 (6)	Randomized withdrawal; 670 randomized after lead-in	Continue tirzepatide vs switch to placebo	88 weeks total	Post-randomization -5.5% vs +14.0%; ≥80% maintenance 89.5% vs 16.6%.	Supports chronic continuation or structured maintenance.

Study	Design and population	Intervention/ comparator	Follow-up	Key numerical finding	Personalization implication
SURMOUNT-5 (7)	Open-label head-to-head RCT; n=751	Tirzepatide vs semaglutide	72 weeks	Weight -20.2% vs -13.7%; difference -6.5 pp; waist -18.4 vs -13.0 cm.	Best direct comparative signal for weight-loss-dominant phenotype.
OASIS 1 (8)	Phase 3 RCT; n=667	Oral semaglutide 50 mg vs placebo	68 weeks	Weight -15.1% vs -2.4%; ≥15% loss: 170/317 (54%) vs 17/295 (6%).	Oral option when administration requirements are acceptable.
Orforglipron phase 2 (9)	Phase 2 RCT; n=272	Orforglipron doses vs placebo	36 weeks	Weight reduction up to -14.7% vs -2.3%.	Oral small-molecule proof of efficacy.
ATTAIN-1 (10)	Phase 3 RCT; n=3,127	Orforglipron 6/12/36 mg vs placebo	72 weeks	Treatment-regimen weight -7.5%, -8.4%, -11.2% vs -2.1%.	Oral route; long-term outcome evidence remains immature.
Retatrutide phase 2 (11)	Phase 2 RCT; n=338	Retatrutide doses vs placebo	48 weeks	Weight reduction up to -24.2%.	Promising but not ready for outcome-based personalization.
SELECT (12)	Event-driven RCT; n=17,604; ASCVD without diabetes	Semaglutide 2.4 mg vs placebo	Mean 39.8 months	MACE 6.5% vs 8.0%; HR 0.80 (95% CI 0.72-0.90).	Strongest evidence for established ASCVD phenotype.
SELECT weight analysis (13)	Randomized longitudinal secondary analysis	Semaglutide 2.4 mg vs placebo	208 weeks	Weight -10.2% vs -1.5%; waist -7.7 vs -1.3 cm.	Durable weight reduction in high cardiovascular-risk population.
STEP-HFpEF (14)	RCT; n=529; HFpEF and obesity	Semaglutide 2.4 mg vs placebo	52 weeks	KCCQ-CSS +16.6 vs +8.7; weight -13.3% vs -2.6%; 6MWD difference +20.3 m.	Direct HFpEF evidence without diabetes.
STEP-HFpEF DM (15)	RCT; n=616; HFpEF, obesity, T2D	Semaglutide 2.4 mg vs placebo	52 weeks	KCCQ difference +7.3; weight difference -6.4 pp; 6MWD difference +14.3 m.	Direct HFpEF evidence with type 2 diabetes.
SUMMIT (16)	RCT; n=731; HFpEF and obesity	Tirzepatide vs placebo	Median 104 weeks	CV death/worsening HF 9.9% vs 15.3%; HR 0.62; KCCQ difference +6.9.	Supports tirzepatide for HFpEF event and symptom outcomes.
SURMOUNT-OSA (17)	Two phase 3 RCTs; n=469	Tirzepatide vs placebo	52 weeks	AHI differences about -20.0 and -23.8 events/h; weight differences -16.1 and -17.3 pp.	Direct OSA phenotype evidence.
Semaglutide NASH (18)	Phase 2 RCT; n=320	Semaglutide 0.4 mg daily vs placebo	72 weeks	NASH resolution 59% vs 17%; fibrosis improvement 43% vs 33% (not significant).	Hepatic efficacy signal; fibrosis uncertainty.
ESSENCE interim (19)	Phase 3 RCT; 1,197 randomized; interim cohort n=800	Semaglutide 2.4 mg vs placebo	72 weeks interim histology	MASH resolution 62.9% vs 34.3%; fibrosis improvement 36.8% vs 22.4%.	Most mature phase 3 hepatic evidence.
SYNERGY-NASH (20)	Phase 2 RCT; n=190; MASH F2-F3	Tirzepatide 5/10/15 mg vs placebo	52 weeks	MASH resolution 44%, 56%, 62% vs 10%; fibrosis improvement 55%, 51%, 51% vs 30%.	Promising hepatic data; phase 3 confirmation needed.
SURMOUNT-1 diabetes prevention (21)	Long-term analysis; prediabetes n=1,032	Tirzepatide vs placebo	176 weeks	T2D 1.3% vs 13.3%; HR 0.07; weight -12.3% to -19.7% vs -1.3%.	Strong option for prediabetes/high diabetes risk.

Study	Design and population	Intervention/ comparator	Follow-up	Key numerical finding	Personalization implication
Real-world semaglutide vs tirzepatide (22)	Retrospective cohort; 18,386 matched	Tirzepatide vs semaglutide	12 months	Greater likelihood of ≥5/10/15% loss; on-treatment difference at 12 months about -6.9 pp.	Routine-care advantage, tempered by confounding and discontinuation.
Discontinuation/ reinitiation cohort (23)	US cohort; n=125,474; restart analysis n=41,792	Liraglutide, semaglutide, or tirzepatide	1 year	1-year discontinuation: 46.5% with T2D vs 64.8% without; restart after stopping: 47.3% vs 36.3%.	Persistence and access are core treatment-selection variables.
SURMOUNT-1 DXA (24)	DXA substudy; n=160	Tirzepatide vs placebo	72 weeks	Weight -21.3%; fat mass -33.9%; lean mass -10.9% (placebo -5.3%, -8.2%, -2.6%).	Monitor function in vulnerable patients; most lost mass was fat.

Abbreviations: 6MWD, six-minute walk distance; AHI, apnea-hypopnea index; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; DXA, dual-energy X-ray absorptiometry; HF, heart failure; HR, hazard ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; NASH, nonalcoholic steatohepatitis; pp, percentage points; RCT, randomized controlled trial; T2D, type 2 diabetes.

Phenotype-oriented synthesis

The evidence does not support a single drug hierarchy for every patient. Table 6 summarizes the best-supported use cases and the maturity of evidence, while Table 7 translates those findings into a clinical monitoring matrix.

Table 6. Phenotype-oriented synthesis by drug or strategy

Drug or strategy	Best-supported phenotype or use	Evidence basis	Principal limitation
Tirzepatide	Weight-loss-dominant treatment; prediabetes; OSA; HFpEF with obesity.	Weight-loss and maintenance trials (5–7); OSA and HFpEF trials (16, 17); long-term prediabetes analysis (21).	Injectable route, gastrointestinal tolerability, cost, chronic-treatment requirement, and no direct HFpEF comparison with semaglutide.
Semaglutide 2.4 mg	Established ASCVD without diabetes; obesity-related HFpEF; biopsy-confirmed MASH when phase 3 histological evidence is relevant.	SELECT cardiovascular and weight outcomes (12, 13); STEP-HFpEF program (14, 15); ESSENCE histology (19).	Lower mean weight loss than tirzepatide in one open-label head-to-head trial; regain after withdrawal.
Oral semaglutide or orforglipron	Injection aversion or logistical barriers to injectable treatment.	Clinically meaningful randomized weight reduction with oral regimens (8–10).	Regimen- and jurisdiction-specific availability; studied doses are not interchangeable. No proven persistence advantage over injections.
Retatrutide	Investigational strategy for severe obesity and high metabolic burden.	Very large phase 2 weight-loss signal (11).	Long-term safety, maintenance, and hard clinical outcomes require confirmation.
Muscle-preserving support	Older, sedentary, frail, or functionally vulnerable patients receiving any high-efficacy therapy.	Predominant fat-mass loss but concurrent lean-mass reduction (24, 25).	Few trials report strength, falls, disability, or independence.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; MASH, metabolic dysfunction-associated steatohepatitis; OSA, obstructive sleep apnea.

Table 7. Clinical matrix for personalization of incretin therapy

Clinical phenotype	Selection logic	Monitoring focus
Prediabetes or high risk of type 2 diabetes	Tirzepatide is strongly supported when accessible and tolerated (21).	HbA1c, fasting glucose, weight, gastrointestinal events, and intended treatment duration.
Established ASCVD without diabetes	Semaglutide 2.4 mg has direct MACE outcome evidence (12).	Cardiovascular risk, blood pressure, lipids, weight, and tolerability.
HFpEF with obesity	Both semaglutide and tirzepatide have direct randomized evidence. Tirzepatide has a clinical-event composite; semaglutide has consistent symptom, function, and weight data with and without diabetes (14–16).	KCCQ, 6MWD, congestion, functional status, weight, blood pressure, and HF therapy.

Clinical phenotype	Selection logic	Monitoring focus
OSA with obesity	Tirzepatide has direct data on AHI and hypoxic burden (17).	AHI, sleepiness, positive airway pressure adherence, weight, and sleep quality.
Biopsy-confirmed MASH	Semaglutide has phase 3 evidence; tirzepatide has positive phase 2 evidence (19, 20).	ALT/AST, noninvasive fibrosis assessment, metabolic risk, and specialist-directed histological follow-up when appropriate.
Sarcopenia risk or functional vulnerability	Assess the clinical significance of lean-mass loss together with nutrition, strength, and mobility; individualize continuation and supportive care (24, 25).	Grip strength, gait or chair-rise performance, protein adequacy, resistance exercise, and body composition when clinically useful.
Low readiness for injections	Consider an authorized oral regimen compatible with the patient's routine; OASIS 1 studied 50 mg daily and does not establish interchangeability with other formulations (8–10).	Adherence to dosing instructions, gastrointestinal events, dose escalation, and response after adequate exposure to a therapeutic or maximally tolerated dose.
Reproductive age or preconception	Use a cautious strategy with contraception counseling and discontinuation before conception according to product information and specialist guidance (32, 33).	Pregnancy plans, informed consent, medication stop plan, and interdisciplinary care.

Abbreviations: 6MWD, six-minute walk distance; AHI, apnea-hypopnea index; ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; OSA, obstructive sleep apnea.

Risk of bias and qualitative confidence in the evidence

The included randomized trials generally support their prespecified outcomes, but confidence varies by endpoint, missing data, and applicability. Open-label treatment, withdrawal-trial enrichment, secondary analyses, and surrogate outcomes have different implications and should not be conflated as bias. Observational estimates remain vulnerable to confounding, treatment selection, dose classification, and discontinuation. Supplementary Tables S3A and S3B identify appraisal considerations and missing formal assessments; Table 8 provides descriptive, non-GRADE confidence judgments.

Table 8. Qualitative appraisal of confidence in the evidence

Outcome or question	Descriptive confidence	Basis
Weight reduction with semaglutide and tirzepatide	Higher	Large randomized trials, objective measurement, consistent direction, and precise estimates (3, 5, 7).
Tirzepatide versus semaglutide for weight reduction	Moderate to higher	One direct randomized head-to-head trial and supportive real-world evidence; external replication and longer outcome follow-up remain limited (7, 22).
ASCVD benefit of semaglutide	Higher	Large event-driven randomized trial with adjudicated MACE (12).
HFpEF benefit	Moderate to higher	Direct randomized data for both semaglutide and tirzepatide, but different endpoints and no head-to-head comparison (14–16).
OSA benefit of tirzepatide	Moderate	Two phenotype-specific randomized trials with objective AHI outcomes; part of benefit is mediated through weight reduction (17).
MASH histological outcomes	Moderate	Phase 3 semaglutide interim evidence and phase 2 tirzepatide evidence; long-term clinical liver outcomes are incomplete (18–20).
Lean mass and physical function	Limited	Body-composition data are available, but strength, falls, disability, and independence are rarely measured (24, 25).
Persistence and discontinuation	Moderate	Large routine-care cohorts; confounding limits causal interpretation, and descriptive rates depend on population, access, and discontinuation definitions (22, 23).
Biomarker-guided drug selection	Limited	No validated, independently replicated clinical algorithm was identified in the included evidence.

DISCUSSION

Main findings

Personalization should begin with the dominant clinical risk and the probability that treatment can be sustained. Among the included comparisons, tirzepatide has the strongest direct comparative evidence when magnitude of weight reduction is the principal objective and is well supported in prediabetes and OSA. Within the included evidence, semaglutide has the most mature evidence for reduction of cardiovascular events in established ASCVD and phase 3 histological outcomes in MASH. In HFpEF, the included evidence supports both agents: semaglutide consistently improves symptoms, physical limitations, exercise function, and weight, while tirzepatide additionally reduced a composite of cardiovascular death or worsening heart failure. This does not establish superiority of either agent in HFpEF or a cardiovascular-mortality benefit for tirzepatide.

The hepatic comparison also requires nuance. Semaglutide has phase 3 evidence, but tirzepatide has clinically important phase 2 histological findings. Neither

evidence base should be generalized without qualification from biopsy-confirmed MASH to the entire MASLD spectrum. Similarly, oral therapies broaden route options but should not be described as proven solutions for discontinuation because direct persistence comparisons are absent.

Comparison with previous reviews and guidance

Indirect and model-based meta-analyses support comparison of average weight effects, but differences in dose, population, follow-up, and estimand limit their use for individual drug selection (31). WHO guidance situates long-term GLP-1-based therapy within comprehensive obesity care (1). This synthesis adds a comorbidity and treatment-pathway perspective while distinguishing randomized outcome evidence from interpretive recommendations.

Clinical implications

A personalized plan includes the molecule, dose-escalation strategy, mitigation of gastrointestinal adverse events, and a realistic discussion of cost and intended duration. Early response should be assessed only after adequate exposure to a therapeutic or maximally tolerated dose rather than by applying an inflexible 12- to 16-week rule during prolonged titration. In functionally vulnerable patients, resistance exercise, adequate protein intake, and simple measures of strength or mobility should begin with treatment rather than after weakness develops (24, 25). Before discontinuation, clinicians should explain the expected risk of regain and define a maintenance or reinitiation pathway (4, 6, 23).

Unresolved questions

Biomarker-guided selection remains promising but premature. Genetic variation, digital phenotypes, body-composition signatures, and metabolomic markers may eventually refine selection, but none currently replaces clinical phenotype. Priorities include direct comparative outcome trials, long-term liver and HFpEF follow-up, trials reporting strength and independence, pregnancy registries, and independent analyses in health systems with different access and reimbursement structures.

Strengths and limitations

Strengths include separation of primary and contextual evidence and presentation of numerical results across cardiovascular, HFpEF, OSA, diabetes-prevention, MASH, withdrawal, body-composition, and persistence domains. The accompanying tables make the selected evidence and its principal limitations explicit.

The review is selective rather than exhaustive across all incretin agents, formulations, doses and clinical indications. The final search date was 8 January 2026; per-source export files and screening records are not published, which limits record-level reproducibility. The protocol was not registered or publicly deposited. Formal risk-of-bias ratings were not assigned, and certainty is discussed without GRADE ratings. Clinical heterogeneity precluded pooling, and no sensitivity analysis was performed. Observational evidence remains susceptible to confounding. Results for the included oral regimens and phase 2 agents should not be read as a current prescribing list or as evidence of superiority across untested indications.

CONCLUSIONS

A phenotype-oriented approach is more clinically defensible than ranking contemporary incretin therapies by mean weight loss alone. Among the included comparisons, tirzepatide has the strongest direct comparative weight-loss signal and direct evidence in prediabetes and OSA. Within the included evidence, semaglutide has the most mature evidence for established ASCVD and phase 3 MASH outcomes. Both semaglutide and tirzepatide are supported by randomized HFpEF evidence, with differences in trial endpoints rather than a proven molecule hierarchy. Oral drugs expand route options but do not yet demonstrate superior persistence. Treatment decisions should incorporate expected clinical benefit, tolerability, cost, route preference, reproductive plans, probability of continuation, and a plan to preserve muscle function and manage withdrawal. A validated biomarker-guided algorithm is not ready for routine practice. A practical framework for applying these findings in clinical decision-making is provided in Table 9.

Table 9. Practical interpretive framework

Step	Content
1	Identify the dominant phenotype: weight-loss priority, prediabetes, ASCVD, HFpEF, OSA, biopsy-confirmed MASH, functional vulnerability, reproductive plans, or injection aversion.
2	Select the agent using direct phenotype-specific outcome evidence, expected weight effect, route, cost, tolerability, and probability of long-term continuation.
3	Record baseline weight, waist circumference, glucose or HbA1c, blood pressure, lipids, comorbidity symptoms, and simple physical-function measures; use body composition when it will change management.
4	Assess response after adequate exposure to a therapeutic or maximally tolerated dose, considering titration, adherence, gastrointestinal adverse events, nutrition, and activity before switching.
5	For patients at risk of sarcopenia or functional decline, initiate resistance exercise and adequate protein intake from the start and monitor strength or mobility.
6	Before stopping treatment, discuss the expected risk of regain and define a maintenance, alternative-treatment, or reinitiation plan.

DECLARATIONS

Author contributions: Ildar Fakhradiyev: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, and Writing – original draft. Timur Fazylov: Methodology, Investigation, Data curation, Validation, and Writing – review and editing. Liliya Ibragimova: Conceptualization, Formal analysis, Validation, Supervision, Project administration, and Writing – review and editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data availability statement: The evidence synthesized here derives from the cited publications and is presented in Supplementary Section S1, Table S2, Tables S3A and S3B, and Tables S4A and S4B. Record-level search exports, screening and exclusion logs and completed appraisal forms are not part of the supplementary material. Table S4A is the extraction template and Table S4B contains the principal study-level summaries.

AI use statement: ChatGPT (OpenAI) assisted with language editing, manuscript organization, formatting, internal consistency checks and verification of selected bibliographic details against the published sources. It did not perform a new systematic search, reconstruct missing screening records or conduct a formal risk-of-bias assessment. The authors verified the manuscript, the methods and these declarations before publication.

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Supplementary Section S1. Search strategies

Search framework

The search framework combines bibliographic coverage beginning on 1 January 2024 with supplementary searching. The final search date was 8 January 2026, and supplementary searches had no lower publication-date limit. The strings below present the search logic for each platform; per-source yields are reported in aggregate within the selection flow.

Table S1.1. Core concept groups

Concept	Controlled vocabulary	Free-text terms
Population	Obesity; Overweight	obes*; overweight
Intervention	GLP-1 receptor agonists; incretin mimetics; indexed drug terms	incretin*; GLP-1 receptor agonist*; GIP/GLP-1; dual agonist*; triple agonist*; semaglutide; tirzepatide; retatrutide; orforglipron
Supplementary phenotype/outcome terms	Body composition; cardiovascular disease; heart failure; OSA; prediabetes; MASH	weight loss; withdrawal; maintenance; ASCVD; MACE; HFpEF; sleep apnea; OSA; MASH; NASH; fibrosis; body composition; lean mass; sarcopen*; persistence; discontinuation; reinitiation; oral; injection; biomarker*; preconception; pregnancy

MEDLINE via PubMed

Platform: PubMed. Coverage: 1 January 2024 to 8 January 2026. Limits: English or Russian; animal-only records excluded.

```
(
 ("Obesity"[Mesh] OR "Overweight"[Mesh] OR obes*[tiab] OR overweight[tiab])
 AND
 ("Glucagon-Like Peptide-1 Receptor Agonists"[Mesh]
  OR incretin*[tiab]
  OR "GLP-1 receptor agonist"[tiab]
  OR "GLP-1 receptor agonists"[tiab]
  OR "GIP/GLP-1"[tiab]
  OR "dual agonist"[tiab]
  OR "dual agonists"[tiab]
  OR "triple agonist"[tiab]
  OR "triple agonists"[tiab]
  OR semaglutide[tiab]
  OR tirzepatide[tiab]
  OR retatrutide[tiab]
  OR orforglipron[tiab])
)
AND ("2024/01/01"[Date - Publication] : "2026/01/08"[Date - Publication])
AND (english[Language] OR russian[Language])
NOT (animals[MeSH Terms] NOT humans[MeSH Terms])
```

Embase

Platform: Embase.com. Coverage: 1 January 2024 to 8 January 2026; publication-year filter 2024–2026. Limits: humans, adults, English or Russian.

```
('obesity'/exp OR 'overweight'/exp OR obes*:ti,ab,kw OR overweight:ti,ab,kw)
AND
('glucagon like peptide 1 receptor agonist'/exp OR 'incretin mimetic agent'/exp
 OR incretin*:ti,ab,kw OR 'glp 1 receptor agonist':ti,ab,kw
 OR 'gip glp 1':ti,ab,kw OR 'dual agonist':ti,ab,kw
 OR 'triple agonist':ti,ab,kw OR semaglutide:ti,ab,kw
```

OR tirzepatide:ti,ab,kw OR retatrutide:ti,ab,kw OR orforglipron:ti,ab,kw)
AND (2024-2026)/py AND [humans]/lim AND [adult]/lim
AND ([english]/lim OR [russian]/lim)

Scopus

Platform: Elsevier Scopus. Coverage: 1 January 2024 to 8 January 2026. The platform publication-year filter was set to 2024–2025; the interval to the final search date was covered by the remaining databases and by supplementary searching. Limits: English or Russian.

TITLE-ABS-KEY((obes* OR overweight) AND (incretin* OR "GLP-1 receptor agonist" OR "GLP-1 receptor agonists" OR "GIP/GLP-1" OR "dual agonist" OR "dual agonists" OR "triple agonist" OR "triple agonists" OR semaglutide OR tirzepatide OR retatrutide OR orforglipron))
AND PUBYEAR > 2023 AND PUBYEAR < 2026
AND (LIMIT-TO(LANGUAGE, "English") OR LIMIT-TO(LANGUAGE, "Russian"))

Web of Science Core Collection

Platform: Clarivate Web of Science Core Collection. Coverage: 1 January 2024 to 8 January 2026. The platform publication-year filter was set to 2024–2025; the interval to the final search date was covered by the remaining databases and by supplementary searching. Limits: English or Russian.

TS=((obes* OR overweight) AND (incretin* OR "GLP-1 receptor agonist" OR "GLP-1 receptor agonists" OR "GIP/GLP-1" OR "dual agonist" OR "dual agonists" OR "triple agonist" OR "triple agonists" OR semaglutide OR tirzepatide OR retatrutide OR orforglipron))
AND PY=(2024-2025) AND LA=(English OR Russian)

Cochrane CENTRAL

#1 MeSH descriptor: [Obesity] explode all trees
#2 MeSH descriptor: [Overweight] explode all trees
#3 (obes* OR overweight):ti,ab,kw
#4 #1 OR #2 OR #3
#5 MeSH descriptor: [Glucagon-Like Peptide-1 Receptor Agonists] explode all trees
#6 (incretin* OR "GLP-1 receptor agonist*" OR "GIP/GLP-1" OR "dual agonist*" OR "triple agonist*" OR semaglutide OR tirzepatide OR retatrutide OR orforglipron):ti,ab,kw
#7 #5 OR #6
#8 #4 AND #7
Limits: Trials; publication years 2024–2025; final search date 8 January 2026

Trial registries

The ClinicalTrials.gov strategy used obesity OR overweight in the condition field and semaglutide, tirzepatide, retatrutide, orforglipron, GLP-1 receptor agonist, or incretin in the intervention field. Filters were interventional study, adult or older adult, phase 2–4, and recruiting, active not recruiting, completed, or enrolling by invitation. WHO ICTRP was searched separately for each intervention term, because the interface handles long Boolean strings inconsistently. No date restriction was applied to registry status; the registry snapshot was taken through 8 January 2026.

Supplementary searches without date restriction

Supplementary searches were run in PubMed and in citation indexes using combinations of intervention, population, and phenotype or outcome terms. No lower publication-date limit was applied, and the upper limit remained 8 January 2026. The search concepts are summarized in Supplementary Table S1.2.

Table S1.2. Phenotype- and outcome-specific supplementary searches

Clinical question	Supplementary search logic
Semaglutide efficacy and withdrawal	(semaglutide AND (obesity OR overweight) AND (randomized OR trial OR withdrawal OR weight regain))
Tirzepatide efficacy and maintenance	(tirzepatide AND (obesity OR overweight) AND (randomized OR trial OR maintenance OR withdrawal))
Head-to-head comparison	tirzepatide AND semaglutide AND (obesity OR overweight)
Cardiovascular outcomes	semaglutide AND (obesity OR overweight) AND (cardiovascular OR MACE OR ASCVD)
HFpEF	(semaglutide OR tirzepatide) AND (obesity OR overweight) AND (HFpEF OR "heart failure with preserved ejection fraction")
Obstructive sleep apnea	tirzepatide AND (obesity OR overweight) AND ("sleep apnea" OR OSA OR "apnea-hypopnea index")

Clinical question	Supplementary search logic
MASH/NASH	(semaglutide OR tirzepatide) AND (MASH OR NASH OR steatohepatitis OR fibrosis)
Oral therapies	("oral semaglutide" OR orforglipron) AND (obesity OR overweight) AND (randomized OR trial)
Retatrutide	retatrutide AND (obesity OR overweight) AND (phase 2 OR randomized OR trial)
Body composition	(semaglutide OR tirzepatide OR GLP-1) AND (obesity OR overweight) AND ("body composition" OR DXA OR "lean mass" OR muscle)
Persistence and discontinuation	(GLP-1 OR semaglutide OR tirzepatide) AND (obesity OR overweight) AND (persistence OR discontinuation OR reinitiation)
Reproductive context	(GLP-1 OR semaglutide OR tirzepatide) AND (preconception OR pregnancy OR reproductive)

Targeted websites, citation searching, and deduplication

- The WHO, FDA and EASO websites were searched for guidelines, approved indications, safety communications and reproductive-context statements.
- Journal websites were searched for online-first and final reports using intervention and clinical-outcome terms.
- Backward citation searching was performed from included primary studies and relevant reviews; forward citation searching used Scopus and Web of Science citation tools.
- Records were deduplicated electronically and checked manually using DOI, title, first author, year, journal and trial name.
- Multiple publications from one trial were retained only when they reported distinct outcomes, follow-up periods, or prespecified secondary analyses.

Search yield

The selection flow comprises 426 database/register records and 43 reports identified through other methods, from which 17 and 11 sources were retained respectively. The 28 sources comprise 22 primary reports or analyses and six contextual sources; linked publications share trial populations. The final search date was 8 January 2026.

Table S1.3. Aggregate search yield

Source group	Search date	Coverage	Records
Bibliographic databases and trial registers	8 January 2026	Bibliographic coverage from 1 Jan 2024; earlier studies retained through supplementary searches.	426
Other methods: websites, citation searching, and supplementary searches	8 January 2026	Websites, citation and supplementary searches; no lower date limit reported.	43
Included from databases/registers	8 January 2026	Database/register route; counts reported in aggregate	17
Included from other methods	8 January 2026	Other-method route; no lower date limit; counts reported in aggregate	11
Total reports/contextual sources			28

Table S2. PRISMA 2020 reporting checklist

Section/topic	Item	Checklist requirement	Location in manuscript
Title	1	Identify the report as a systematic review.	Title.
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract.
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction.
Objectives	4	Provide an explicit statement of the objective(s) or question(s).	Introduction, final paragraph.
Eligibility criteria	5	Specify inclusion and exclusion criteria and how studies were grouped for synthesis.	PICO and eligibility criteria; Inclusion and exclusion criteria.
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources, including the last search date.	Methods and search supplement: databases and registers searched through 8 January 2026
Search strategy	7	Present full search strategies, including filters and limits.	Section S1: full search strings by platform
Selection process	8	Specify methods used to decide whether a study met inclusion criteria, including reviewer independence.	Methods — Study selection: two reviewers, independent screening with third-reviewer adjudication
Data collection process	9	Specify methods used to collect data, reviewer independence, and confirmation procedures.	Methods — Data extraction: two reviewers, independent extraction
Data items: outcomes	10a	List and define all outcomes sought and assumptions about eligible measures, time points, and analyses.	PICO; Study selection and data extraction; Supplementary Tables S4A and S4B.
Data items: other variables	10b	List and define all other variables sought and assumptions about missing or unclear information.	Study selection and data extraction; Supplementary Tables S4A and S4B.
Risk of bias	11	Specify methods used to assess risk of bias, including tools, domains, and reviewer independence.	Methods — Appraisal: descriptive appraisal (Tables S3A/S3B)
Effect measures	12	Specify effect measures used for each outcome.	Data synthesis; Table 5 and Supplementary Tables S4A and S4B.
Synthesis methods: eligibility	13a	Describe processes used to decide which studies were eligible for each synthesis.	Data synthesis.
Synthesis methods: data preparation	13b	Describe methods required to prepare data for presentation or synthesis.	Data synthesis; Supplementary Tables S4A and S4B.
Synthesis methods: tabulation/visual display	13c	Describe methods used to tabulate or visually display results.	Tables 4-8; Supplementary Tables S4A and S4B.
Synthesis methods: statistical synthesis	13d	Describe methods used to synthesize results and rationale for model choice.	Data synthesis; meta-analysis not performed.
Synthesis methods: heterogeneity	13e	Describe methods used to explore possible causes of heterogeneity.	Data synthesis; phenotype-stratified narrative synthesis.
Synthesis methods: sensitivity analyses	13f	Describe any sensitivity analyses conducted.	Not performed; no narrative sensitivity analysis reported.
Reporting bias assessment	14	Describe methods used to assess risk of bias due to missing results.	Risk of bias and confidence in evidence; qualitative assessment.
Certainty assessment	15	Describe methods used to assess certainty or confidence in the evidence.	Methods — Evidence confidence: certainty described narratively
Study selection	16a	Describe results of the search and selection process, ideally with a flow diagram.	Results - Study selection; Figure 1.
Excluded studies	16b	Cite studies that appeared eligible but were excluded and explain why.	Table 3: exclusions reported by category (45 database/register and 32 other-method reports)
Study characteristics	17	Cite each included study and present its characteristics.	Table 5; Supplementary Tables S4A and S4B.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appraisal tables show descriptive considerations or documentation gaps; no verified formal risk-of-bias ratings.

Section/topic	Item	Checklist requirement	Location in manuscript
Results of individual studies	19	Present summary statistics and effect estimates with precision for each study where available.	Results; Table 5; Supplementary Tables S4A and S4B.
Results of syntheses: characteristics and risk of bias	20a	Summarize characteristics and risk of bias of contributing studies.	Tables 4 and 8; Supplementary Tables S3A and S3B.
Results of statistical syntheses	20b	Present results of all statistical syntheses.	Not applicable; no meta-analysis.
Investigations of heterogeneity	20c	Present results of investigations of heterogeneity.	Narrative phenotype-stratified synthesis; no statistical heterogeneity analysis.
Sensitivity analyses	20d	Present results of sensitivity analyses.	Not performed.
Reporting biases	21	Present assessments of risk of bias due to missing results.	Table 8 and Discussion; qualitative only.
Certainty of evidence	22	Present assessments of certainty or confidence for each outcome.	Table 8: certainty described narratively
Discussion: interpretation	23a	Provide a general interpretation of results in context of other evidence.	Discussion – Main findings; Comparison with previous reviews and guidance.
Discussion: limitations of evidence	23b	Discuss limitations of the evidence included.	Discussion - Strengths and limitations.
Discussion: limitations of review processes	23c	Discuss limitations of the review processes.	Discussion - Strengths and limitations.
Discussion: implications	23d	Discuss implications for practice, policy, and future research.	Clinical implications; Unresolved questions; Conclusions.
Registration	24a	Provide registration information or state that the review was not registered.	Review design and reporting standard. Not prospectively registered.
Protocol access	24b	Indicate where the protocol can be accessed or state that it was not prepared.	Methods — Protocol: protocol prepared before extraction, not publicly deposited
Amendments	24c	Describe and explain amendments to registration or protocol.	Methods — Protocol: no registered amendment history
Support	25	Describe financial or non-financial support and the role of funders.	Declarations – Funding.
Competing interests	26	Declare competing interests.	Declarations – Conflict of interest.
Availability of data, code, and materials	27	Report which materials are publicly available and where.	Data availability statement; Supplementary Section S1 and Tables S2–S4B

Table S3A. Descriptive appraisal of randomized reports

Study/report	Principal outcome	Assessment status	Descriptive consideration
STEP 1 (3)	Weight change	Descriptive appraisal	Masked RCT; objective outcome; prespecified estimands.
SURMOUNT-1 (5)	Weight change	Descriptive appraisal	Masked RCT with objective outcome.
SURMOUNT-4 (6)	Maintenance/regain	Descriptive appraisal	Randomization after lead-in; enriched population affects applicability, not internal validity.
SURMOUNT-5 (7)	Weight/waist	Descriptive appraisal	Open-label active comparison could influence adherence; outcomes objective.
OASIS 1 (8)	Weight change	Descriptive appraisal	Double-blind RCT; prespecified estimands.
Orforglipron phase 2 (9)	Weight change	Descriptive appraisal	Randomized, double-blind, objective outcome.
ATTAIN-1 (10)	Weight change	Descriptive appraisal	Large double-blind phase 3 RCT.
Retatrutide phase 2 (11)	Weight change	Descriptive appraisal	Phase 2 dose-ranging study; attrition across groups.
SELECT (12)	MACE	Descriptive appraisal	Masked event-driven trial; adjudicated endpoint.
SELECT weight analysis (13)	Longitudinal weight	Descriptive appraisal	Secondary analysis with missing longitudinal measurements.
STEP-HFpEF (14)	KCCQ/weight/6MWD	Descriptive appraisal	Patient-reported KCCQ may be influenced by perceived effects; masking retained.
STEP-HFpEF DM (15)	KCCQ/weight/6MWD	Descriptive appraisal	As above; objective weight and 6MWD complement patient report.
SUMMIT (16)	CV death/worsening HF	Descriptive appraisal	Masked RCT with adjudicated event outcome.
SURMOUNT-OSA (17)	AHI	Descriptive appraisal	Two masked RCTs; objective sleep-study outcomes.
Semaglutide NASH (18)	Histological resolution	Descriptive appraisal	Masked RCT with central pathology assessment.
ESSENCE interim (19)	MASH/fibrosis histology	Descriptive appraisal	Interim analysis of 800 participants; assess missing biopsies separately. Pending clinical outcomes limit directness, not automatically D3.
SYNERGY-NASH (20)	MASH/fibrosis histology	Descriptive appraisal	Missing biopsy outcomes require evaluation; the small phase 2 sample also limits precision, which is separate from bias.
SURMOUNT-1 diabetes analysis (21)	Incident T2D	Descriptive appraisal	Long follow-up increases attrition risk; randomized assignment maintained.
SURMOUNT-1 DXA (24)	Body composition	Descriptive appraisal	Substudy sample and selection limit robustness; measurements objective.

Note: Domains D1–D5 concern randomization, deviations from intended intervention, missing outcome data, outcome measurement and selective reporting; they are consolidated in the assessment-status column. Entries are descriptive appraisals and are not RoB 2 ratings.

Table S3B. Descriptive appraisal of non-randomized reports

Study/report	Principal outcome	Assessment status	Descriptive consideration
STEP 1 extension (4)	Off-treatment extension; weight regain	Descriptive appraisal	Selected extension subset and no randomized continued-treatment comparator.
Real-world semaglutide vs tirzepatide (22)	Retrospective cohort; weight change	Descriptive appraisal	Matching reduced measured confounding, but treatment selection and differential discontinuation remained.
Discontinuation/reinitiation cohort (23)	Retrospective cohort; persistence	Not applicable to causal inference	Descriptive persistence cohort; no causal treatment contrast. Selection, dispensing records, missing weights, and access limit interpretation.

Note: Domains D1–D7 concern confounding, selection, classification of intervention, deviations from intended intervention, missing data, outcome measurement and reporting; entries are consolidated in the assessment-status column without assigning formal ratings. N/A denotes a descriptive persistence cohort to which causal appraisal does not apply.

Table S4A. Data extraction template

Field	Extraction fields
Citation and trial program	Author, year, journal, DOI, trial name, related publications.
Design	Randomization, masking, phase, setting, allocation, withdrawal/extension status.
Population	Sample size, age, sex, BMI, diabetes status, dominant phenotype, key eligibility criteria.
Intervention and comparator	Drug, dose, escalation, route, background intervention, placebo or active comparator.
Follow-up and estimand	Duration, analysis population, treatment-regimen or efficacy estimand, missing-data method.
Outcomes	Weight, waist, glycemia, incident T2D, MACE, KCCQ, 6MWD, AHI, MASH/fibrosis, body composition, quality of life.
Effect estimates	Group values, between-group difference, ratio measure, 95% CI, P value when reported.
Safety and persistence	Adverse events, discontinuation, reinitiation, withdrawal effects.
Personalization variables	Comorbidity, route, functional vulnerability, reproductive context, access and maintenance implications.
Risk of bias notes	Descriptive methodological concerns; formal domain judgments and supporting records, if available.

Table S4B. Extracted study-level data

Study	Design/population	Intervention/comparator	Follow-up	Extracted result	Clinical interpretation
STEP 1 (3)	RCT; n=1,961; adults without diabetes	Semaglutide 2.4 mg vs placebo	68 weeks	Weight -14.9% vs -2.4%; difference -12.4 pp (95% CI -13.4 to -11.5).	High-efficacy semaglutide; maintenance planning required.
STEP 1 extension (4)	Off-treatment extension of trial subset	Prior semaglutide vs prior placebo	1 year after withdrawal	Regain 11.6 pp after semaglutide; net change -5.6% from baseline at week 120.	Withdrawal commonly reverses part of benefit.
SURMOUNT-1 (5)	RCT; n=2,539; obesity without diabetes	Tirzepatide 5/10/15 mg vs placebo	72 weeks	Weight -15.0%, -19.5%, -20.9% vs -3.1%.	Strong option when magnitude of weight loss dominates.
SURMOUNT-4 (6)	Randomized withdrawal; 670 randomized after lead-in	Continue tirzepatide vs switch to placebo	88 weeks total	Post-randomization -5.5% vs +14.0%; ≥80% maintenance 89.5% vs 16.6%.	Supports chronic continuation or structured maintenance.
SURMOUNT-5 (7)	Open-label head-to-head RCT; n=751	Tirzepatide vs semaglutide	72 weeks	Weight -20.2% vs -13.7%; difference -6.5 pp; waist -18.4 vs -13.0 cm.	Best direct comparative signal for weight-loss-dominant phenotype.
OASIS 1 (8)	Phase 3 RCT; n=667	Oral semaglutide 50 mg vs placebo	68 weeks	Weight -15.1% vs -2.4%; ≥15% loss: 170/317 (54%) vs 17/295 (6%).	Oral option when administration requirements are acceptable.
Orforglipron phase 2 (9)	Phase 2 RCT; n=272	Orforglipron doses vs placebo	36 weeks	Weight reduction up to -14.7% vs -2.3%.	Oral small-molecule proof of efficacy.
ATTAIN-1 (10)	Phase 3 RCT; n=3,127	Orforglipron 6/12/36 mg vs placebo	72 weeks	Treatment-regimen weight -7.5%, -8.4%, -11.2% vs -2.1%.	Oral route; long-term outcome evidence remains immature.
Retatrutide phase 2 (11)	Phase 2 RCT; n=338	Retatrutide doses vs placebo	48 weeks	Weight reduction up to -24.2%.	Promising but not ready for outcome-based personalization.
SELECT (12)	Event-driven RCT; n=17,604; ASCVD without diabetes	Semaglutide 2.4 mg vs placebo	Mean 39.8 months	MACE 6.5% vs 8.0%; HR 0.80 (95% CI 0.72-0.90).	Strongest evidence for established ASCVD phenotype.
SELECT weight analysis (13)	Randomized longitudinal secondary analysis	Semaglutide 2.4 mg vs placebo	208 weeks	Weight -10.2% vs -1.5%; waist -7.7 vs -1.3 cm.	Durable weight reduction in high cardiovascular-risk population.
STEP-HFpEF (14)	RCT; n=529; HFpEF and obesity	Semaglutide 2.4 mg vs placebo	52 weeks	KCCQ-CSS +16.6 vs +8.7; weight -13.3% vs -2.6%; 6MWD difference +20.3 m.	Direct HFpEF evidence without diabetes.
STEP-HFpEF DM (15)	RCT; n=616; HFpEF, obesity, T2D	Semaglutide 2.4 mg vs placebo	52 weeks	KCCQ difference +7.3; weight difference -6.4 pp; 6MWD difference +14.3 m.	Direct HFpEF evidence with type 2 diabetes.
SUMMIT (16)	RCT; n=731; HFpEF and obesity	Tirzepatide vs placebo	Median 104 weeks	CV death/worsening HF 9.9% vs 15.3%; HR 0.62; KCCQ difference +6.9.	Supports tirzepatide for HFpEF event and symptom outcomes.
SURMOUNT-OSA (17)	Two phase 3 RCTs; n=469	Tirzepatide vs placebo	52 weeks	AHI differences about -20.0 and -23.8 events/h; weight differences -16.1 and -17.3 pp.	Direct OSA phenotype evidence.
Semaglutide NASH (18)	Phase 2 RCT; n=320	Semaglutide 0.4 mg daily vs placebo	72 weeks	NASH resolution 59% vs 17%; fibrosis improvement 43% vs 33% (not significant).	Hepatic efficacy signal; fibrosis uncertainty.
ESSENCE interim (19)	Phase 3 RCT; 1,197 randomized; interim cohort n=800	Semaglutide 2.4 mg vs placebo	72 weeks interim histology	MASH resolution 62.9% vs 34.3%; fibrosis improvement 36.8% vs 22.4%.	Most mature phase 3 hepatic evidence.

Study	Design/population	Intervention/comparator	Follow-up	Extracted result	Clinical interpretation
SYNERGY-NASH (20)	Phase 2 RCT; n=190; MASH F2-F3	Tirzepatide 5/10/15 mg vs placebo	52 weeks	MASH resolution 44%, 56%, 62% vs 10%; fibrosis improvement 55%, 51%, 51% vs 30%.	Promising hepatic data; phase 3 confirmation needed.
SURMOUNT-1 diabetes prevention (21)	Long-term analysis; prediabetes n=1,032	Tirzepatide vs placebo	176 weeks	T2D 1.3% vs 13.3%; HR 0.07; weight -12.3% to -19.7% vs -1.3%.	Strong option for prediabetes/high diabetes risk.
Real-world semaglutide vs tirzepatide (22)	Retrospective cohort; 18,386 matched	Tirzepatide vs semaglutide	12 months	Greater likelihood of ≥5/10/15% loss; on-treatment difference at 12 months about -6.9 pp.	Routine-care advantage, tempered by confounding and discontinuation.
Discontinuation/ reinitiation cohort (23)	US cohort; n=125,474; restart analysis n=41,792	Liraglutide, semaglutide, or tirzepatide	1 year	1-year discontinuation: 46.5% with T2D vs 64.8% without; restart after stopping: 47.3% vs 36.3%.	Persistence and access are core treatment-selection variables.
SURMOUNT-1 DXA (24)	DXA substudy; n=160	Tirzepatide vs placebo	72 weeks	Weight -21.3%; fat mass -33.9%; lean mass -10.9% (placebo -5.3%, -8.2%, -2.6%).	Monitor function in vulnerable patients; most lost mass was fat.

Note: These summaries contain the principal numerical results used in the narrative synthesis, not complete extraction forms. Related reports from STEP 1, SELECT, and SURMOUNT-1 contain overlapping participants. Percentages and denominators refer to the stated analysis; trial-wide sample sizes must not be substituted for substudy populations.