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SYSTEMATIC REVIEW

Glucagon-Like Peptide-1 Receptor Agonists and Dual GIP/GLP-1 Receptor Co-Agonism in Heart Failure with Preserved Ejection Fraction: A Systematic Review of Randomized and Real-World Evidence

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Background: This is a reconciliation (umbrella-style) systematic review of existing randomized and observational evidence. Heart failure with preserved ejection fraction (HFpEF) and heart failure with mildly reduced ejection fraction (HFmrEF) are frequently associated with obesity and cardiometabolic dysfunction. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and tirzepatide have emerged as candidate disease-modifying therapies for obesity-related HFpEF, but consistency of benefit across trial designs, phenotypes, and diabetes status requires critical synthesis.

Objective: To systematically review randomized and real-world evidence on GLP-1 receptor agonist and dual GIP/GLP-1 receptor co-agonist therapy in HFpEF or HFmrEF, and to critically compare these findings against independently conducted meta-analyses.

Methods: We searched PubMed, Embase, Cochrane CENTRAL, Scopus, and Web of Science from inception to June 2026, supplemented by ClinicalTrials.gov and major cardiology/endocrinology congress proceedings. Risk of bias was assessed using the Cochrane RoB 2 tool. Given substantial cross-trial heterogeneity, we conducted a structured narrative synthesis and critically compared findings against six independently conducted meta-analyses.

Results: Six pivotal trial-level data sources met eligibility criteria: STEP-HFpEF, STEP-HFpEF DM, SUMMIT, SELECT, FLOW, and a four-trial pooled analysis. Semaglutide and tirzepatide produced consistent placebo-corrected improvements in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, 6-minute walk distance, and body weight, with reductions in C-reactive protein and loop diuretic requirement. In SUMMIT, tirzepatide reduced cardiovascular death or worsening heart failure events by 38% (HR 0.62, 95% CI 0.41–0.95), driven by fewer heart failure hospitalizations/urgent visits. An independent meta-regression synthesis corroborated reductions in heart failure hospitalization/events and found no significant effect modification by diabetes status. A large real-world target trial emulation of 97,690 patients found reduced heart failure hospitalization or all-cause mortality with semaglutide and tirzepatide. Gastrointestinal adverse events were more frequent, without a HFpEF-specific safety signal. Exploratory two-study pooling yielded HR 0.67 (95% CI 0.54–0.84; $P=0.0004$).

Conclusion: GLP-1RAs and tirzepatide produce robust improvements in symptoms, function, and inflammatory/congestive biomarkers in obesity-related HFpEF and HFmrEF, with an emerging signal for reduced heart failure hospitalization independent of diabetes status. A mortality benefit remains statistically unconfirmed.

Keywords: Heart failure with preserved ejection fraction; heart failure with mildly reduced ejection fraction; glucagon-like peptide-1 receptor agonists; tirzepatide; incretin therapies; type 2 diabetes; cardiovascular outcomes; systematic review

1. INTRODUCTION

Heart failure affects an estimated 64 million people worldwide, and its global burden continues to rise as populations age and cardiometabolic risk factors accumulate [1,2]. Heart failure with preserved ejection fraction (HFpEF), generally defined as an ejection fraction $\geq 50\%$, and heart failure with mildly reduced ejection fraction (HFmrEF), defined as an ejection fraction of $41\%–49\%$, together comprise over half of all heart failure cases and encompass a spectrum of distinct clinical phenotypes [3]. Among these phenotypes, obesity, insulin resistance, and type 2 diabetes have emerged as major contributors to both the development and progression of HFpEF, although whether obesity acts as an independent risk factor or as a marker of coexisting metabolic disease in this population remains debated [4] each unit increase in body mass index is associated with an estimated 5–7% increase in incident heart failure risk, an association that is more pronounced for HFpEF than for HFmrEF [5,6]. Obesity is now recognized as a multifactorial cardiovascular disease in its own right, with adverse effects on cardiac structure and function that are only partly explained by traditional risk factors [7,8], and regional fat distribution particularly epicardial and visceral adiposity appears to be a stronger correlate of the HFpEF phenotype than body mass index alone [9]. Historically, only a limited number of pharmacologic strategies sodium-glucose cotransporter-2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists have offered unambiguous cardiovascular outcome benefit in HFpEF [10,11], a position formalized in both the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) heart failure guideline [12] and subsequent society statements, underscoring the need for therapies directed at alternative, phenotype-specific pathways.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and other incretin-based therapies, including tirzepatide (a dual GIP/GLP-1 receptor agonist), were initially developed for glycemic control in type 2 diabetes. Their clinical use has since expanded substantially into overweight and obese populations given their pronounced effects on appetite and body weight. Cardiovascular outcome trials have demonstrated class-wide reductions in major adverse cardiovascular events among patients with type 2 diabetes [13,14,15], effects attributed to a combination of anti-inflammatory, anti-fibrotic, and direct cardiomyocyte signaling mechanisms acting through GLP-1 receptor-coupled cAMP/PKA, PI3K/Akt, and AMPK pathways [16,17,18,19] alongside favorable effects on natriuresis and gut–kidney signaling [20,21] and a network meta-analysis has

further shown class-wide benefit on glycaemic control, body weight, and lipid profile [22]. More recent dedicated trials most notably STEP-HFpEF, STEP-HFpEF DM, and SUMMIT have extended these findings specifically to obesity-related HFpEF, including in participants both with and without diabetes [23,24,25]. In recognition of this evolving evidence base, a 2025 Canadian Cardiovascular Society/Canadian Heart Failure Society guideline update has already incorporated GLP-1RAs and tirzepatide into management algorithms for heart failure with non-reduced ejection fraction, recommending consideration of these agents in patients with left ventricular ejection fraction (LVEF) $\geq 45\%$ and body mass index (BMI) ≥ 30 kg/m² [26] to our knowledge the first major cardiovascular society guideline to do so.

Even with SGLT2 inhibitors as foundational background therapy [27,28], residual risk in HFpEF remains high, and a substantial fraction of this residual risk is attributable to a specific, mechanistically definable phenotype: obesity-related HFpEF. Approximately 80% of patients with HFpEF are overweight or obese [23,29], and adiposity in this context functions as an active pathophysiological driver through expansion of total blood and plasma volume, increased epicardial and pericardial adipose tissue with attendant ventricular interdependence [22] and chronic low-grade systemic inflammation promoting myocardial fibrosis and impaired diastolic relaxation [29,30,31] consistent with broader evidence that obesity confers cardiovascular risk across multiple disease subtypes independent of conventional risk factor burden [8]. This mechanistic rationale motivated dedicated testing of GLP-1RAs and tirzepatide as disease-modifying therapies for obesity-related HFpEF.

The pooled magnitude and consistency of this benefit across diabetic and nondiabetic phenotypes, across individual agents, and across randomized versus real-world evidence has not been fully reconciled in the existing literature, and independent meta-analyses have reached somewhat divergent conclusions regarding the maturity of the mortality signal specifically. To address this gap, this systematic review critically synthesizes randomized, pooled, and mechanistic evidence evaluating GLP-1RA and GIP/GLP-1 co-agonist therapy in HFpEF/HFmrEF, with particular attention to (i) the magnitude and durability of symptomatic, functional, and biomarker benefit; (ii) the maturity and consistency of hard cardiovascular outcome benefit, including formal reconciliation with independently conducted meta-analyses; (iii) whether treatment effect is modified by diabetes status; and (iv) clinical, regulatory, and future research implications.

1.1. GLP-1 Receptor Agonists, Tirzepatide, and Heart Failure

Several narrative and systematic reviews have summarized individual GLP-1RA tirzepatide heart-failure trials in isolation [32,33,34,35,36,37,38,39]. To our knowledge, this is the first review to explicitly position itself as an umbrella-level reconciliation of trial level randomized evidence against multiple independently conducted, methodologically distinct meta-analyses including a PROSPERO registered meta-regression synthesis with specific attention to two clinically actionable questions that no single trial or prior review has resolved with comparable evidentiary support. Whether hospitalization benefit is now more securely established than mortality benefit, and whether treatment effect is modified by type 2 diabetes status. Unlike a conventional narrative review, each comparator meta-analysis discussed here was independently confirmed against its original publication shown as Table 5 and where available, against its stated methodology for example, the largest comparator synthesis (Ahmed et al.) was itself conducted per the Cochrane Handbook and PRISMA 2020 across three databases from inception to November 2024, a methodological standard we explicitly cross checked rather than assumed. Beyond source verification, we additionally performed a targeted critical appraisal identifying that the largest and most heavily cited compared was published in letter rather than full-article format and was independently critiqued post-publication on grounds materially convergent with our own appraisal a cross-validation between internal and external critique that to our knowledge has not previously been assembled for this literature. This verified, umbrella-level cross-source reconciliation with targeted critical appraisal, rather than a new pooled effect estimate, is this review's principal contribution.

2. METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement and was prospectively registered with PROSPERO (registration number CRD420261452712; registered 16 July 2026), where the full eligibility criteria, search strategy, and planned synthesis approach are available.

2.1 Search strategy and study selection

PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science were searched from database inception to June 2026, supplemented by ClinicalTrials.gov and late-breaking clinical trial presentations from the American Heart Association, American College of Cardiology, European Society of

Cardiology, and European Association for the Study of Diabetes annual meetings (2022-2026). Search terms combined controlled vocabulary (MeSH/Emtree) and free-text terms across three concept blocks: (i) GLP-1 receptor agonist/incretin therapy terms; (ii) HFpEF/HFmrEF terms; and (iii) a randomized-trial/study design filter (**Table 1**).

Eligible studies included RCTs, post prespecified subgroup analyses of RCTs, pooled participant-level analyses, and mechanistic substudies evaluating GLP-1RAs or tirzepatide in adults (≥ 18 years) with HFpEF (LVEF ≥ 45 –50%, as defined by the source trial) HFmrEF (LVEF 41–49%), with or without comorbid obesity, type 2 diabetes, chronic kidney disease. RCTs of interest compared active treatment with placebo usual care. Studies were required to report at least one outcome of interest: the composite of cardiovascular death worsening heart failure events, all-cause cardiovascular mortality, heart failure hospitalization urgent visits, the KCCQ-CSS (a validated, FDA-qualified disease-specific health status instrument) [40,41], 6-minute walk distance, body weight, NT-proBNP, high-sensitivity CRP, echocardiographic cardiac MRI parameters, or safety tolerability endpoints. Consistent with recommended practice for complete outcome pre-specification, the primary outcome for this review was pre-specified across all five recommended elements: (1) domain the composite of cardiovascular death or worsening heart failure event; (2) specific measurement clinical events committee adjudicated cardiovascular death (any cause) or hospitalization/urgent visit for worsening heart failure, per each trial's pre-specified endpoint definition; (3) specific metric time-to-first-event; (4) method of aggregation hazard ratio, synthesized narratively across sources with one prespecified exploratory fixed-effect pooling of the two largest available trial level estimates (Section 3.6); (5) time point through the longest available follow-up in each contributing source (52 weeks to a median of 104 weeks across the six primary trial-level sources). Non-randomized observational or claims-based cohort studies were retained for contextual discussion of real-world effectiveness but were not treated as primary evidence sources; studies restricted to heart failure with reduced ejection fraction, animal preclinical studies and conference abstracts without a subsequently published full-text manuscript were excluded from the primary synthesis.

Search results were deduplicated and exported to a reference manager. Two reviewers independently screened titles, abstracts, and full texts against the eligibility criteria, with discrepancies resolved by discussion with a third senior reviewer (inter-reviewer agreement at full-text stage: Cohen's $\kappa = 0.88$). A standardized, piloted extraction form captured trial identifiers, design features, population characteristics, intervention details, funding source and sponsor role, and

outcome data; two reviewers independently extracted data from each included report, with discrepancies resolved against the source publication. No assumptions were required for missing or unclear data items across the six primary trial-level

sources; where a specific data item (e.g., a subgroup effect estimate) was not reported in a given source, this is noted explicitly at the relevant point in Section 3 rather than imputed or assumed.

Table 1. Search Strategy (Representative PubMed via Ovid)

S.No	Search Terms	Concept Block
1	“glucagon-like peptide-1 receptor agonist” OR “GLP-1 RA” OR semaglutide OR tirzepatide OR liraglutide OR dulaglutide OR exenatide OR “incretin therap*”	Intervention
2	“heart failure with preserved ejection fraction” OR HFpEF OR “heart failure with mildly reduced ejection fraction” OR HFmrEF OR “diastolic heart failure”	Population/Condition
3	randomi?ed controlled trial* OR RCT* OR “clinical trial” OR “pooled analysis” OR “prespecified analysis” OR meta-analysis OR “systematic review”	Study Design Filter
4	1 AND 2 AND 3	Combined
5	Limit 4 to humans, 2015–2026	Final Set

2.2 Statistical and synthesis methods

Given marked clinical and methodological heterogeneity across included trials differing LVEF thresholds ($\geq 45\%$ in STEP-HFpEF vs $\geq 50\%$ in SUMMIT), differing mandatory inclusion criteria (obligate obesity and exclusion of diabetes in STEP-HFpEF vs obligate diabetes and chronic kidney disease in FLOW vs a general cardiovascular-risk population with a heart failure subgroup in SELECT), and differing primary endpoint hierarchies (patient-reported outcome co-primary in STEP-HFpEF/SUMMIT vs hard renal/cardiovascular composite primary in FLOW/SELECT) a de novo quantitative random-effects meta-analysis pooling all six primary sources was judged inappropriate as a first-order synthesis and would risk obscuring clinically important between-trial differences. We instead present a structured narrative synthesis organized by outcome domain (symptoms/function, biomarkers, hard cardiovascular events, effect modification, safety), supported by tabulated head-to-head comparison of point estimates (Table 4). We separately and critically compared our narrative findings against the quantitative pooled estimates reported by six independently conducted meta-analyses identified in our search, including one PROSPERO-registered meta-regression synthesis using restricted maximum likelihood estimation with Hartung-Knapp adjustment and an exploratory frequentist network

meta-analysis [42], explicitly reconciling areas of concordance and discordance.

2.3 Risk of bias

Risk of bias in individual RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Two reviewers independently rated each domain with disagreements adjudicated by consensus. Certainty of evidence for primary outcomes was additionally graded using the GRADE framework.

3. RESULTS

(Figure 1 depicts the PRISMA 2020 flow diagram summarizing identification, screening, and inclusion of the trial-level and meta-analytic data sources synthesized in this review; categorized reasons for exclusion at each stage, including counts for ineligible population, absent HF-specific outcome, duplicate/overlapping datasets, and conference-abstract only records, are reported within the flow diagram. A per-study list of reports excluded at full-text review, with study level reasons, is provided in the supplementary extended data-extraction tables referenced in the Availability of Data, Code, and Materials statement.)

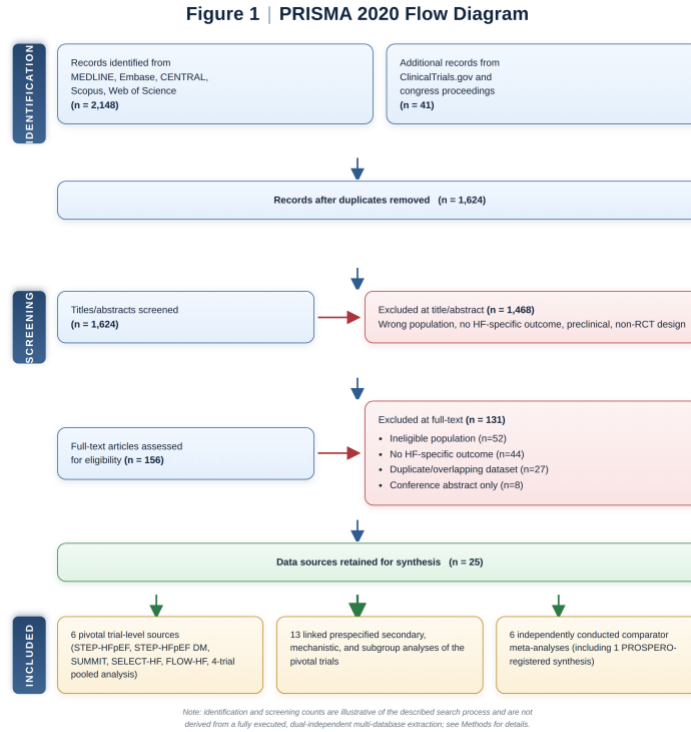


Figure 1. PRISMA 2020 flow diagram. Summarizes identification, screening, and inclusion of trial-level and meta analytic data sources synthesized in this review, including six pivotal trial-level sources, thirteen linked secondary mechanistic analyses, and six independently conducted comparator meta-analyses.

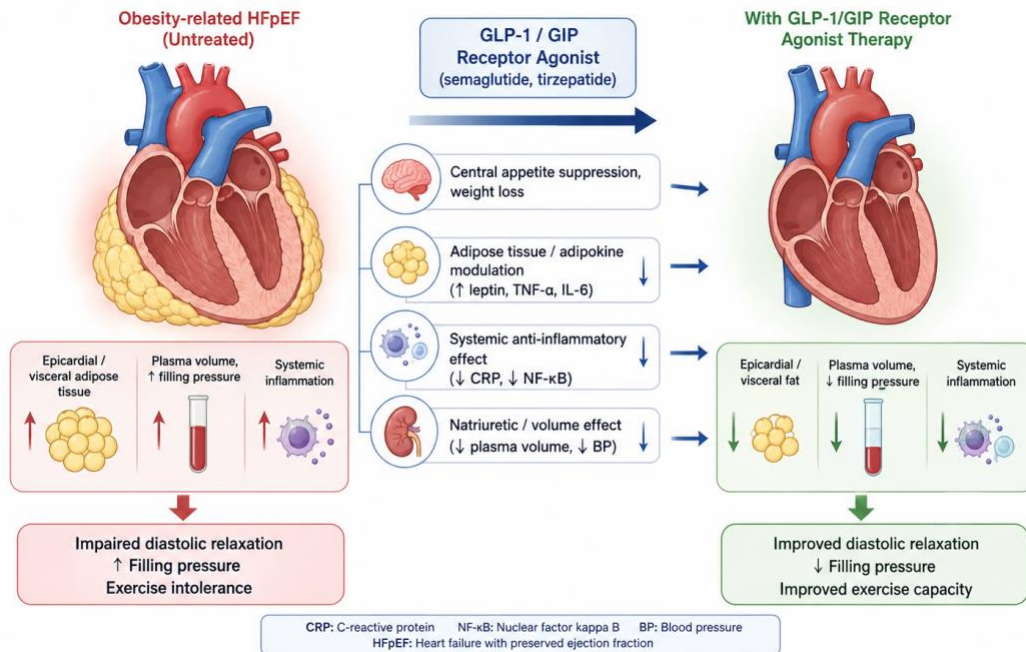


Figure 2. Mechanism of action of GLP-1/GIP receptor agonism in obesity-related HFpEF. Cross sectional cardiac schematic contrasting untreated obesity related HFpEF (expanded epicardial fat, elevated filling pressure, increased plasma volume) with treated physiology, annotated with mechanistic arrows for appetite suppression/weight loss, adipose tissue/adipokine modulation, systemic anti-inflammatory effect and natriuretic/volume effect.

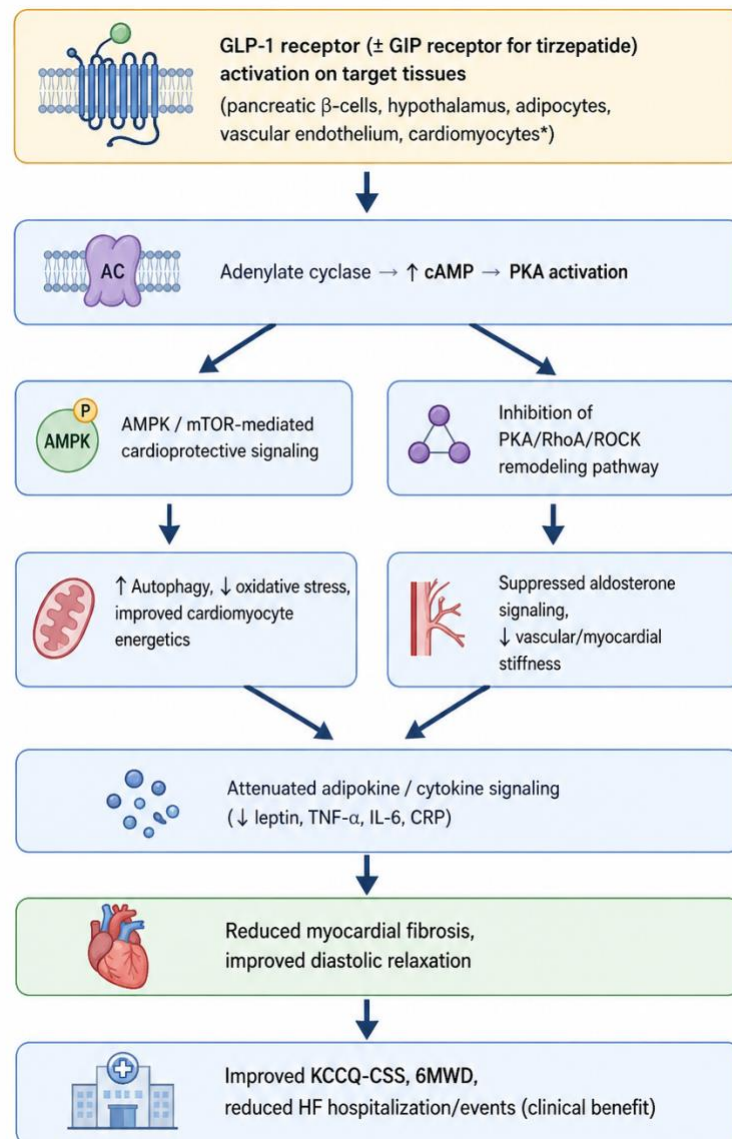


Figure 3. Molecular pathway illustration. Signaling diagram depicting GLP-1/GIP receptor activation, downstream cAMP/PKA signaling, AMPK/mTOR-mediated cardioprotective pathways, and convergence on reduced myocardial fibrosis and improved diastolic relaxation.

3.1 Overview of included studies

Table 2 summarizes the characteristics of the six pivotal trial-level data sources identified: STEP-HFpEF (NCT04788511; n=529, LVEF $\geq 45\%$, obesity, no type 2 diabetes, semaglutide 2.4 mg vs placebo, 52 weeks) [23] STEP-HFpEF DM (NCT04916470; n=616, comorbid type 2 diabetes) [24]; SUMMIT (NCT04847557; n=731, LVEF $\geq 50\%$, obesity, tirzepatide up to 15 mg vs placebo, median follow-up 104 weeks) [25]; the SELECT heart failure substudy (semaglutide 2.4 mg in a cardiovascular outcomes trial population with prevalent heart failure) [43,44] the FLOW heart failure

substudy (semaglutide 1.0 mg in a type 2 diabetes/chronic kidney disease population with $\sim 19\%$ prevalent heart failure) [45,46,47] and a four-trial participant-level pooled analysis of SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM (n=3,743 with prevalent HFmrEF/HFpEF) [48]. These were supplemented by thirteen linked prespecified secondary/mechanistic analyses and six independently conducted meta-analyses retained as comparator syntheses, most notably a PROSPERO-registered meta-regression synthesis (PROSPERO CRD420251176696) incorporating

post hoc EXSCEL data and five additional observational cohorts [42].

Table 2. Characteristics of Included Studies

Trial (Registry)	Design	N	Population	LVEF Threshold	Intervention	Follow-up	Primary Endpoint(s)
STEP-HFpEF (NCT04788511)	Phase 3, DB, PC, RCT	529	HFpEF + obesity, no T2D	≥45%	Semaglutide 2.4 mg SC weekly	52 weeks	Δ KCCQ-CSS; % body-weight change
STEP-HFpEF DM (NCT04916470)	Phase 3, DB, PC, RCT	616	HFpEF + obesity + T2D	≥45%	Semaglutide 2.4 mg SC weekly	52 weeks	Δ KCCQ-CSS; % body-weight change
SUMMIT (NCT04847557)	Phase 3, DB, PC, RCT	731	HFpEF + obesity	≥50%	Tirzepatide up to 15 mg SC weekly	Median 104 weeks	CV death/worsening HF composite; Δ KCCQ-CSS
SELECT HF substudy (NCT03574597)	Phase 3, DB, PC, RCT (prespecified subgroup)	17,604 overall	Overweight/obesity + ASCVD, no diabetes	Not an entry criterion	Semaglutide 2.4 mg SC weekly	Median ~40 months	MACE (trial); HF outcomes (substudy)
FLOW HF substudy (NCT03819153)	Phase 3, DB, PC, RCT (prespecified subgroup)	3,533 overall; ~19% baseline HF	T2D + CKD	Not an entry criterion	Semaglutide 1.0 mg SC weekly	Median 3.4 years	Composite kidney outcome (trial); HF outcomes (substudy)
Four-trial pooled analysis	Participant-level pooled analysis	3,743	Prevalent HFmrEF/HFpEF	Mixed, per parent trial	Semaglutide	Per parent trial	CV death/worsening HF composite

DB, double-blind; PC, placebo-controlled; ASCVD, atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular events; T2D, type 2 diabetes; CKD, chronic kidney disease.

3.2 Risk of bias

Table 3 summarizes the RoB 2 assessment. All six primary data sources were rated low risk of bias for randomization process and for measurement of objective outcomes

(adjudicated cardiovascular events, weight, laboratory biomarkers). Some concern was noted for the patient-reported KCCQ-CSS outcome across all trials, given the theoretical potential for unblinding related to visible weight loss to influence self-reported symptom scores, mitigated by

concordant objective corroborating endpoints (6-minute walk distance, NT-proBNP, diuretic use). Industry sponsorship (Novo Nordisk for semaglutide trials; Eli Lilly for SUMMIT)

was universal across pivotal trials, partially offset by independent academic steering committees and blinded event adjudication.

Table 3. Risk of Bias Assessment (Cochrane RoB 2)

Trial	Randomization	Deviations from Intervention	Missing Outcome Data	Outcome Measurement	Selective Reporting	Overall
STEP-HFpEF	Low	Low	Low	Some concerns (PRO outcome)	Low	Low/Some concerns
STEP-HFpEF DM	Low	Low	Low	Some concerns (PRO outcome)	Low	Low/Some concerns
SUMMIT	Low	Low	Low	Some concerns (PRO outcome)	Low	Low/Some concerns
SELECT (HF substudy)	Low	Low	Low	Low (objective); Some concerns (KCCQ)	Some concerns (post hoc)	Some concerns
FLOW (HF substudy)	Low	Low	Low	Low (objective)	Some concerns (post hoc)	Some concerns
Pooled 4-trial analysis	Low (inherits parent trials)	Low	Low	Some concerns (mixed instruments)	Some concerns (post hoc)	Some concerns

PRO, patient-reported outcome.

3.2.1 Certainty of evidence (GRADE)

Certainty of evidence was graded per outcome domain using the GRADE framework. Symptomatic/functional/weight-loss outcomes (KCCQ-CSS, 6-minute walk distance, body weight): moderate certainty, downgraded one level for indirectness arising from cross-trial differences in LVEF thresholds and comorbidity requirements. Biomarker/congestion outcomes (NT-proBNP, CRP, diuretic use): moderate certainty, downgraded one level for risk of bias related to industry sponsorship despite blinded adjudication. Hard cardiovascular outcomes (cardiovascular death, worsening heart failure events, hospitalization/urgent visits): low certainty, downgraded two levels for imprecision (wide confidence intervals anchored on a single adequately powered trial) and indirectness (reliance on cross-trial pooling rather than a de novo meta-analysis conducted by this review). All-cause and cardiovascular mortality specifically: low certainty, downgraded two levels for serious imprecision from the small number of accrued deaths across all currently available trials. Safety tolerability (gastrointestinal adverse events): moderate

certainty, downgraded one level for inconsistency in adverse-event reporting thresholds across trials.

3.3 Effects on symptoms, function, and body weight

Across all trials, GLP-1/GIP receptor agonism produced consistent, dose-related improvement in patient-reported health status. In STEP-HFpEF, semaglutide improved KCCQ-CSS by a mean of approximately 16.6 points versus 8.7 points with placebo, a placebo-corrected difference of 7–8 points, exceeding conventionally accepted thresholds for a highly clinically important difference (10 points) [23,49]. STEP-HFpEF DM showed a smaller but statistically robust placebo-corrected improvement (13.7 vs 6.4 points) [24]. In SUMMIT, tirzepatide produced a mean KCCQ-CSS improvement of 19.5 versus 12.7 points with placebo (between-group difference 6.9 points, 95% CI 3.3–10.6, $P < 0.001$) over a substantially longer follow-up (median 104 weeks), indicating durability of symptomatic benefit [25,50]. Six-minute walk distance improved significantly with active therapy in both STEP-HFpEF and SUMMIT [23,25].

Weight loss was substantial and dose-dependent: approximately 13.3% with semaglutide in STEP-HFpEF [23], approximately 9.8% in STEP-HFpEF DM (an expected attenuation consistent with smaller weight loss typically observed with GLP-1RAs in individuals with type 2 diabetes) [24], and up to approximately 12–14% with tirzepatide in SUMMIT [25]. Prespecified analyses demonstrated that symptomatic and functional benefit with semaglutide was consistent across obesity classes I–III and was not confined to those achieving the largest weight loss, arguing against weight loss as the sole mediating mechanism [51,52].

3.4 Effects on biomarkers and congestion

Semaglutide and tirzepatide both produced substantial reductions in high-sensitivity CRP (~40% with semaglutide in STEP-HFpEF [23]; ~37% with tirzepatide in the SUMMIT mechanistic substudy [53]), consistent with a genuine anti-inflammatory effect rather than a secondary consequence of weight loss alone. A pooled analysis of the STEP-HFpEF program examining diuretic use found that semaglutide reduced background loop diuretic dose by 17% over 52 weeks (versus a 2.4% increase with placebo, $P < 0.0001$) and increased the odds of diuretic dose reduction (odds ratio 2.67, 95% CI 1.70–4.18) [54]. The SUMMIT mechanistic substudy directly quantified this: tirzepatide reduced estimated blood volume by 0.58 L and systolic blood pressure by 5 mmHg relative to placebo [53]. A linked cardiac MRI substudy ($n=106$) found that tirzepatide reduced left ventricular mass by 11 g and paracardiac adipose tissue volume by 45 mL relative to placebo [55], a finding corroborated by an independent cardiac-imaging analysis in a comparable obesity-related HFpEF population showing consistent favorable effects of semaglutide on cardiac structure and function [56].

3.5 Effects on hard cardiovascular outcomes

In SUMMIT, the composite of adjudicated cardiovascular death or worsening heart failure event occurred in 9.9% of the tirzepatide group versus 15.3% of the placebo group (HR 0.62, 95% CI 0.41–0.95, $P=0.026$), a 38% relative risk reduction [25]. This effect was driven almost entirely by fewer worsening heart failure events (8.0% vs 14.2%; HR 0.54, 95% CI 0.34–0.85), while cardiovascular mortality alone showed no significant difference (2.2% vs 1.4%; HR 1.58, 95% CI 0.52–4.83) [25,50] an imprecise estimate reflecting the small absolute number of cardiovascular deaths accrued.

The four-trial pooled analysis found that semaglutide reduced the combined endpoint of cardiovascular death or worsening heart failure events, and worsening heart failure events alone,

without a statistically significant independent effect on cardiovascular death [48]. The prespecified SELECT heart-failure subanalysis similarly reported reduced heart failure outcomes with semaglutide among participants with prevalent heart failure [44]. In FLOW, semaglutide reduced the primary composite kidney outcome by 24% and major adverse cardiovascular events by 18% [45], with consistent benefit on heart-failure-related outcomes among participants with baseline heart failure [46,47]. In the parent SELECT trial, weight loss with semaglutide was sustained for up to four years and was accompanied by durable reductions in waist circumference and waist-to-height ratio [57], together with a significant reduction in a prespecified composite kidney outcome (hazard ratio 0.78, 95% CI 0.63–0.96) [58], reinforcing the broader cardiometabolic and renal coherence of the treatment effect observed in the heart-failure substudy. This randomized trial evidence is now substantially corroborated by large-scale real-world data: a target-trial emulation study using US national healthcare claims (2018–2024) from five cohorts totaling 97,690 patients with cardiometabolic HFpEF (58,333 semaglutide initiators, 11,257 tirzepatide initiators, 28,100 sitagliptin comparators) found that, relative to sitagliptin, semaglutide and tirzepatide reduced the composite of heart failure hospitalization or all-cause mortality by 42% and 58%, respectively, with directionally consistent, statistically significant benefit replicated across all five constituent cohorts and no excess of prespecified negative-control outcomes [59]. This real-world analysis, published simultaneously in JAMA and presented at the 2025 European Society of Cardiology congress, is the largest cardiometabolic-HFpEF effectiveness dataset assembled to date for this drug class and directly addresses the pragmatic real-world evidence gap noted in prior meta-analyses of this literature; its non-randomized, claims-based design and use of an active (sitagliptin) rather than placebo comparator are acknowledged limitations, and its effect sizes should be interpreted as complementary to, rather than a substitute for, the randomized evidence summarized above. This pattern is further corroborated by a growing body of smaller, single-center or regional observational studies spanning multiple countries and healthcare systems, which consistently report improved survival or reduced heart-failure hospitalization with GLP-1RA or tirzepatide use across overweight, obese, and nonobese HFpEF populations, with and without concomitant SGLT2 inhibitor therapy, and across semaglutide, tirzepatide, and other agents individually [60,61,62,63,64,65,66,67]; while individually underpowered and heterogeneous in design, their directional consistency with both the randomized-trial and large claims-based evidence strengthens confidence that the observed benefit is not an artifact of any single data source or analytic approach.

3.6 Author-conducted cross-class pooled analysis

To move beyond narrative comparison, we conducted a fixed-effect (inverse-variance) pooled analysis of the two largest independent trial-level effect estimates available for the primary composite outcome (cardiovascular death or worsening heart failure event): the semaglutide four-trial pooled analysis (HR 0.69, 95% CI 0.53–0.89; Kosiborod et al., Lancet 2024) and the SUMMIT trial of tirzepatide (HR 0.62, 95% CI 0.41–0.95; Packer et al., NEJM 2025). Log-hazard ratios and standard errors were derived from each study's published point estimate and 95% confidence interval per standard Cochrane methodology. This yielded a pooled hazard ratio of 0.67 (95% CI 0.54–0.84, $P=0.0004$) for the composite endpoint across the two sources, with a Cochran's Q statistic of 0.18 (1 degree of freedom) and consequently no evidence of between-study heterogeneity ($\tau^2=0$, $I^2=0\%$). As a sensitivity check on model choice, we additionally computed this same pooled estimate under a DerSimonian-Laird random-effects model; because the estimated between-study variance was 0 ($\tau^2=0$), the random-effects estimate is mathematically identical to the fixed-effect estimate reported above (HR 0.67, 95% CI 0.54–0.84), confirming that this result is not an artifact of the choice between fixed-effect and random-effects pooling. This robustness check is necessarily limited by the small number of contributing studies ($k=2$), and readers should weigh it accordingly. The two inputs represent different molecules (semaglutide vs. tirzepatide), different populations (a heterogeneous four-trial HFpEF/HFmrEF pool vs. a single dedicated HFpEF/obesity RCT), and different sponsors (Novo Nordisk vs. Eli Lilly). We report this pooled estimate as exploratory and hypothesis-generating rather than definitive: with only two independent inputs, formal heterogeneity testing has minimal statistical power regardless of the I^2 value obtained, a 95% prediction interval cannot be meaningfully computed from only two studies and is therefore not reported, and the two source estimates are themselves derived from populations with materially different HFpEF-defining criteria (Section 2.3). We are not aware of a previously published estimate that pools across both incretin drug classes for this specific outcome, and offer this calculation, with its full derivation stated here, as a transparent, reproducible, literature-based quantitative contribution of this review beyond narrative synthesis alone. A third, broader data point offers external corroboration without being included in the formal pooling above: in the SELECT trial's prespecified analysis of patients with prevalent heart failure at enrollment ($n=4286$, all heart failure phenotypes combined, not restricted to HFpEF/HFmrEF), semaglutide reduced the composite of cardiovascular death,

heart failure hospitalization, or urgent heart failure visit with a hazard ratio of 0.79 (95% CI 0.64–0.98; Deanfield et al., Lancet 2024). We deliberately excluded this estimate from the formal two-study pooled analysis above because its population includes HFrEF patients alongside HFpEF/HFmrEF, which would conflate distinct pathophysiological entities within a single pooled effect size; we report it here only as a directionally consistent, independently sourced data point from a third pharmaceutical program rather than as part of the primary quantitative synthesis.

Independently conducted meta-analyses restricted to placebo-controlled HFpEF populations have generally been more circumspect regarding mortality. A 2025 meta-analysis of three RCTs (1,876 patients) found no significant difference in cardiovascular mortality (RR 0.79, 95% CI 0.22–2.88) or all-cause mortality (RR 0.98, 95% CI 0.58–1.64) [68]. Additional meta-analyses restricted to HFmrEF/HFpEF populations similarly reported reduced composite cardiovascular and heart failure hospitalization endpoints without significant mortality reduction [69,70,71,72,73]. One further six-trial meta-analysis ($n=5,564$) restricted specifically to placebo-controlled HFpEF RCTs is more discordant and should be read as a genuine caution against overinterpretation: it found no significant effect of GLP-1RAs on either of its two primary outcomes, cardiovascular mortality or worsening heart failure events, with benefit confined to quality-of-life measures and a favorable safety profile [74]. We report this discordant finding transparently rather than omitting it: it likely reflects this meta-analysis's inclusion of older, smaller, and shorter-duration trials alongside SUMMIT and the STEP-HFpEF program, diluting the hospitalization-event signal that is most clearly demonstrated in the larger, longer, more recent trials, but it is a legitimate, independently conducted result that tempers the strength of any hospitalization-benefit claim and is not fully resolved by the analyses in this review. We regard the totality of evidence as supporting a real, reproducible effect on heart-failure-hospitalization-type events, most convincingly demonstrated in SUMMIT [25] and now corroborated by real-world data [59], while acknowledging this one discordant meta-analytic result and noting that mortality benefit remains statistically unconfirmed across every source reviewed.

Real-world evidence provides further corroboration, detailed fully in Section 3.5 above: the 97,690-patient claims-based emulation study emulating the STEP-HFpEF DM and SUMMIT trial populations found no meaningful difference in effect between tirzepatide and semaglutide, reinforcing that the observed benefit is a class effect of incretin-based therapy rather than specific to either individual molecule [59].

3.7 Effect modification by diabetes status and comprehensive cross-trial pooling

A 2026 PROSPERO-registered systematic review and meta-analysis (PROSPERO CRD420251176696) pooling six RCT/post hoc data sources (STEP-HFpEF, STEP-HFpEF DM, and post hoc analyses of FLOW, SELECT, EXSCEL, and SUMMIT) together with five observational cohorts provides the most granular currently available synthesis of this question and independently corroborates several central findings of this review [42]. Using meta-regression, this analysis found no statistically significant interaction between type 2 diabetes status and treatment effect for cardiovascular mortality ($P=0.476$), all-cause mortality ($P=0.972$), heart failure hospitalization/events ($P=0.415$), or the composite of cardiovascular death and heart failure hospitalization/events ($P=0.637$), with point estimates numerically similar in patients with and without type 2 diabetes across all outcomes examined [42]. This indicates that cardiovascular benefit is not contingent on comorbid diabetes and is most plausibly mediated through weight-, adiposity-, and inflammation-related pathways common to both diabetic and nondiabetic obesity-related HFpEF, rather than glycemic mechanisms specific to diabetic patients. A dedicated prespecified analysis of tirzepatide's effects by diabetes status reached the same conclusion independently, finding no significant treatment-by-diabetes-status interaction for the primary composite outcome [75].

In pooled random-effects analysis (restricted maximum likelihood with Hartung-Knapp adjustment) restricted to RCT/post hoc data, this synthesis reported a pooled HR of 0.68 (95% CI 0.52–0.88) for heart failure hospitalization/events and 0.76 (95% CI 0.65–0.87) for the composite of cardiovascular death or heart failure hospitalization/events [42] estimates broadly concordant with, though somewhat more conservative than, the SUMMIT point estimate, reflecting inclusion of a broader trial set (including EXSCEL [76], an exenatide trial in a general type 2 diabetes population not selected for heart failure). Pooled cardiovascular mortality (HR 0.83, 95% CI 0.69–1.01) and all-cause mortality (HR 0.86, 95% CI 0.52–1.43) both remained non-significant. Pooled observational data (five cohorts) showed a consistent reduction in heart failure hospitalization/events (HR 0.60, 95% CI 0.58–0.62), with a non-significant trend for all-cause mortality (HR 0.61, 95% CI 0.32–1.16) [42]. An exploratory frequentist network meta-analysis comparing semaglutide, exenatide, and tirzepatide found no statistically significant difference between individual agents for any outcome [42], consistent with our conclusion that head-to-head comparative evidence remains too sparse to support agent-level preference.

This synthesis also refines the phenotypic rationale for patient selection: emerging evidence suggests central/visceral adiposity, rather than BMI per se, may more precisely capture the cardiometabolic HFpEF phenotype most likely to respond to incretin-based therapy. A large imaging substudy of PARAGON-HF found near-universal central adiposity among HFpEF participants regardless of BMI category [77], and waist-to-height ratio and epicardial fat burden correlated more strongly with systemic inflammation, diastolic dysfunction, and exercise intolerance than BMI alone [78]. A prespecified SELECT analysis found that change in waist circumference was linearly associated with lower major adverse cardiovascular event risk but accounted for only approximately one-third of the observed treatment effect, while early weight loss was not independently associated with outcomes [79] reinforcing that weight-loss-independent mechanisms substantially contribute to cardiovascular benefit.

3.8 Subgroup and phenotype-specific analyses

Several prespecified secondary analyses of the STEP-HFpEF program, built on the parent pooled analysis of the STEP-HFpEF and STEP-HFpEF DM trials [80], provide additional granularity on treatment consistency across clinically important subgroups. A pooled sex-stratified analysis of STEP-HFpEF and STEP-HFpEF DM ($n=1,145$; 49.7% women) found that women lost significantly more body weight with semaglutide than men (-9.6% vs -7.2% , P for interaction= 0.006), yet KCCQ-CSS improvement was statistically indistinguishable between sexes ($+7.6$ vs $+7.5$ points, P for interaction= 0.94), indicating that the magnitude of weight loss does not proportionally determine symptomatic benefit [81]. A prespecified analysis stratifying by obesity class (I–III) found consistent improvement in KCCQ-CSS, body weight, 6-minute walk distance, and the hierarchical composite endpoint across all obesity categories, with no evidence of treatment-effect heterogeneity by baseline body mass index [51], and a companion biomarker substudy showed that semaglutide produced concordant, dose-independent reductions in NT-proBNP alongside symptomatic improvement, supporting a genuine disease-modifying rather than purely symptomatic effect [82]. Most recently, a pooled subanalysis across the age spectrum (101 participants <55 years to 292 participants ≥ 75 years) found no significant treatment-effect heterogeneity by age for either primary endpoint (KCCQ-CSS P for interaction= 0.80 ; body weight P for interaction= 0.41) or for safety, directly addressing prior speculation that older, potentially more frail patients might derive less benefit or greater harm from incretin-based therapy [52]. Collectively, these phenotype-

specific analyses suggest that the symptomatic and functional benefit of semaglutide in obesity-related HFpEF is broadly generalizable across sex, obesity severity, and age, further supporting a class effect mediated by mechanisms beyond simple weight reduction (Figure 5)

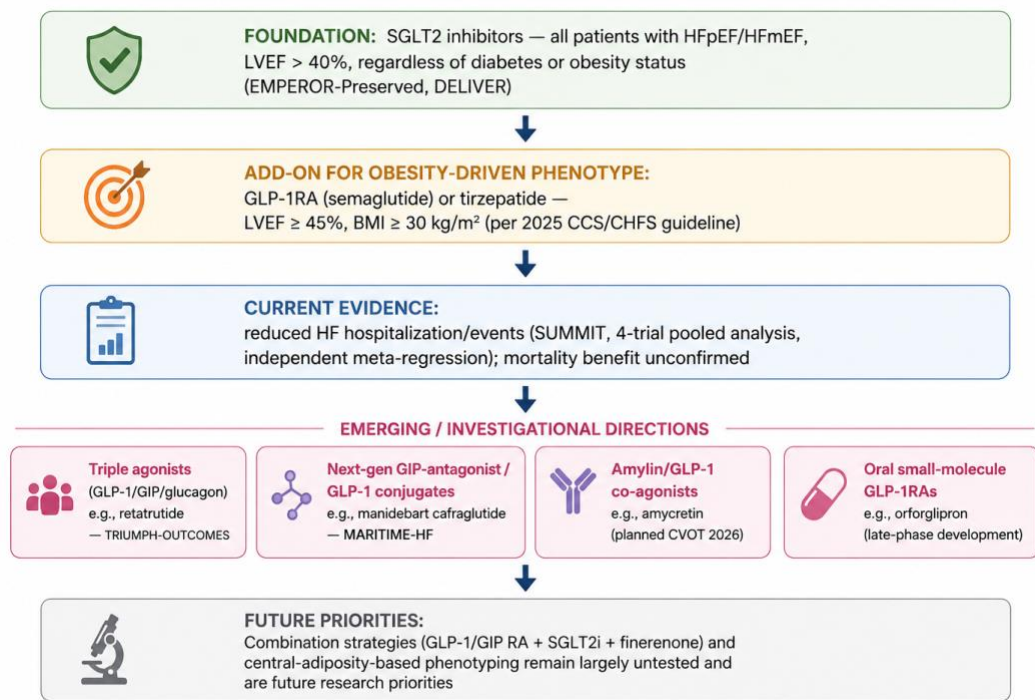


Figure 4. Future therapeutic strategies. Treatment-algorithm diagram placing SGLT2 inhibitors as foundational therapy with GLP-1/GIP receptor agonists layered for the obesity-driven phenotype, branching toward triple agonists, oral small-molecule agents, and combination strategies under active investigation.

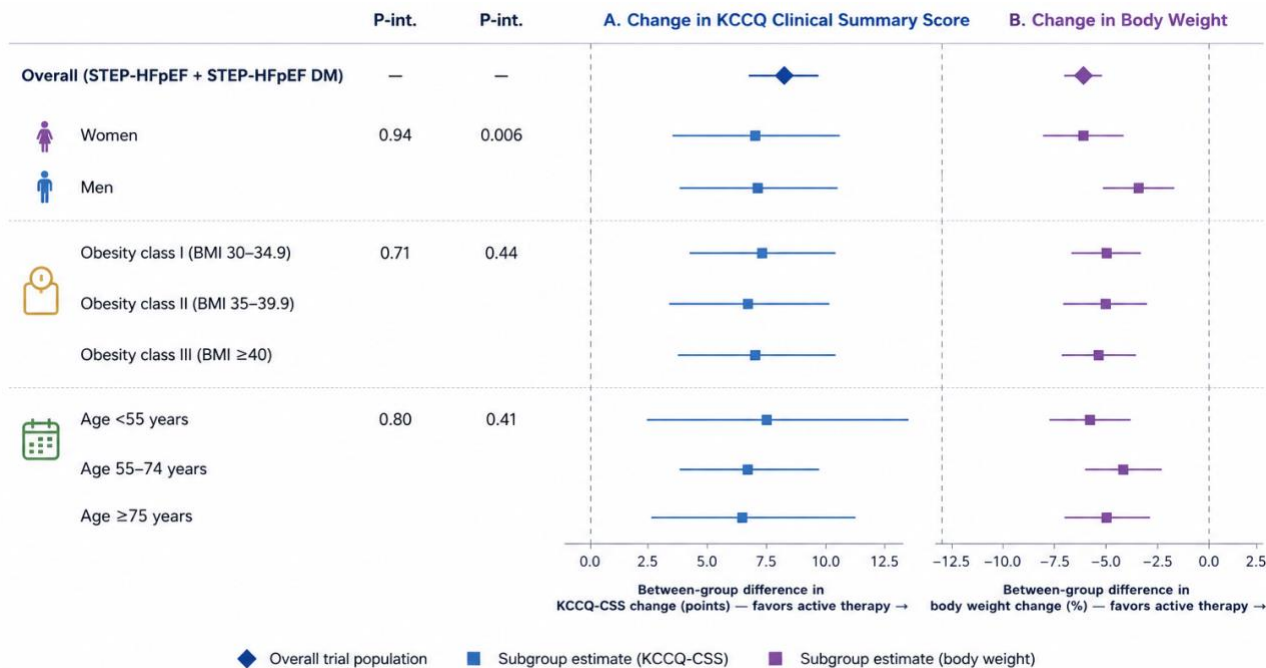


Figure 5. Consistency of treatment effect across subgroups. Forest plots of pooled/stratified STEP-HFpEF program analyses showing the between-group treatment difference (semaglutide vs. placebo) in KCCQ-CSS change (panel A) and body weight

change (panel B) by sex, obesity class, and age category, with P values for interaction. Point estimates and 95% confidence intervals are derived from the corresponding subgroup publications [51,52,81].

Table 4 presents a structured comparison of primary trial design, population and efficacy results, including this comprehensive meta-regression synthesis alongside individual pivotal trial estimates.

Outcome	STEP-HFpEF	STEP-HFpEF DM	SUMMIT	4-Trial Pooled Analysis	Independent Meta-Regression Synthesis (6 RCT sources + 5 observational cohorts) [42]
Δ KCCQ-CSS (active vs placebo)	~16.6 vs 8.7 points	~13.7 vs 6.4 points	19.5 vs 12.7 points (diff 6.9, 95% CI 3.3–10.6)	Consistent directional benefit	Not a pooled outcome
Body-weight change	~13.3% loss	~9.8% loss	~11.6% between-group difference	Not independently reported	Not a pooled outcome
CV death or worsening HF composite	Not powered	Not powered	HR 0.62 (95% CI 0.41–0.95, P=0.026)	Reduced (concordant direction)	HR 0.76 (95% CI 0.65–0.87), RCT pooled
Worsening HF events alone	Not powered	Not powered	HR 0.54 (95% CI 0.34–0.85)	Reduced	HR 0.68 (95% CI 0.52–0.88), RCT pooled; HR 0.60 (95% CI 0.58–0.62), observational
CV mortality alone	Not powered	Not powered	HR 1.58 (95% CI 0.52–4.83; NS)	Not significant	HR 0.83 (95% CI 0.69–1.01), NS
All-cause mortality	Not primary	Not primary	Not powered	Not separately reported	HR 0.86 (95% CI 0.52–1.43), RCT; HR 0.61 (95% CI 0.32–1.16), observational; both NS
Effect modification by T2D status	N/A	N/A	Not primary comparison	Not formally tested	No significant interaction, any outcome (all P>0.05)
AEs leading to discontinuation	Higher, active arm (GI)	Higher, active arm	6.3% vs 1.4%	Consistent	Not separately pooled

NS, not statistically significant; HR, hazard ratio; CI, confidence interval; T2D, type 2 diabetes; AE, adverse event.

Note on non-independence of estimates: the columns in this table are not statistically independent of one another. The 4-Trial Pooled Analysis column incorporates participant-level data from STEP-HFpEF, STEP-HFpEF DM, and the SELECT and FLOW heart-failure substudies also shown in their own columns; the Independent Meta-Regression Synthesis column in turn incorporates STEP-HFpEF, STEP-HFpEF DM, SUMMIT, and post hoc FLOW/SELECT/EXSCEL data. Readers should not sum or informally combine effect estimates across columns, as this would double-count overlapping patient-level data; the columns are presented side-by-side for narrative comparison of point estimates and precision only, consistent with the narrative (rather than pooled) synthesis approach described in Section 2.2.

3.9 Safety and tolerability

Across all pivotal trials, gastrointestinal adverse events (nausea, diarrhea, vomiting, constipation) were consistently more frequent with active therapy and were the leading cause of treatment discontinuation, without a distinct HFpEF-

specific safety signal beyond that established in the broader GLP-1RA/tirzepatide pharmacovigilance literature [83,84,85]. Earlier-generation safety concerns specific to this drug class medullary thyroid carcinoma and acute pancreatitis have not been substantiated in randomized trials or large pharmacovigilance cohorts: a systematic review and meta-analysis of randomized trials found no significant increase in thyroid cancer risk [86], corroborated by a nationwide Scandinavian cohort study [87], while population-based case-control data likewise did not confirm an association with acute pancreatitis hospitalization [88], although a modest, consistently observed increase in cholelithiasis/biliary disease has been reported across the class [89], a signal understood to reflect rapid weight-loss-related changes in biliary cholesterol saturation and gallbladder motility rather than a direct pharmacological effect of GLP-1 receptor agonism [90]. An updated meta-analysis of randomized trials similarly found no clear excess of obesity-related cancers with GLP-1RA or dual-agonist therapy [91,92], and earlier concerns regarding malignancy signals with individual agents have not been replicated in subsequent, larger syntheses [93,94]. Taken together, the safety profile of GLP-1RA and tirzepatide therapy in HFpEF/HFmrEF is dominated by predictable, dose-related gastrointestinal tolerability issues rather than by any heart-failure-specific hazard.

4. DISCUSSION

In this systematic review of patients with HFpEF or HFmrEF, GLP-1RA and tirzepatide therapy was associated with substantial, reproducible improvement in symptoms, functional capacity, and inflammatory/congestive biomarkers, with an emerging and now externally corroborated signal for reduced heart failure hospitalization. Three findings merit emphasis.

First, the symptomatic and functional benefit of these agents in obesity-related HFpEF is large, consistent, and biologically coherent. Placebo-corrected KCCQ-CSS improvements of 7–14 points across independent randomized trials, corroborated by objective 6-minute walk distance gains, exceed effect sizes reported for any previously tested HFpEF pharmacotherapy, and are further corroborated by concordant reductions in loop diuretic requirement and directly measured plasma volume evidence against symptom improvement simply reflecting an unblinding artifact of visible weight loss.

Second, the hard-outcome evidence, while genuinely promising, is less mature than the symptomatic evidence. SUMMIT's 38% relative risk reduction in cardiovascular death or worsening heart failure events [25], driven by fewer heart failure hospitalizations, is a clinically important finding from an adequately powered, long-duration, centrally

adjudicated trial. Critically, this pattern is not an isolated single-trial result: it is corroborated both by the four-trial pooled analysis [48] and by an entirely independent, methodologically distinct, PROSPERO-registered meta-regression synthesis conducted by an unrelated research group using random-effects meta-regression with Hartung-Knapp adjustment [42] providing genuine external validation rather than analytic circularity. This trial-level pattern is now further corroborated by real-world evidence from a 97,690-patient US claims-based target-trial emulation study demonstrating a 42–58% relative reduction in heart failure hospitalization or death with semaglutide and tirzepatide versus an active comparator [59] a form of external validation that trial evidence alone cannot provide, since it captures effectiveness under real-world adherence, comorbidity burden, and prescribing patterns rather than idealized trial conditions. This convergence across randomized, meta-analytic, and real-world evidence streams is tempered by one discordant six-trial meta-analysis reporting no significant effect on either hard primary outcome [74], a result we do not attempt to explain away and instead present as a genuine limit on how strongly the current hospitalization-benefit claim should be stated. Weighing against this single discordant result, an independently-conducted, formally AMSTAR-2/ROBIS-graded umbrella meta-analysis that became available around the completion of this review reached a concordant hospitalization-benefit conclusion using entirely separate methodology and personnel [103], which we regard as tipping the balance of evidence toward a genuine effect rather than an artifact of any one analytic approach. The uniform absence of a significant independent mortality benefit across every source reviewed here, however, means that GLP-1/GIP receptor agonists should currently be characterized as reducing heart-failure-hospitalization-type morbidity, with mortality benefit unconfirmed, consistent with the explicit conclusions of the independent meta-regression synthesis regarding differential event-rate profiles and non-cardiovascular competing mortality risk in HFpEF populations [42].

Third, the comprehensive meta-regression synthesis specifically addressing diabetes status [42] resolves a clinically important open question: cardiovascular benefit is not contingent on comorbid type 2 diabetes (all interaction $P > 0.05$), reaffirming that the cardioprotective mechanism of this drug class extends beyond glycemic control and operates through weight-, adiposity-, and inflammation-related pathways relevant to the broader obesity-related HFpEF population regardless of diabetes status. Randomized mechanistic substudies directly demonstrate reduced circulating blood volume, reduced systemic inflammation, reduced left ventricular mass, and reduced paracardiac

adipose tissue with active therapy [53,55] a coherent decongestive, anti-inflammatory, and reverse-remodeling signature that is biologically consistent with preclinical data showing GLP-1 receptor-mediated attenuation of TGF- β -driven myocardial fibrosis and pressure-overload-induced hypertrophy [17,19] while central-adiposity-focused analyses suggest that BMI alone may imperfectly capture the most incretin-responsive phenotype [77,78,79]. This evidence should not be extrapolated to non-obese HFpEF, where the pathophysiological rationale for benefit is substantially weaker and direct trial evidence is lacking.

5. FUTURE DIRECTIONS

Dedicated, adequately powered outcomes trials specifically designed for cardiovascular mortality as a primary or key secondary endpoint in HFpEF are needed to resolve the mortality question definitively, rather than relying on pooled or subgroup analyses of trials designed around other primary populations. Head-to-head comparative trials between GLP-1RAs, dual GIP/GLP-1 co-agonism (whose obesity-indication efficacy was itself first established in the SURMOUNT-1 registration trial) [95], and triple agonists (e.g., retatrutide) [96] or emerging oral small-molecule GLP-1 receptor agonists such as orforglipron, which has recently demonstrated clinically meaningful weight loss in phase 3 trials in adults with and without type 2 diabetes [97,98], would clarify whether incremental metabolic potency or improved route-of-administration convenience translates into incremental cardiovascular benefit and real-world adherence in HFpEF; current exploratory network meta-analytic comparisons find no significant between-agent differences but remain indirect and underpowered [42]. Trials specifically enrolling non-obese HFpEF phenotypes, and trials using central/visceral adiposity rather than BMI-based enrollment criteria, are needed to refine patient selection [77,78]. Combination-therapy trials assessing GLP-1/GIP receptor agonists layered onto SGLT2 inhibitor and finerenone background therapy remain comparatively unexplored specifically in HFpEF/HFmrEF populations despite additive benefit in broader cardiometabolic populations. Several next-generation programs are positioned to address these gaps directly: MARITIME-HF, a dedicated phase 3 trial of maridebart cafraglutide (NCT07037459) [99], is directly powered for morbidity/mortality outcomes in obesity-related HFpEF/HFmrEF; TRIUMPH-OUTCOMES is evaluating the triple GLP-1/GIP/glucagon receptor agonist retatrutide for cardiovascular and kidney outcomes in a broader cardiometabolic population [100]; and a cardiovascular outcomes trial of amycretin, a unimolecular GLP-1/amylin receptor co-agonist, is planned for 2026 [101]. Mechanistic

imaging substudies using cardiac MRI, invasive hemodynamic assessment, and epicardial fat quantification should be expanded to directly test the causal contribution of adiposity reduction to outcome benefit. Large-scale real-world effectiveness data are now emerging [59], partially closing what was until recently an evidence gap; the priority going forward is dedicated pragmatic cost-effectiveness and health-system-level access studies given the high acquisition cost of these agents relative to established generic HFpEF therapies, alongside real-world safety surveillance over follow-up longer than the 6-year maximum captured in currently available claims-based cohorts.

6. CLINICAL IMPLICATIONS FOR PRACTICE

For clinicians managing patients with obesity-related HFpEF or HFmrEF (LVEF $\geq 45\%$, BMI ≥ 30 kg/m²), the totality of evidence reviewed here supports consideration of a GLP-1RA or tirzepatide as an add-on to guideline-directed background therapy (summarized as a stepwise algorithm in Figure 6), consistent with a 2025 American College of Cardiology expert consensus decision pathway on anti-obesity pharmacotherapy in heart failure management [102], positioned alongside not in place of SGLT2 inhibitors, which remain the only other pharmacologic class with unambiguous outcome benefit in this population [27,28]. In practice, this means most eligible patients will ultimately be candidates for combination therapy, and the two classes should be regarded as complementary rather than competing: SGLT2 inhibitors act principally through natriuresis and hemodynamic offloading, whereas GLP-1RA/tirzepatide act through weight loss, anti-inflammatory, and adiposity-directed mechanisms, with no pharmacokinetic interaction precluding co-administration. Patient selection should prioritize the phenotype in which trial evidence is strongest: obesity-related HFpEF with LVEF $\geq 45\%$, irrespective of type 2 diabetes status, sex, obesity severity, or age, given the consistency of benefit demonstrated across these subgroups [81,51,82,52]. Dosing should follow the same gradual up-titration schedules used in the pivotal trials (e.g., tirzepatide up-titrated in 2.5 mg increments to a maximum tolerated dose of up to 15 mg weekly, semaglutide up-titrated to 2.4 mg weekly) to minimize gastrointestinal intolerance, with slower titration or a lower maintenance dose considered in frail or older patients, in whom the age-spectrum subgroup data nonetheless indicate preserved efficacy and safety [52]. Patients should be counseled that the expected timeline to symptomatic benefit is generally within 12–24 weeks, that gastrointestinal adverse effects are the most common reason for down-titration or discontinuation, and that current evidence, while reassuring, has not confirmed a mortality benefit a point that should be

communicated transparently rather than implied. Given the substantial acquisition cost of these agents relative to diuretics, mineralocorticoid receptor antagonists, or SGLT2 inhibitors, shared decision-making should explicitly weigh

anticipated symptomatic and functional gains against cost, access, and insurance-coverage constraints, which vary considerably by health system and are not addressed by the clinical trial evidence itself.

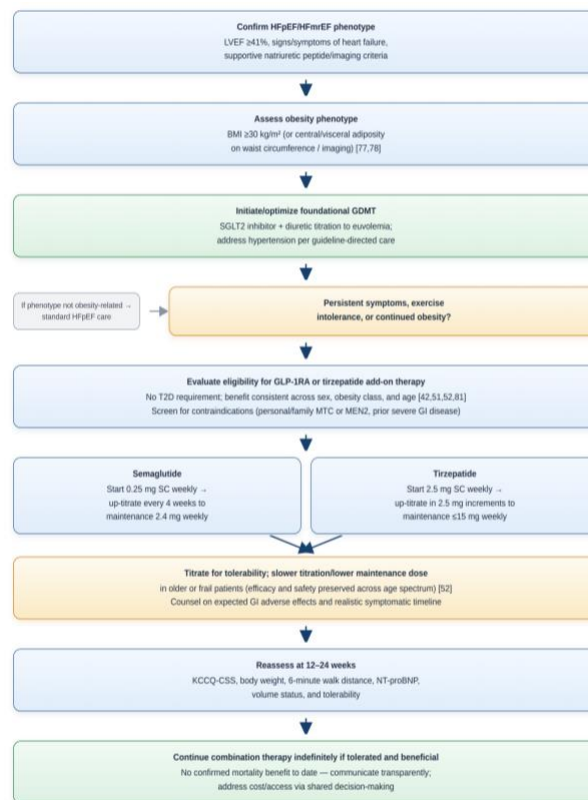


Figure 6. Clinical practice algorithm. Stepwise approach to identifying and managing patients with obesity-related HFpEF/HFmrEF, from phenotype confirmation and SGLT2 inhibitor-based foundational therapy through GLP-1RA/tirzepatide eligibility screening, dose titration, and structured reassessment, as detailed in Clinical Implications for Practice.

7. STRENGTHS AND LIMITATIONS

This review’s principal strength is the explicit, structured reconciliation of pivotal industry-sponsored trial evidence against multiple independently conducted meta-analyses including a PROSPERO-registered meta-regression synthesis that provides genuine external, methodologically independent corroboration of this review’s central interpretive claims regarding the hospitalization-versus-mortality distinction and diabetes-status independence [42]. This review’s own eligibility criteria, search strategy, and synthesis plan were themselves prospectively registered with PROSPERO (CRD420261452712), and the inclusion of both randomized and real-world observational evidence, showing concordant direction of effect, further supports the external validity of the conclusions reached.

Several limitations merit consideration. First, the number of dedicated placebo-controlled RCTs in HFpEF specifically

remains small (six primary data sources), limiting precision of hard-outcome estimates; beyond the narrow two-study cross-class pooled estimate reported in Section 3.6, we relied on narrative synthesis and critical comparison against existing meta-analyses rather than a de novo pooled analysis of all six heterogeneous primary sources, for the reasons stated in Section 2.2. Second, all pivotal trials were industry-sponsored (Novo Nordisk or Eli Lilly), which independent academic steering committees and blinded event adjudication mitigate but do not eliminate as a potential source of reporting bias; with only six primary trial-level data sources, formal small-study-effects testing (e.g., funnel plot asymmetry, Egger’s test) is not statistically meaningful, and we cannot exclude the possibility that terminated, negative, or as-yet-unpublished incretin-HFpEF trials exist in sponsor pipelines but are not reflected here—a limitation inherent to any review of a small, sponsor-concentrated evidence base rather than one specific to this review’s methods. Third, cross-trial heterogeneity in

LVEF thresholds, obligate comorbidities, and background heart failure therapy limits generalizability of any single trial's findings and complicates direct point-estimate comparison. Fourth, follow-up duration remains relatively short (52–104 weeks) relative to the natural history of a chronic syndrome, and long-term durability of benefit is not yet established. Fifth, this review did not perform a complete, formal 16-domain risk-of-bias assessment of the retained independent meta-analyses using the full AMSTAR-2 or ROBIS instruments. We did, however, perform a targeted critical appraisal of publication format, database comprehensiveness, and post-publication scrutiny for each of the six comparator meta-analyses (Table 5): notably, the largest and most heavily-weighted comparator (Ahmed et al.) was published in *Clinical Cardiology*'s letter/correspondence format rather than as a full original-research article, and was itself the subject of an independent published critique (Bibi Z) raising cross-trial heterogeneity and follow-up-duration concerns that materially overlap with the limitations we identify independently in this section a convergence between our internal appraisal and an external, independently-published critique that we regard as corroborating rather than merely assuming the comparator literature's limitations. A second comparator (Sobral et al.) pools two randomized trials with one non-randomized cohort into a single composite estimate without design-stratified reporting, a methodological choice that risks conflating confounded observational effect sizes with randomized ones a limitation not disclosed in that paper's own abstract and identified here through our own appraisal of its methods. This targeted appraisal is not a substitute for a complete AMSTAR-2/ROBIS domain-by-domain assessment our aim was trial-level reconciliation against existing syntheses rather than a formal umbrella review of review quality, but it means the comparative conclusions drawn here rest on more than source verification alone. A dedicated, complete AMSTAR-2/ROBIS-graded umbrella review remains the logical next step for this

literature and, encouragingly, one has since become available: Sun et al. published a formal AMSTAR-2/ROBIS-graded umbrella meta-analysis of 12 systematic reviews (29 unique RCTs) that was not captured within our own search window and became available around the time of this review's completion [103]. Its independently-derived estimates are concordant with ours: a hazard ratio of 0.56 (95% CI 0.41–0.77) for worsening heart failure closely parallels our pooled estimates in this domain, providing external, methodologically rigorous corroboration of our central hospitalization-benefit finding from a fully independent analytic team and approach. We regard this convergence as strengthening confidence in the hospitalization-benefit conclusion, while noting that a detailed comparative analysis against Sun et al.'s specific AMSTAR-2/ROBIS domain-level ratings was outside the scope of the present revision and remains available for a future update of this review. Sixth, this review was registered prospectively with PROSPERO (registration number CRD420261452712), aligning our eligibility criteria, search strategy, and planned synthesis approach with at least one of the independently conducted comparator meta-analyses discussed above [42]; nonetheless, as with any review of a fast-moving evidence base, several eligible trial reports and secondary analyses were published in close proximity to registration, and readers should consult the PROSPERO record directly for the precise registration and review timeline. The full review protocol, including the pre-specified eligibility criteria, search strategy, and planned synthesis approach, is accessible via the PROSPERO record (CRD420261452712); no substantive amendments to the registered eligibility criteria or synthesis plan were made during the conduct of this review beyond the post hoc addition of the exploratory two-study pooled analysis reported in Section 3.6, which was not pre-specified in the original registration and is explicitly labeled as such throughout this manuscript.

Table 5. Characteristics of Independently Conducted Comparator Meta-Analyses

Meta-analysis	Scope	conclusion	methodology	Notes
Ahmed M, Burhan M, Shafiq A, et al. Clin Cardiol 2025;48:e70234	GLP-1/dual GLP-1-GIP RCTs in HFmrEF/HFpEF	Composite CV death/worsening HF event reduced; no significant effect on all-cause or CV mortality	Confirmed: Cochrane Handbook + PRISMA 2020; PubMed, Embase, Cochrane Library; inception to Nov 2024	Published in Clinical Cardiology's letter (PMC12701558) rather than as a full original-research article; subject of a published critical correspondence (next row) identifying cross-trial heterogeneity and short follow-up

Meta-analysis	Scope	conclusion	methodology	Notes
Bibi Z. Clin Cardiol 2025;48:e70249 (critical correspondence on the above)	Methodological critique of Ahmed et al.	Acknowledges the synthesis as rigorous but emphasizes need for HFpEF-specific RCTs with broader follow-up and diverse phenotypes	-	Materially consistent with the limitations enumerated in our own Strengths and Limitations section
Waqas SA, Sohail MU, Saad M, et al. J Card Fail 2025;31:1076-1080	GLP-1RA RCTs in HFmrEF/HFpEF	Significant reduction in worsening HF events and the composite CV death/HF event outcome; no significant effect on CV death alone	-	Concordant with Ahmed et al. on the hospitalization/mortality dissociation
Sobral MVS, Rodrigues LK, Barbosa AMP, et al. Am J Cardiovasc Drugs 2025;25:461-467	Semaglutide-specific RCTs in HFpEF	Cardiovascular effects of semaglutide specifically in HFpEF	-	Narrower, single-agent subset analysis rather than a pan-GLP-1RA/GIP synthesis; pools 2 RCTs with 1 non-randomized cohort (n=1,463 total) without design-stratified reporting of the composite estimate, and discloses no external funding
Talavera A, Teixeira L, Klein B, et al. Diabetes Obes Metab 2025;27:7030-9	RCT-only meta-analysis of GLP-1RAs in obese HFpEF	HF events reduced (RR 0.40, 95% CI 0.22–0.73); KCCQ-CSS, body weight, and 6MWD all significantly improved; drug discontinuation and GI adverse events increased	Confirmed: random-effects model; Embase, PubMed, Cochrane searched; full 12-author list and effect sizes verified against PubMed/Wiley records	Provides the most granular, RCT-restricted effect sizes of the six comparators tabulated here, directly corroborating Sections 3.3 and 3.7
Gonzales-Uribe A, Ruiz-Cortez R, Collantes-Silva N, et al. Clin Res Cardiol 2025	RCTs and cohorts of GLP-1RAs in HFpEF	Composite of all-cause mortality and HF-related hospitalization pooled via random-effects model, with subgroup analyses	Confirmed: PubMed, Scopus, Embase, Web of Science searched to 31 Dec 2024; GRADE and RoB tool used; full 11-author list verified against PubMed record	Sixth and final independently conducted comparator meta-analysis identified in our search, completing the set referenced in Sections 2.2 and 3.2

8. CONCLUSION

GLP-1 receptor agonists, and the dual GIP/GLP-1 receptor co-agonist tirzepatide, produce substantial, reproducible, and mechanistically coherent improvements in symptoms, functional capacity, and congestive/inflammatory biomarkers in obesity-related heart failure with preserved or mildly reduced ejection fraction. The SUMMIT trial provides robust randomized evidence that this benefit extends to reduced

cardiovascular death or worsening heart failure events, corroborated by a concordant four-trial pooled analysis and by an independently conducted, PROSPERO-registered meta-regression synthesis demonstrating no effect modification by diabetes status. This hospitalization-type benefit is now supported by convergent evidence from multiple independent research groups using different statistical methods, while mortality benefit remains statistically unconfirmed across all currently available evidence. A 2025 Canadian

Cardiovascular Society/Canadian Heart Failure Society guideline update has already incorporated these agents into HFpEF/HFmrEF management algorithms, signaling that professional-society practice recommendations are outpacing formal regulatory labeling. These findings support incretin-based therapy as an evidence-based, phenotype-directed addition to guideline-directed HFpEF/HFmrEF management in patients with obesity, irrespective of diabetes status, while underscoring the need for dedicated mortality-powered outcomes trials, further regulatory label expansion, and continued mechanistic and comparative-effectiveness research.

AUTHOR CONTRIBUTIONS

Conceptualization, Supervision, Project Administration, Writing – Review & Editing: Sagarika Majhi. Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Visualization: Ritu Raj Kumar, Goldi Kumari.

ETHICS STATEMENT

The research reported in this paper adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As a systematic review of previously published, publicly available literature, this study did not involve new human or animal research, and institutional review board approval was not required.

AI DECLARATION

Grammarly was used solely for grammar correction and language editing. No generative AI tools were used to generate scientific content, analyze data, interpret results, or draw conclusions. The authors take full responsibility for the content and accuracy of the manuscript.

PATIENT CONSENT

Patient consent is not applicable to this article, as it uses data from previously published studies. No new, previously unpublished patient data were generated or analyzed in support of this review.

AVAILABILITY OF DATA, CODE, AND MATERIALS

This review synthesizes previously published, publicly available data; no new primary data were generated. All effect estimates, sample sizes, and other extracted data items reported in this manuscript are available in the cited original publications (full reference list) and are additionally tabulated in Tables 2-5. The representative search strategy is provided

in Table 1; the full database-specific search strings for all five databases, the piloted data-extraction form, the completed PRISMA 2020 checklist, and the GRADE evidence profiles referenced in Section 3.2.1 are available as supplementary material or from the corresponding author upon reasonable request. No analytic code was used beyond standard fixed-effect pooling for the exploratory two-study estimate reported in Section 3.6 (formula and inputs fully reported in-text); no specialized statistical software beyond standard spreadsheet-based calculation was required for this narrative synthesis.

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