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Systematic review

PERSONALIZATION OF CONTEMPORARY INCRETIN THERAPY FOR OBESITY: A FOCUSED SYSTEMATIC REVIEW

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ABSTRACT

Background: Contemporary incretin-based therapy has shifted obesity management from ranking drugs by mean weight loss alone toward selection based on dominant comorbidity, treatment persistence, route preference, tolerability, body composition, and the consequences of withdrawal.

Objective: To synthesize evidence supporting phenotype-oriented selection of semaglutide, tirzepatide, oral incretin strategies, and triple GIP, GLP-1, and glucagon agonism in adults with obesity or overweight and clinically relevant comorbidity.

Materials and methods: A focused systematic review was conducted according to PRISMA 2020. MEDLINE via PubMed, Embase, Scopus, Web of Science Core Collection, and CENTRAL were searched for evidence published from 1 January 2024 to 8 July 2026. Clinical trial registries, organizational and regulatory websites, reference lists, and citation indexes were searched without date restriction to ensure coverage of relevant earlier and ongoing evidence. Two reviewers independently screened records, extracted data, and assessed risk of bias with RoB 2 or ROBINS-I. Because interventions, populations, and outcomes were heterogeneous, findings were synthesized narratively rather than meta-analyzed.

Results: After deduplication, 296 records were screened. Sixty-two database or register reports and 43 reports identified through other methods were assessed; 28 studies or contextual documents were included, comprising 22 primary reports or analyses and 6 secondary, regulatory, or policy sources. In SURMOUNT-5, mean weight change at 72 weeks was -20.2% with tirzepatide and -13.7% with semaglutide. In SELECT, semaglutide reduced major adverse cardiovascular events (6.5% vs 8.0%; hazard ratio 0.80, 95% confidence interval 0.72-0.90). Both semaglutide and tirzepatide had randomized evidence in obesity-related heart failure with preserved ejection fraction, while tirzepatide reduced apnea-hypopnea index in obstructive sleep apnea. Semaglutide had phase 3 evidence for metabolic dysfunction-associated steatohepatitis, and tirzepatide had positive phase 2 histological data. One-year discontinuation in routine care was common, reaching 64.8% among patients without type 2 diabetes in a large cohort.

Conclusion: Phenotype-oriented selection is better supported than a single hierarchy based on weight loss. Tirzepatide has the strongest direct comparative weight-loss signal and evidence in prediabetes and obstructive sleep apnea. Semaglutide has the most mature cardiovascular and phase 3 hepatic evidence. In obesity-related heart failure with preserved ejection fraction, both agents are supported by direct randomized data. Route, cost, tolerability, persistence, reproductive plans, and muscle function should be incorporated into treatment planning. A validated biomarker-guided algorithm is not ready for routine use.

Keywords: obesity; GLP-1; tirzepatide; semaglutide; retatrutide; orforglipron; personalized medicine; PRISMA 2020; body composition; HFpEF; OSA; MASH.

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 larger reductions across 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].

Most reviews rank agents by mean weight loss. A clinically useful synthesis should instead ask which outcome matters most for a particular patient, whether the patient can sustain the selected route and cost, and what monitoring is needed to preserve function and manage discontinuation.

Objective and research questions

The objective was to determine how contemporary incretin therapy can be selected and continued in adults with obesity or overweight to maximize clinically relevant benefit and reduce avoidable discontinuation, adverse events, and functionally meaningful muscle loss. The review addressed five questions: (1) which clinical phenotypes are best supported for semaglutide, tirzepatide, oral strategies, and triple agonism; (2) how the drugs affect cardiovascular, HFpEF, OSA, prediabetes, and hepatic outcomes; (3) what happens after withdrawal; (4) how route preference and real-world persistence should influence selection; and (5) whether biomarker-guided selection is ready for routine practice.

Materials and methods

Review design and reporting standard

This manuscript was prepared as a focused systematic review with a structured narrative synthesis. Reporting followed PRISMA 2020 and PRISMA-S [26-28]. The protocol was developed before full-text data extraction but was not prospectively registered. Eligibility criteria, information sources, screening procedures, data extraction, risk-of-bias assessment, and synthesis methods were defined before study selection was completed.

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

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

The bibliographic search covered 1 January 2024 to 8 July 2026 in MEDLINE via PubMed, Embase, Scopus, Web of Science Core Collection, and Cochrane CENTRAL. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched without date restriction. To ensure coverage of earlier and ongoing evidence, the database search was complemented by searches of organizational, regulatory, and journal websites, backward and forward citation searching, and supplementary searches based on intervention and clinical-outcome concepts. English- and Russian-language reports were eligible.

The core strategy combined obesity or overweight terms with drug-class and individual-drug terms. Outcome terms were not applied as a mandatory search block because phenotype-relevant outcomes may be reported only in the full text. Outcome and phenotype terms were used in supplementary searches and during screening. Full strategies are provided in Supplementary File S1.

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

Table 2. Search design and source coverage

Contemporary bibliographic search	PubMed, Embase, Scopus, Web of Science Core Collection, CENTRAL	1 Jan 2024 to 8 Jul 2026	Recent phase 3, outcome, extension, comparative, body-composition, and observational evidence.
Trial-register search	ClinicalTrials.gov, WHO ICTRP	No 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	No date restriction	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	No date restriction	Regulatory, policy, reproductive-context, online-first, and citation-linked evidence.

Study selection and data extraction

Two reviewers independently screened titles and abstracts and assessed full texts. Disagreements were resolved by consensus, with a third reviewer involved if needed. Two reviewers independently extracted study design, sample size, population, intervention, comparator, dose, duration, weight and waist outcomes, glycemic outcomes, major adverse cardiovascular events, HFpEF measures, apnea-hypopnea index and hypoxic burden, MASH histology, body composition, adverse events, treatment discontinuation, and reinitiation. The extraction template and study-level extracted data are provided in Supplementary File S4.

Risk of bias and confidence in the evidence

Randomized trials were assessed with the Cochrane RoB 2 tool [29]. Observational studies and non-randomized extensions were assessed with ROBINS-I [30]. Two reviewers independently completed the assessments and resolved disagreements by consensus. Study-level judgments are presented in Supplementary Tables S3A and S3B. Confidence was appraised qualitatively by considering risk of bias, directness, consistency, precision, and

applicability. Because formal outcome-specific GRADE evidence profiles and Summary of Findings tables were not produced, the categories used in Table 8 are descriptive and should not be interpreted as formal GRADE ratings.

Risk of bias due to missing results was assessed qualitatively by comparing reported outcomes with trial registrations and published protocols when available and by considering selective availability of favorable or mature outcomes. Funnel plots and statistical tests for small-study effects were not performed because no meta-analysis was conducted and the number of studies within individual outcome domains was insufficient.

Data synthesis

Meta-analysis was not performed because the included evidence differed substantially in drugs, doses, follow-up, populations, estimands, and clinical outcomes. A structured narrative synthesis was conducted for weight-loss-dominant treatment, prediabetes, established ASCVD, HFpEF, OSA, MASH, route preference, body composition, functional vulnerability, and persistence. Numerical results were extracted from primary reports and are presented with effect estimates and confidence intervals where available.

Results

Study selection

A total of 426 records were identified from databases and registers. After removal of 112 duplicates and 18 records before screening, 296 titles and abstracts were screened and 232 were excluded. The 18 records removed before screening did not constitute eligible study reports and comprised protocols or registry-only records without reported results, conference abstracts without sufficient extractable data, and corrections, editorials, or other non-primary publications without an independent dataset. The study selection process is shown in Figure 1, and the reasons for exclusion of database or register full-text reports are summarized in Table 3.

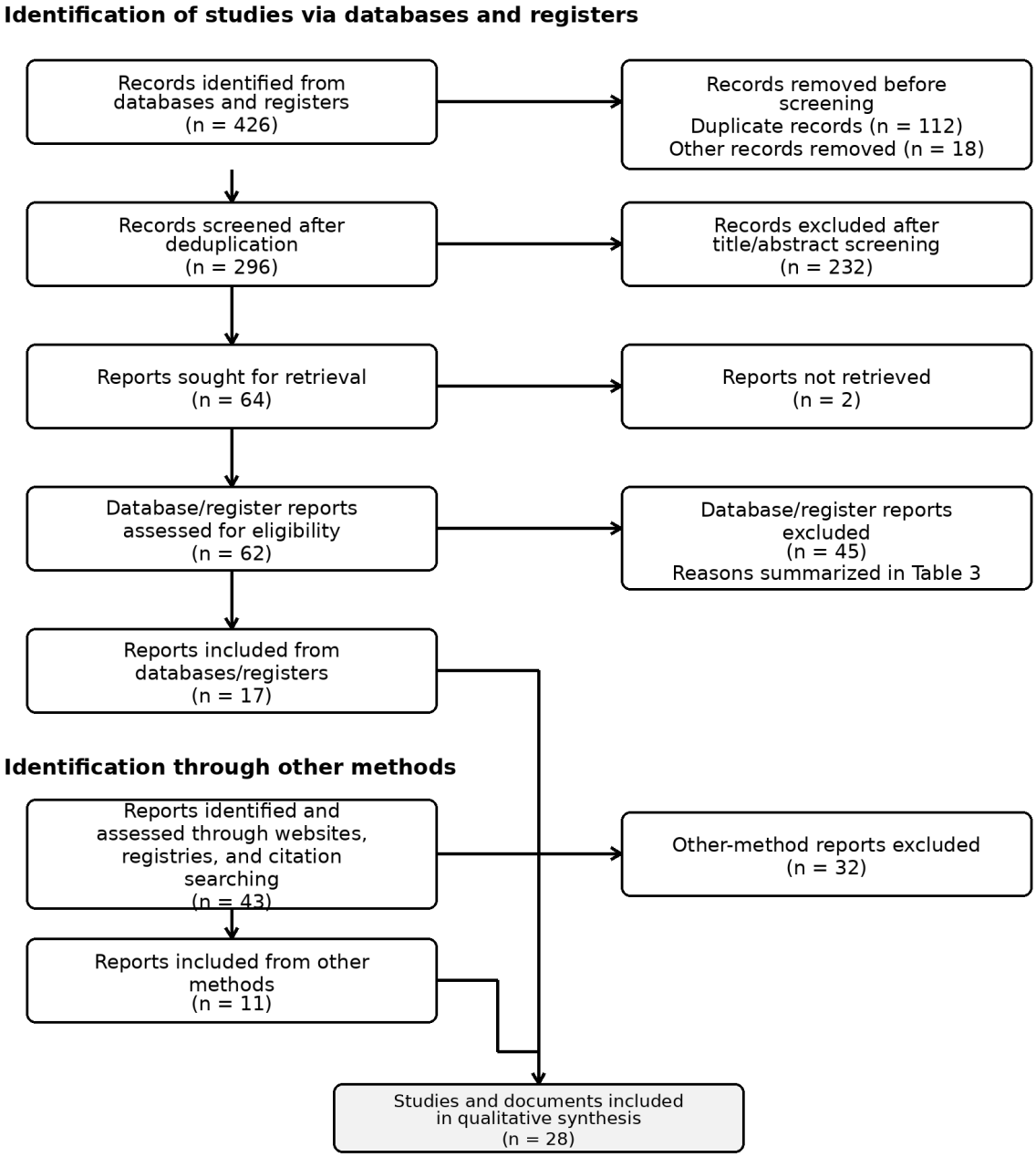

Figure 1. PRISMA 2020 study selection diagram

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

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 included evidence was separated into primary studies and contextual sources. Randomized trials and real-world cohorts informed clinical effects, whereas guidelines, regulatory sources, reviews, and professional statements informed implementation, regulatory context, or interpretation. This distinction is summarized in Table 4.

Table 4. Structure of the evidence base

Randomized efficacy, comparative, outcome, and withdrawal studies	STEP 1, SURMOUNT-1, SURMOUNT-4, SURMOUNT-5, SELECT, STEP-HFpEF, STEP-HFpEF DM, SUMMIT, SURMOUNT-OSA, OASIS 1, orforglipron, retatrutide, semaglutide MASH/NASH, and SYNERGY-NASH [3,5-20].	Primary estimates of efficacy, comparative effects, clinical outcomes, maintenance, and safety.
Long-term 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].	Fat mass, lean mass, and limits of functional interpretation.
Real-world cohorts	Semaglutide versus tirzepatide and discontinuation/reinitiation cohorts [22,23].	Applicability under routine dosing, access, discontinuation, and reinitiation.
Contextual sources	WHO, FDA, comparative meta-analysis, and reproductive-context sources [1,2,31-33].	Guideline, regulatory, comparative, and reproductive interpretation; not primary comparative evidence.

Quantitative synthesis by clinical question

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]. No direct semaglutide-tirzepatide HFpEF comparison is available; 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 interim 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 54.8% versus 5.7% 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 cohort of 125,474 adults, one-year discontinuation reached 46.5% among patients with type 2 diabetes and 64.8% among those without diabetes; reinitiation within one year occurred in 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 [5,7,9,10,18-20]. 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

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 54.8% vs 5.7%.	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	Median 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.

Table 5. Continued

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	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.
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]	Retrospective cohort; n=125,474	GLP-1 therapies in routine care	1 year	Discontinuation 46.5% with T2D and 64.8% without; reinitiation 47.3% and 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

Tirzepatide	Weight-loss-dominant treatment; prediabetes; OSA; HFpEF with obesity.	Head-to-head superiority for weight loss; long-term prediabetes data; direct OSA and HFpEF randomized trials [5-7,16,17,21].	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 outcomes; STEP-HFpEF program; ESSENCE phase 3 histology [12-15,19].	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].	No evidence that oral route itself improves long-term persistence; administration requirements and gastrointestinal events remain important.
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

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.
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	Do not discontinue effective therapy solely because lean mass decreases; initiate muscle-preserving support and monitor function [24,25].	Grip strength, gait or chair-rise performance, protein adequacy, resistance exercise, and body composition when clinically useful.
Low readiness for injections	Consider oral semaglutide or orforglipron when available and compatible with the administration routine [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

Randomized trials generally provided reliable estimates for objective weight, cardiovascular, sleep, and histological outcomes, although open-label designs, secondary analyses, attrition, and enriched withdrawal designs reduced confidence in selected questions. Real-world studies improved applicability to routine care but remained vulnerable to residual confounding, treatment selection, dose misclassification, and differential discontinuation. Detailed judgments are provided in Supplementary File S3. Table 8 presents a qualitative, non-GRADE appraisal.

Table 8. Qualitative appraisal of confidence in the evidence

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, downgraded for residual confounding and changes in access and dosing [22,23].
Biomarker-guided drug selection	Limited	No validated, independently replicated clinical algorithm is available for routine selection.

Discussion

Main findings

Personalization should begin with the dominant clinical risk and the probability that treatment can be sustained. Tirzepatide has the strongest direct comparative evidence when magnitude of weight reduction is the principal objective and is well supported in prediabetes and OSA. Semaglutide has the most mature evidence for reduction of cardiovascular events in established ASCVD and phase 3 histological outcomes in MASH. In HFpEF, the revised evidence base 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. The available evidence does not justify presenting HFpEF as an exclusively tirzepatide-supported phenotype.

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

Network meta-analyses are useful for estimating comparative weight loss but necessarily combine heterogeneous trials and may not capture differences in comorbidity-specific outcomes, withdrawal, access, or route [31]. WHO guidance emphasizes long-term therapy as one element of comprehensive chronic obesity care [1]. The present synthesis adds a phenotype and treatment-pathway layer while separating direct 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. Before discontinuation, clinicians should explain the expected risk of regain and define a maintenance or reinitiation pathway.

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 evidence from contextual sources, incorporation of direct cardiovascular, HFpEF, OSA, diabetes-prevention, MASH, withdrawal, body-composition, and real-world persistence evidence, provision of numerical study-level results, and study-level RoB 2 and ROBINS-I assessment.

Several limitations remain. The review focused on contemporary higher-efficacy incretin therapies and did not comprehensively evaluate older agents. The protocol was not prospectively registered, the search was limited to English and Russian, and meta-analysis was not performed because of substantial clinical and methodological heterogeneity. The confidence categories are descriptive rather than formal GRADE ratings. Some newer agents have limited long-term outcome data, and observational estimates remain susceptible to residual confounding.

Conclusion

A phenotype-oriented approach is more clinically defensible than ranking contemporary incretin therapies by mean weight loss alone. Tirzepatide has the strongest direct comparative weight-loss signal and direct evidence in prediabetes and OSA. 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 Box 1.

Box 1. Practical interpretive framework

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.

Additional information

Registration and protocol. The protocol was developed before full-text screening and data extraction but was not prospectively registered or deposited in a public repository.

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Conflicts of interest. The authors declare no conflicts of interest.

Data availability. Detailed search strategies, the completed PRISMA 2020 checklist, study-level risk-of-bias assessments, the extraction template, and extracted study-level data are provided in Supplementary Files S1-S4. Individual participant-level data were not collected or used in this review.

Reporting guideline. The completed PRISMA 2020 checklist is provided as Supplementary File S2.

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Supplementary File S1

Detailed search strategies and supplementary methods

Manuscript: Personalization of contemporary incretin therapy for obesity: a focused systematic review

Final search date: 8 July 2026

1. Search framework

The search combined a contemporary bibliographic search from 1 January 2024 to 8 July 2026 with complementary searches of trial registries, citation indexes, organizational websites, and supplementary topic-based searches without date restriction. The core strategy combined the population and intervention concepts. Phenotype and outcome terms were used in supplementary searches and during screening rather than as a mandatory AND block, thereby reducing the risk of excluding eligible reports whose abstracts did not contain specific outcome terminology.

Supplementary Table S1.1. Core concept groups

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

2. MEDLINE via PubMed

Platform: PubMed. Search date: 8 July 2026. Coverage: 1 January 2024 to 8 July 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] : "2026/07/08"[Date - Publication])
AND (english[Language] OR russian[Language])
NOT (animals[MeSH Terms] NOT humans[MeSH Terms])
```

3. Embase

Platform: Embase.com. Search date: 8 July 2026. Coverage: publication years 2024-2026 to the search date. 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)
```

4. Scopus

Platform: Elsevier Scopus. Search date: 8 July 2026. Coverage: publication years 2024-2026. 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 < 2027 AND (LIMIT-TO(LANGUAGE, "English") OR LIMIT-TO(LANGUAGE, "Russian"))
```

5. Web of Science Core Collection

Platform: Clarivate Web of Science Core Collection. Search date: 8 July 2026. Coverage: publication years 2024-2026. 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=(2024-2026) AND LA=(English OR Russian)
```

6. 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 year 2024-2026; current to 8 July 2026

7. Trial registries

ClinicalTrials.gov was searched using 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 long Boolean strings may be handled inconsistently by the interface. No date restriction was applied.

8. Supplementary searches without date restriction

Supplementary searches were conducted in PubMed and citation indexes using combinations of intervention, population, and phenotype or outcome terms. The search concepts are summarized in Supplementary Table S1.2.

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

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")
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)

9. Targeted websites, citation searching, and deduplication

- 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.

10. Search yield

The PRISMA flow reports 426 records identified from bibliographic databases and trial registers and 43 reports identified through other methods. After deduplication and screening, 17 reports from databases or registers and 11 reports identified through other methods were included, giving a total of 28 studies or contextual documents.

Supplementary Table S1.3. Aggregate search yield

Bibliographic databases and trial registers	8 Jul 2026	Contemporary database search 1 Jan 2024-8 Jul 2026; registers without date restriction	426
Other methods: websites, citation searching, and supplementary searches	8 Jul 2026	No date restriction	43
Included from databases/registers	8 Jul 2026	Eligible reports after full-text assessment	17
Included from other methods	8 Jul 2026	Eligible reports after assessment	11
Total included studies/documents			28

Supplementary File S2

Manuscript: Personalization of contemporary incretin therapy for obesity: a focused systematic review

Completed PRISMA 2020 checklist

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).	Objective and research questions.
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.	Information sources and search strategy; Supplementary File S1.
Search strategy	7	Present full search strategies, including filters and limits.	Supplementary File S1.
Selection process	8	Specify methods used to decide whether a study met inclusion criteria, including reviewer independence.	Study selection and data extraction.
Data collection process	9	Specify methods used to collect data, reviewer independence, and confirmation procedures.	Study selection and data 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 File S4.
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 File S4.
Risk of bias	11	Specify methods used to assess risk of bias, including tools, domains, and reviewer independence.	Risk of bias and confidence in evidence; Supplementary File S3.
Effect measures	12	Specify effect measures used for each outcome.	Data synthesis; Table 5 and Supplementary File S4.
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 File S4.
Synthesis methods: tabulation/visual display	13c	Describe methods used to tabulate or visually display results.	Tables 4-8; Supplementary File S4.
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 applicable; no meta-analysis.
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.	Risk of bias and confidence in evidence; Table 8. Categories explicitly described as non-GRADE.
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 presents reason categories for excluded database/register full-text reports; other-method reports are summarized in the PRISMA flow.
Study characteristics	17	Cite each included study and present its characteristics.	Table 5; Supplementary File S4.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Tables S3A and S3B.
Results of individual studies	19	Present summary statistics and effect estimates with precision for each study where available.	Quantitative synthesis; Table 5; Supplementary File S4.
Results of syntheses: characteristics and risk of bias	20a	Summarize characteristics and risk of bias of contributing studies.	Tables 4 and 8; Supplementary File S3.
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 applicable.
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; descriptive non-GRADE confidence.
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; Conclusion.
Registration	24a	Provide registration information or state that the review was not registered.	Review design; Additional information. Not prospectively registered.
Protocol access	24b	Indicate where the protocol can be accessed or state that it was not prepared.	A protocol was prepared but was not deposited in a public repository; stated in Methods and Additional information.
Amendments	24c	Describe and explain amendments to registration or protocol.	Not applicable; the review was not prospectively registered.
Support	25	Describe financial or non-financial support and the role of funders.	Additional information - Funding.
Competing interests	26	Declare competing interests.	Additional information - Conflicts of interest.
Availability of data, code, and materials	27	Report which materials are publicly available and where.	Additional information; Supplementary Files S1-S4.

Supplementary File S3

Study-level risk of bias assessments

Supplementary Table S3A. RoB 2 assessment of randomized trials and randomized analyses

STEP 1 [3]	Weight change	Low	Low	Low	Low	Low	Low	Masked RCT; objective outcome; prespecified estimands.
SURMOUNT-1 [5]	Weight change	Low	Low	Low	Low	Low	Low	Masked RCT with objective outcome.
SURMOUNT-4 [6]	Maintenance/regain	Low	Low	Low	Low	Low	Low	Randomization after lead-in; enriched population affects applicability, not internal validity.
SURMOUNT-5 [7]	Weight/waist	Low	Some concerns	Low	Low	Low	Some concerns	Open-label active comparison could influence adherence; outcomes objective.
OASIS 1 [8]	Weight change	Low	Low	Low	Low	Low	Low	Double-blind RCT; prespecified estimands.
Orforglipron phase 2 [9]	Weight change	Low	Low	Low	Low	Low	Low	Randomized, double-blind, objective outcome.
ATTAIN-1 [10]	Weight change	Low	Low	Low	Low	Low	Low	Large double-blind phase 3 RCT.
Retatrutide phase 2 [11]	Weight change	Low	Low	Some concerns	Low	Low	Some concerns	Phase 2 dose-ranging study; attrition across groups.
SELECT [12]	MACE	Low	Low	Low	Low	Low	Low	Masked event-driven trial; adjudicated endpoint.
SELECT weight analysis [13]	Longitudinal weight	Low	Low	Some concerns	Low	Low	Some concerns	Secondary analysis with missing longitudinal measurements.
STEP-HFpEF [14]	KCCQ/weight/6MWD	Low	Low	Low	Some concerns	Low	Some concerns	Patient-reported KCCQ may be influenced by perceived effects; masking retained.
STEP-HFpEF DM [15]	KCCQ/weight/6MWD	Low	Low	Low	Some concerns	Low	Some concerns	As above; objective weight and 6MWD complement patient report.
SUMMIT [16]	CV death/worsening HF	Low	Low	Low	Low	Low	Low	Masked RCT with adjudicated event outcome.
SURMOUNT-OSA [17]	AHI	Low	Low	Low	Low	Low	Low	Two masked RCTs; objective sleep-study outcomes.
Semaglutide NASH [18]	Histological resolution	Low	Low	Low	Low	Low	Low	Masked RCT with central pathology assessment.
ESSENCE interim [19]	MASH/fibrosis histology	Low	Low	Some concerns	Low	Low	Some concerns	Prespecified interim histology; final clinical outcomes pending.
SYNERGY-NASH [20]	MASH/fibrosis histology	Low	Low	Some concerns	Low	Low	Some concerns	Phase 2 sample size and missing biopsies create some concern.
SURMOUNT-1 diabetes analysis [21]	Incident T2D	Low	Low	Some concerns	Low	Low	Some concerns	Long follow-up increases attrition risk; randomized assignment maintained.
SURMOUNT-1 DXA [24]	Body composition	Low	Low	Some concerns	Low	Some concerns	Some concerns	Substudy sample and selection limit robustness; measurements objective.

RoB 2 domains: D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, outcome measurement; D5, selection of the reported result.

Supplementary Table S3B. ROBINS-I assessment of non-randomized studies

STEP 1 extension [4]	Off-treatment extension; weight regain	Serious	Serious	Low	Moderate	Serious	Low	Moderate	Serious	Selected extension subset and no randomized continued-treatment comparator.
Real-world semaglutide vs tirzepatide [22]	Retrospective cohort; weight change	Serious	Moderate	Moderate	Moderate	Serious	Low	Moderate	Serious	Matching reduced measured confounding, but treatment selection and differential discontinuation remained.
Discontinuation/ reinitiation cohort [23]	Retrospective cohort; persistence	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Serious	Stopping and restarting were related to access, response, tolerability, and unmeasured patient factors.

ROBINS-I domains: D1, confounding; D2, participant selection; D3, intervention classification; D4, deviations from intended intervention; D5, missing data; D6, outcome measurement; D7, selection of the reported result.

Supplementary File S4

Data extraction template and extracted study-level data

Supplementary Table S4A. Data extraction template

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	RoB 2 or ROBINS-I domain judgments and basis.

Supplementary Table S4B. Extracted study-level data

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 54.8% vs 5.7%.	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	Median 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.

Supplementary Table S4B. Continued

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	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.
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]	Retrospective cohort; n=125,474	GLP-1 therapies in routine care	1 year	Discontinuation 46.5% with T2D and 64.8% without; reinitiation 47.3% and 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.

The table reports the principal numerical outcome used in the narrative synthesis. Full secondary outcome sets should be retained in the study-level dataset if the manuscript is updated or converted to a quantitative synthesis.