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Systematic Review/Meta-analysis

Glucagon-Like Peptide-1 Receptor Agonists Improve Cardiovascular Outcomes in Heart Failure with Preserved Ejection Fraction, Independent of Diabetes: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Heart failure (HF) with preserved or mildly reduced ejection fraction (HFpEF or HFmrEF) is often associated with obesity and metabolic dysfunction. Recent data suggest that incretin-based therapies, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) and tirzepatide improve cardiovascular outcomes in patients with HFpEF or HFmrEF both with and without diabetes. However, whether the effects differ by diabetes status across the broader literature remains unclear.

Methods: MEDLINE and Embase were searched through October 2025 to identify randomized controlled trials (RCTs), post-hoc RCT analyses, and observational studies evaluating GLP-1RAs and tirzepatide effects on cardiovascular outcomes in patients with HFpEF or HFmrEF. Meta-regression examined effect modification by type 2 diabetes (T2D) status. Exploratory network meta-analysis of RCTs was performed to evaluate comparative efficacy across therapies.

Results: Eleven studies met the inclusion criteria. In a meta-regression of RCTs, all *P*-values for interaction were > 0.05, indicating no evidence that T2D modified treatment effects. In pooled RCT analyses, incretin-based therapies significantly reduced HF hospitalization and events (hazard ratio [HR] 0.68 [95% confidence interval {CI} 0.52-0.88]) and composite of cardiovascular death or HF hospitalization and/or events (HR 0.76 [95% CI 0.65-0.87]). Pooled observational data demonstrated significant reduction in HF hospitalization and events (HR 0.60 [95% CI 0.58-0.62]). Exploratory

RÉSUMÉ

Contexte : L'insuffisance cardiaque (IC) avec fraction d'éjection préservée ou légèrement réduite (ICFEP/ICFELR) est souvent associée à l'obésité et à une dysfonction métabolique. Des données récentes suggèrent que les traitements à base d'incrétines, notamment les agonistes du récepteur du GLP-1 (AR-GLP-1) et le tirzepatide, améliorent les perspectives cliniques cardiovasculaires chez les patients atteints d'ICFEP/ICFELR, qu'ils soient diabétiques ou non. Cependant, la littérature scientifique ne permet pas de déterminer clairement si les effets diffèrent selon le statut diabétique.

Méthodologie : Les bases de données MEDLINE et Embase ont été consultées jusqu'en octobre 2025 afin d'identifier les essais contrôlés randomisés (ECR), les analyses post-hoc d'ECR et les études observationnelles évaluant les AR-GLP-1 et le tirzepatide sur le pronostic cardiovasculaire (CV) dans l'ICFEP/ICFELR. Une méta-régression a examiné une éventuelle modification de l'effet en fonction du statut du diabète de type 2 (DT2). Une méta-analyse exploratoire en réseau (MAER) des ECR a été réalisée pour évaluer l'efficacité comparative des différents traitements.

Résultats : Onze études répondaient aux critères d'inclusion. Dans la méta-régression des ECR, toutes les valeurs *p* pour l'interaction étaient $> 0,05$, indiquant qu'il n'y a aucune preuve que le DT2 modifie les effets du traitement. Dans les analyses groupées des ECR, les traitements à base d'incrétines ont réduit de manière significative les hospitalisations/événements liés à l'IC (risque relatif [RR] 0,68,

Heart failure with preserved ejection fraction (HFpEF), defined as an ejection fraction $\geq$ 50%, and mildly reduced ejection fraction (HFmrEF), defined as an ejection fraction of 41%-49%, comprises over half of heart failure cases, encompassing a spectrum of distinct phenotypes.[1,2] Among the different phenotypes, obesity, insulin resistance, and type 2 diabetes (T2D) have emerged as major contributors to both the development and progression of HfpEF.[3] A limited number of pharmacologic strategies, including sodium-

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

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network meta-analysis found no significant difference in efficacy between individual agents.

Conclusions: **Incretin-based therapies with GLP-1RA activity reduce HF hospitalization and events in patients with HFpEF or HFmrEF, with comparable benefits irrespective of T2D status. These findings support cardiovascular benefits of incretin-based therapies beyond glucose lowering and reinforce their role in obesity-associated HFpEF and HFmrEF.**

Registration: **PROSPERO CRD420251176696.**

intervalle de confiance [IC] à 95 % 0,52-0,88) ainsi que la combinaison des décès d'origine CV ou des hospitalisations/événements liés à l'IC (RR 0,76, IC à 95 % 0,65-0,87). Les données observationnelles regroupées ont démontré une réduction significative des hospitalisations/événements liés à l'IC (RR 0,60 [IC à 95 % 0,58-0,62]). La MAER n'a révélé aucune différence significative en termes d'efficacité entre les différents agents pris individuellement.

Conclusions : **Les traitements à base d'incrétines avec activité AR-GLP-1 réduisent les hospitalisations/événements liés à l'IC chez les patients atteints d'ICFEP/ICFELR, avec des bénéfices comparables indépendamment du statut DT2. Ces résultats confirment les bénéfices cardiovasculaires des traitements à base d'incrétines au-delà de la réduction du taux de glucose et renforcent leur rôle dans l'ICFEP/ICFELR associée à l'obésité.**

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glucose cotransporter-2 inhibitors (SGLT2is) and mineralocorticoid receptor agonists (MRAs), offer cardiovascular outcome risk reduction in HFpEF, suggesting the need for further therapies that directly target alternative pathways.[4]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and other incretin-based therapies, including tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA, were initially developed for glycemic control in type 2 diabetes (T2D). Their use has since expanded to overweight and obese populations, given their effects on appetite and body weight reduction.[5] Cardiovascular outcome trials have demonstrated class-wide reductions in major adverse cardiovascular events (MACE) among patients with T2D,[4] whereas more recent trials, most notably STEP-HFpEF (Semaglutide Treatment Effect in People With Obesity and Heart Failure with Preserved Ejection Fraction), STEP-HFpEF DM (Semaglutide Treatment Effect in People With Obesity and Heart Failure Preserved Ejection Fraction and Type 2 Diabetes), and SUMMIT (Study of Tirzepatide in Participants With Heart Failure with Preserved Ejection Fraction and Obesity), have extended these findings to obesity-related HFpEF, including in participants with and without diabetes.[6-8]

In recognition of evolving data, a recent Canadian Cardiovascular Society/Canadian Heart Failure Society guideline update has incorporated GLP-1RAs and tirzepatide into management algorithms for heart failure with non-reduced ejection fraction (HFnrEF), a term that encompasses HFpEF and HFmrEF, now recommending that these agents be considered for patients with left ventricular ejection fraction (LVEF) $\geq$ 45% and body mass index (BMI) $\geq$ 30 kg/m^2.[9] However, the pooled magnitude and consistency of benefit between diabetic and nondiabetic HFpEF and HFmrEF populations across the literature remain unclear.

To address this gap, this systematic review and meta-analysis assesses whether incretin-based therapies with GLP-1RA activity confer comparable cardiovascular benefits in both diabetic and nondiabetic HFpEF and HFmrEF phenotypes, using meta-regression of randomized controlled trial (RCT) data. In addition, a complementary meta-analysis of real-world observational studies was conducted to evaluate the benefits of the GLP-1RA class in patients with HFpEF or HFmrEF. Finally, an exploratory network meta-analysis (NMA) of RCTs compared the relative efficacy of individual GLP-1RAs and tirzepatide within the population with HFpEF or HFmrEF.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement and was registered prospectively in PROSPERO (CRD420251176696).

Search strategy and study selection

A comprehensive search was performed in MEDLINE and Embase from database inception to October 2025. Search terms combined controlled keywords, including HFpEF, GLP-1RA, and tirzepatide. The complete search strategy can be found in Supplemental Appendix S1.

Eligible studies included RCTs, post-hoc subgroup analyses of RCTs, and observational studies evaluating GLP-1RAs or tirzepatide in adults with HFpEF (EF $\geq$ 50%) or HFmrEF (EF 41%-49%). RCTs of interest compared active treatment with placebo, and observational studies of interest compared GLP-1RA users with nonusers. Studies were included if they reported hazard ratios (HRs) for at least one cardiovascular (CV) outcome of interest, including CV mortality, all-cause mortality, heart failure (HF) hospitalization and/or events, combined CV or HF hospitalization and/or events, or MACE. Reviews, editorials, and conference abstracts were excluded. Two reviewers independently screened titles, abstracts, and full texts using Covidence systematic review software[10] with discrepancies resolved by consensus.

Statistical methods

Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were pooled using random-effects models. For the pooled HFpEF analysis, restricted maximum likelihood (REML) estimators with both Wald CI estimates and Hartung-Knapp (HK) adjustment were conducted for sensitivity analysis, given the anticipated heterogeneity and limited number of trials. Wald CIs can underestimate between-study variance and produce overly narrow CIs, whereas REML with HK adjustment may produce overly wide CIs when few

studies are available, or narrow CIs when between-study variance is 0%.[11] The Cochrane Handbook suggests that the statistical properties of meta-analytic approaches vary depending on the number of included studies, particularly when study counts are low, with no single method being uniformly optimal. Accordingly, both Wald and HK-adjusted CIs were presented as sensitivity analyses to allow assessment of the robustness of the findings.[11]

Heterogeneity was assessed using Cochran's Q test ($\alpha = 0.05$), quantified with the I^2 statistic ($I^2 < 25\%$ = low; 25%-49% = moderate; $\geq 50\%$ = substantial heterogeneity), and expressed as between-study variance (τ^2). Subgroup analyses comparing participants with and without T2D were conducted using the REML-HK model. Meta-regression was performed to evaluate whether T2D status modified treatment effects. Forest plots were generated using the meta and metafor packages.[12,13] An exploratory NMA was performed using a frequentist framework to compare the relative efficacy of individual GLP-1RAs and tirzepatide in HFpEF using the netmeta package.[14]

Risk of bias

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool for RCTs.[15] Observational trials were evaluated using the Newcastle-Ottawa Scale (NOS).[16]

Results

Overview of included studies

A total of 11 studies[6-8,17-24] were identified through searches of MEDLINE, Embase, and the gray literature. The study selection process is illustrated in Figure 1. Six RCTs or post-hoc analyses of RCTs met the inclusion criteria, including 4 evaluating semaglutide (STEP-HFpEF, STEP-HFpEF DM, and post-hoc of FLOW [Effect of Semaglutide versus Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and Chronic Kidney Disease] and SELECT [Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity] trials), one evaluating exenatide (post-hoc of EXSCEL [Exenatide Study of Cardiovascular Event Lowering] trial), and one evaluating tirzepatide (post-hoc of SUMMIT trial). Additionally, 5 observational studies were included. Baseline characteristics of all included studies are summarized in Supplemental Tables S1 and S2.

Risk of bias

Using the Cochrane RoB 2.0 tool, the EXSCEL, FLOW, SELECT, and SUMMIT trials were judged to have a low risk of bias across all domains, whereas the STEP-HFpEF and STEP-HFpEF DM studies were deemed to have some concerns (Supplemental Table S3). Overall, the observational trials demonstrated high quality, with all studies achieving high Newcastle-Ottawa Scale scores (7-9/9; Supplemental Table S4).

Meta-regression of T2D status

Meta-regression was performed to evaluate whether T2D status modified the treatment effect of incretin-based therapies with GLP-1RA activity across outcomes. For CV mortality, no significant interaction was observed ($P = 0.476$), with a pooled HR of 0.80 (95% CI 0.62-1.02) in patients with T2D and a single-trial estimate from a SELECT subgroup with an HR of 0.87 (95% CI 0.56-1.34) in patients without T2D, indicating comparable relative effects irrespective of diabetes status (Fig. 2A). For all-cause mortality, no significant interaction was observed ($P = 0.972$), with a pooled HR of 0.92 (95% CI 0.47-1.82) in patients with T2D and a single-trial estimate from a post-hoc SUMMIT analysis showing a HR of 0.89 (95% CI 0.29-2.77) in those without T2D (Fig. 2B). For HF hospitalization and/or events, no significant interaction was observed ($P = 0.415$), with similar estimates in patients with T2D (HR 0.70 [95% CI 0.55-0.88]) and without T2D (HR 0.58 [95% CI 0.37-0.90]; Fig. 2C). For the composite of CV death or HF hospitalization and/or events, no significant interaction was observed ($P = 0.637$), with comparable estimates in patients with T2D (HR 0.76 [95% CI 0.63-0.91]) and without T2D (HR 0.71 [95% CI 0.52-0.97]; Fig. 2D). For MACE, data were limited to subgroup data from 2 trials (EXSCEL and SELECT), precluding formal meta-regression; however, effect estimates were directionally consistent in patients with T2D (HR 0.84 [95% CI 0.71-0.98]) and without T2D (HR 0.72 [95% CI 0.60-0.87]).

Pooled HFpEF analysis

Forest plots of the pooled analysis including all RCTs irrespective of diabetes status are presented in Supplemental Figs. S1-S10. The pooled HR for CV mortality was 0.83 (95% CI 0.69-1.01) using REML with HK adjustment, with similar findings using Wald CIs. For all-cause mortality, the HR was 0.86 (95% CI 0.03-22.85) with REML and HK adjustment and 0.86 (95% CI 0.52-1.43) with Wald estimates. For HF hospitalization and/or events, the HR was 0.68 (95% CI 0.52-0.88) with REML and HK adjustment, with similar findings using Wald estimates. The composite of CV death or HF hospitalization and/or events yielded an HR of 0.76 (95% CI 0.65-0.87) using REML with HK adjustment, with similar findings using Wald estimates. The pooled HR for MACE was 0.78 (95% CI 0.30-2.08) with REML and HK adjustment and reached statistical significance with the Wald estimate (HR 0.78, 95% CI 0.67-0.91).

Observational data

Given the limited availability of T2D-stratified data, observational studies were pooled irrespective of T2D status, to assess the association between incretin-based therapies with GLP-1RA activity and cardiovascular outcomes in the broader HFpEF population. In the analysis, incretin-based therapy use was associated with a 40% lower risk of HF hospitalization and/or events compared with untreated patients, with consistent results across REML with HK adjustment (HR 0.60 [95% CI 0.58-0.62]) and Wald CIs (HR 0.60 [95% CI 0.59-0.62]; $I^2 = 0\%$; Fig. 3A; Supplemental Fig. S11). Pooled observational data showed no significant association between incretin-based therapy use and all-cause mortality, with a pooled HR of 0.61 (95% CI 0.14-2.55) using REML with HK

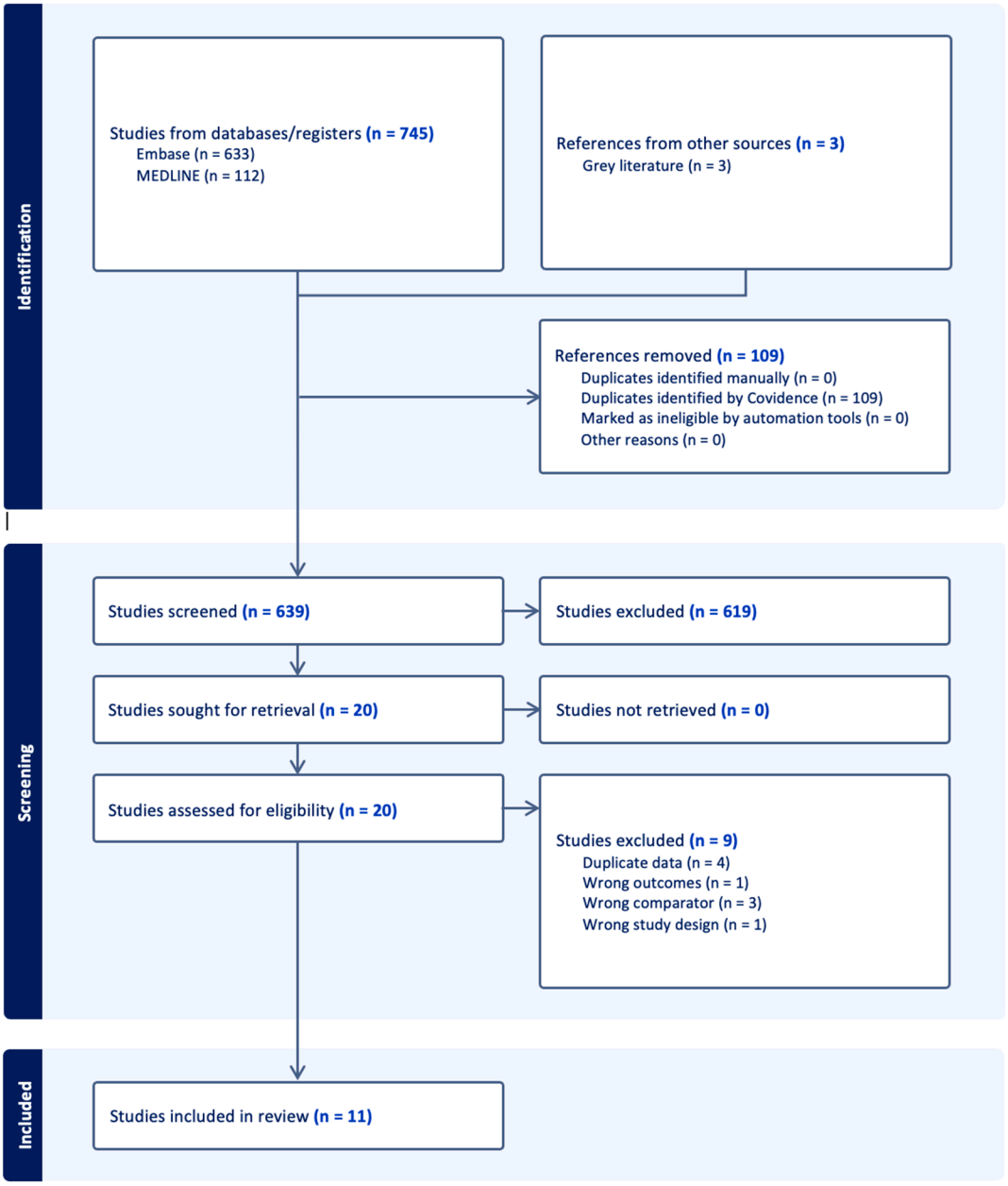

Figure 1. **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) flow diagram summarizing the study selection process.

adjustment and 0.61 (95% CI 0.32-1.16) using Wald CIs (Fig. 3B; Supplemental Fig. S12). One observational trial (Karlström et al., 2025) reported CV mortality, showing a nonsignificant reduction with GLP-1RA use compared with untreated individuals (HR 0.67 [95% CI 0.44-1.03]).[20] Another observational study (Lin et al., 2025) evaluated MACE outcomes, showing a significant reduction with tirzepatide, compared with untreated individuals (HR 0.64 [95% CI 0.51-0.79]).[24] Another observational study (Wallner et al., 2024) reported the composite outcome of CV mortality or HF hospitalization, showing no significant association with GLP-1RA use in patients with HFmrEF (HR 0.88 [95% CI 0.58-1.34]) or HFpEF (HR 0.93 [95% CI 0.57-1.53]), compared with untreated individuals.[23]

Network meta-analysis

An exploratory NMA was conducted across all GLP-1RA agents, including semaglutide, exenatide, and tirzepatide, to evaluate potential differences in efficacy within the broader HFpEF population irrespective of T2D status. No significant differences were observed between agents for CV mortality, HF hospitalization and/or events, or the composite of CV mortality and HF hospitalization and/or events. The corresponding network diagrams, league tables, and forest plots are presented in Supplemental Figures S13-S27.

Discussion

In this systematic review and meta-analysis in patients with HFpEF or HFmrEF, incretin-based therapies with GLP-1RA

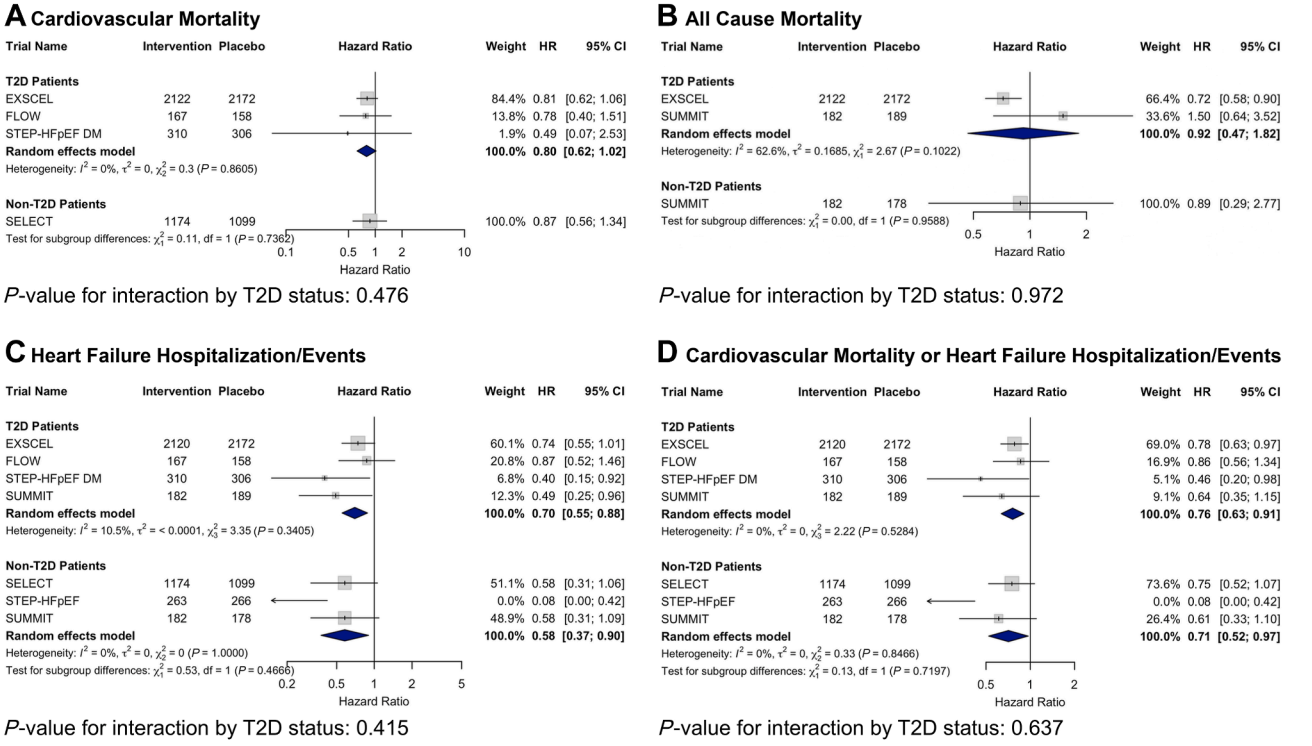

Figure 2. Meta-regression and subgroup analyses evaluating treatment effects of incretin-based therapies with glucagon-like peptide-1 receptor agonists (GLP-1RA) activity by type 2 diabetes (T2D) status on (**A**) cardiovascular mortality, (**B**) all-cause mortality, (**C**) heart failure hospitalization and.or events, or (**D**) the composite of cardiovascular mortality or heart failure hospitalization and/or events. CI, confidence interval; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; FLOW, Effect of Semaglutide versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease; HR, hazard ratio; SELECT, Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity; STEP HFpEF, Semaglutide Treatment Effect in People with Obesity and Heart Failure With Preserved Ejection Fraction; STEP HfpEF DM, Semaglutide Treatment Effect in People with Obesity and Heart Failure With Preserved Ejection Fraction and Type 2 Diabetes; SUMMIT, Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity.

activity were associated with improved CV outcomes compared to placebo, with no evidence of diabetes-status effect modification. Statistically significant reductions were observed in HF hospitalization and/or events and in the composite of CV mortality and HF hospitalization and/or events across the RCT evidence, including both T2D and non-T2D subgroups as well as the pooled HFpEF and HFmrEF analyses. Similar reductions in HF hospitalization and/or events were seen in the pooled observational analysis. The uniform efficacy across diabetic and nondiabetic subgroups reaffirms that GLP-1RAs confer their cardioprotective effects through metabolic mechanisms beyond glycemic control. These findings are in keeping with previous meta-analyses, particularly those applied to the broader T2D population, which have shown consistent results for MACE across overweight or obese patients with and without diabetes on GLP-1RAs.[25] Clinically, our findings suggest that patients with HFpEF and overweight or obesity likely derive similar benefits from GLP-1RA therapy irrespective of diabetes status.

Across the included trials, populations were representative of an overweight/obese HFpEF phenotype. STEP-HFpEF (mean BMI, 37 kg/m^2) and STEP-HFpEF DM (mean BMI, 36.9 kg/m^2) explicitly enrolled patients with obesity,[6,7] whereas the SUMMIT trial similarly had a mean BMI in the obese range (mean BMI, 38.3 kg/m^2).[8] Although EXSCEL did not include a BMI cutoff,[26] the mean BMI was $>$ 30 kg/m^2, and SELECT enrolled a mix of overweight and obese participants.[27] Taken together, the observed benefits of GLP-1RA use in HFpEF and HFmrEF appear to be concentrated within an obese or cardiometabolic phenotype. In this context, the consistent efficacy across diabetes status further supports that GLP-1RAs benefits go beyond glycemic control. The GLP-1RA cardioprotective effects are multifaceted and incompletely understood, mediated in part through weight reduction, decreased visceral and epicardial adiposity, blood pressure reduction, improvement in endothelial function, attenuation of systemic inflammation, and stabilization of atherosclerotic plaque.[28]

Emerging data suggest that measures of central or visceral adiposity more accurately capture HFpEF and cardiometabolic risk than does BMI alone.[29] This finding is supported by results from a large imaging-based cohort showing that a majority of patients with HFpEF exhibit central adiposity, and that compared to BMI, waist-to-height ratio and epicardial fat burden were more strongly associated with systemic inflammation, diastolic dysfunction, and exercise intolerance.[30] Taken together, central adiposity measures may more precisely characterize an adiposity-driven HFpEF phenotype, warranting further evaluation of GLP-1RA responsiveness in phenotypes not fully captured by BMI. A recent SELECT post-hoc analysis suggests that semaglutide's

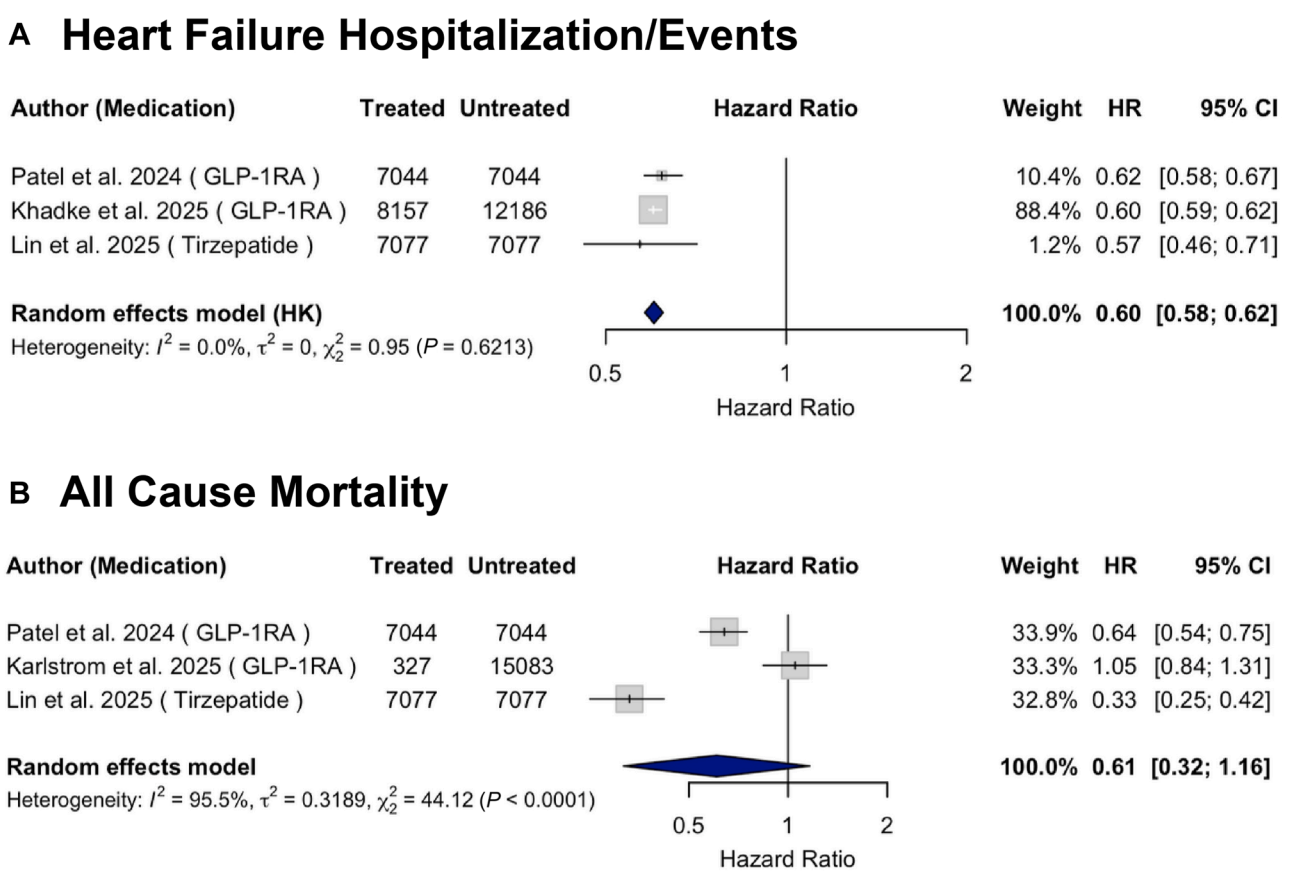

Figure 3. Meta-analysis of observational data comparing incretin-based therapies with glucagon-like peptide-1 receptor agonist (GLP-1RA) activity vs no therapy in patients with heart failure with preserved ejection fraction or heart failure with mildly reduced ejection fraction (HFpEF/HfmrEF) irrespective of type 2 diabetes status, using random-effects models with Hartung-Knapp (HK) adjustment for (**A**) heart failure hospitalization and/or events and (**B**) all-cause mortality. Wald estimates can be found in Supplemental Figures S11 and S12. CI, confidence interval; HR, hazard ratio.

effects go beyond adiposity reduction.[31] In the semaglutide group of the post-hoc analysis, early weight loss over the first 20 weeks was not associated with subsequent MACE outcomes. Similarly, adjustment for time-varying weight loss did not attenuate the treatment effect (unadjusted HR 0.80 [95% CI 0.72-0.90] vs adjusted HR 0.81 [95% CI 0.71-0.93]). In contrast, greater reductions in waist circumference, a marker of central adiposity, were linearly associated with lower MACE risk (HR 0.91 [95% CI 0.84-0.98]), although only accounting for approximately 33% of the observed benefit, suggesting that the cardioprotective effects of semaglutide extend beyond adiposity reduction.[31]

Although GLP-1RAs have consistently reduced CV and all-cause mortality in patients with chronic kidney disease, or T2D and established atherosclerotic CVD and/or high CV disease,[4] the present analysis in those with HFpEF showed only a nonsignificant trend toward lower mortality in CV or all-cause mortality. This likely reflects differences in pathophysiology and event profiles; HFpEF populations have lower overall event rates and a higher proportion of non-CV deaths.[32,33] Although reductions in HF hospitalization and/or events were statistically significant across both RCT and observational analyses, this endpoint carries important methodological limitations. HF hospitalization may represent a subjective, physician- and patient-dependent decision rather than a definitive biological event, influenced by local practice patterns and comorbidity burden.[34] Although statistically significant, these findings should be considered in the context of these nuances.

Our NMA did not show any significant differences between the effects of individual GLP-1RA agents on CV outcomes. However, the evidence base remains limited, and no head-to-head randomized trials in HFpEF populations examining CV outcomes are currently available. In a recent observational study including 5 cohorts comparing tirzepatide to semaglutide, tirzepatide trended toward lower rates of HF hospitalization and/or events (HR 0.88 [95% CI 0.74-1.05]) and all-cause mortality (HR 0.96 [95% CI 0.70-1.31]) in patients with overweight or obesity, T2D, and HFpEF, although neither outcome was statistically significant.[35] In an observational study of patients with HFpEF and T2D, similarly, no significant differences were observed between tirzepatide and semaglutide in acute heart failure, all-cause death, or hospitalization.[36] Beyond the HFpEF population, results remain heterogeneous. In individuals with overweight or obesity and established atherosclerotic CVD but without diabetes, findings from the STEER (Semaglutide and Tirzepatide Effects on Cardiovascular Outcomes in People With Overweight and Obesity in the Real World) study suggest that semaglutide was associated with a lower risk of MACE, compared with

tirzepatide, in both the intention-to-treat and per-protocol analyses.[37] These findings should be interpreted cautiously, given the short follow-up time and the limitations of retrospective observational data. Additionally, other studies have reported the opposite direction of effect,[38,39] with tirzepatide associated with lower all-cause mortality and fewer adverse CV and kidney events compared with GLP-1RA therapy in patients with T2D.[38] Overall, evidence regarding the optimal incretin-based therapy remains limited and heterogeneous, particularly within the HFpEF or HFmrEF population, and even more when stratified by diabetes status.

Future Directions

Future research should clarify the role of dual and triple combination therapy in the population with HFpEF or HFmrEF. Combination approaches using GLP-1RAs, SGLT2 inhibitors, and finerenone have shown additive cardiovascular benefits, but they remain less explored in HF populations.[40] Upcoming evidence from the MARITIME-HF (Maridebart Cafraglutide in Heart Failure With Preserved or Mildly Reduced Ejection Fraction and Obesity) trial will inform the effects of maridebart cafraglutide, a long-acting GLP-1RA and GIP receptor antagonist on functional and clinical outcomes.[41,42] Next-generation agents such as retatrutide, a GLP-1/GIP/glucagon tri-agonist, have shown strong metabolic efficacy, but they have yet to be studied in HF.[43] An important point to note is that incretin-based therapies are mechanistically distinct; among GLP-1RAs, pharmacokinetic and receptor-binding differences may yield varied CV effects.[44] As more data emerge, further head-to-head trials and comprehensive NMAs will be required to identify class- and agent-specific efficacy.

Strengths and limitations

To our knowledge, this review is the first to comprehensively synthesize randomized evidence evaluating agents with GLP-1RA activity specifically in patients with either HFpEF or HFmrEF, stratified by diabetes phenotype. Strengths of this review include the use of random-effects models with both Hartung-Knapp and Wald CIs. The addition of both RCT and observational data showing similar findings in the pooled analysis suggests consistency of effect across both trial and real-world HFpEF populations, supporting the external validity of the findings. The inclusion of an exploratory NMA provides preliminary comparative insights into relative efficacy across GLP-1RA agents, supporting future hypothesis generation.

Several limitations merit consideration in regard to interpretation of the findings of this review. First, the majority of the RCT data were derived from post-hoc analyses and subgroups, including SELECT, EXSCEL, FLOW, and SUMMIT; such analyses are often underpowered to detect treatment effects. Second, the meta-regression of diabetes status was constrained by limited available data. Only a few trials, mostly subgroups and/or post-hoc analyses of SELECT and SUMMIT, contributed to the nondiabetic estimates. Given the limited RCT data, drug-level NMA by T2D status could not be performed. NMAs also depend on assumptions of transitivity and consistency, which are likely limited by heterogeneity in trial design and patient characteristics. Similarly, observational data were sparse and heterogeneous; several analyses utilized shared datasets (eg, TriNetX), and some degree of patient overlap may have occurred, potentially limiting the independence of effect estimates. Further, data were limited for observational trials, precluding drug-level NMA and meta-analysis for many outcomes. Lastly, given the limited study count, we were unable to assess publication bias via a formal Egger's test and funnel plots.

Conclusion

In this systematic review and meta-analysis of patients with HFpEF or HFmrEF, incretin-based therapies with GLP-1RA activity were associated with improved CV outcomes, particularly reductions in HF hospitalization and/or events and composite CV mortality and HF hospitalization and/or events, without evidence of effect modification by T2D status. These findings reaffirm the finding that the cardioprotective benefits of this drug class extend beyond glycemic control. The consistency of benefit across both randomized and observational evidence in the broader overweight or obese or cardiometabolic HFpEF population supports the clinical utility of these agents. Future research should prioritize adequately powered, phenotype-specific trials and direct head-to-head comparisons among incretin-based therapies to determine class- and agent-specific differences, optimize combination strategies with established heart failure therapies, and define their role within the evolving heart failure therapeutic landscape.

Ethics Statement

The research reported in this paper adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT to proofread, and improve readability of the text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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.

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Disclosures

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Supplementary Material

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