Revista Médica del
Hospital General de México

PERMANYER

Check for updates

ORIGINAL ARTICLE

Clinical outcomes with GLP-1 receptor agonists in obese HFpEF: systematic review and meta- analysis

Paul E. Hernández-Montes[1], Jonathan C. Cruz-Estrada[2], and Kevin O. Palomino-Rendon[3]*

[1]Department of Medicine, Centro de Salud Juan Escutia; [2]Department of Medicine, Clínica Santa María; [3]Department of Medicine, Centro de Salud Matatipac, IMSS Bienestar. Unidad Académica de Medicina, Universidad Autónoma de Nayarit. Tepic, Nayarit, México

Abstract

Introduction: *Heart failure with preserved ejection fraction (HFpEF) accounts for nearly half of all HF cases and lacks effective disease-modifying therapies, particularly in the high-risk obese phenotype associated with increased mortality and hospitalization.* **Objectives:** *The objective of the study was to evaluate the efficacy of glucagon-like peptide-1 (GLP-1) agonists in reducing mortality and hospitalizations for heart failure (HF) exacerbations in patients with preserved ejection fraction and obesity, through a systematic review and meta-analysis.* **Material and methods:** *Studies with patients diagnosed with HF with preserved ejection fraction, NYHA functional class II-IV, patients with obesity, body mass index > 30 kg/m^2 and use of GLP-1 agonists compared to placebo were included.* **Results:** *The search was conducted in PubMed, Scopus and Web of Science until March 23, 2025. Risk of bias was assessed using the RoB 2 tool and ROBINS-E, while statistical analysis was performed with Review Manager 5.4.1 software. The following were included: 2,194 patients from 4 studies, 1,041 patients received GLP-1 agonists and 1,153 placebo. The use of GLP-1 agonists compared with placebo showed a non-significant decrease in terms of all-cause mortality (Odds ratio [OR] 0.77; 95% confidence interval [CI] [0.31-1.89], p = 0.56). Meanwhile, in terms of hospitalizations for HF exacerbation, the use of GLP-1 agonists showed a significant reduction (OR 0.43; 95% CI [0.27-0.69], p = 0.0005).* **Conclusion:** *Although a significant reduction in mortality was not observed, GLP-1 agonists were associated with a significant decrease in hospitalizations for HF, suggesting a potential benefit in the management and control of disease progression.*

Keywords: *Glucagon-like peptide receptor-1 agonists. Heart failure. Obesity. Mortality. Systematic review.*

Introduction

Heart failure (HF) is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or blood ejection[1]. HF has been divided into different phenotypes according to the measurement of left ventricular ejection fraction (LVEF); Reduced LVEF is defined as < 40%, this is called HF with reduced ejection fraction (HFrEF), patients with LVEF between 41% and 49% have a slightly reduced left ventricular (LV) systolic function, called HF with slightly HFrEF and those patients with symptoms and signs of HF, with evidence of structural or functional cardiac abnormalities or elevated natriuretic peptides (NPs) and LVEF > 50%, they present HF with preserved ejection fraction (HFpEF)[2].

HFpEF is one of the leading causes of morbidity and mortality worldwide. Although HFpEF currently accounts for 50% of all HF cases, few medical therapies have been established[3]. Large trials evaluating neurohumoral inhibition consistently failed to achieve a positive primary outcome[4]. Sodium-glucose cotransporter Type 2 (SGLT2) inhibitors are the only drugs that have

***Correspondence:**
Paul E. Hernández-Montes
E-mail: paul.hernandez@uan.edu.mx

Date of reception: 03-05-2025
Date of acceptance: 17-06-2025
DOI: 10.24875/HGMX.25000035

Available online: 24-04-2026
Rev Med Hosp Gen Mex. 2026;89(2):74-80
www.hospitalgeneral.mx

0185-1063/© 2025 Sociedad Médica del Hospital General de Mexico. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

demonstrated an improvement in clinical outcomes in a population with heart failure with mildly reduced ejection fraction and HFpEF[5]. Consequently, previous studies have proposed the existence of phenotypes other than HFpEF; however, there are few data on differences in underlying biological processes or response between groups of HFpEF phenotypes[6].

The sub-analysis of the TOPCAT trial distinguished three different phenotypes based on the analysis of latent classes analysis: the first composed of young patients with LV geometry, filling pressures, arterial stiffness and normal NPs, the second, composed of elderly patients, usually women, with small LV and atrial fibrillation, the third composed of obese and diabetic patients, usually with advanced symptoms[7]. Both phenotypes 2 and 3 demonstrated a similarly increased risk in all-cause mortality and hospitalization for HF. The analysis adjusted for the score of the Maggic registry, phenotype 3 continued to be with higher all-cause mortality and hospitalization for HF[6].

Glucagon-like peptide receptor-1 (GLP-1) agonists are used in the treatment of type 2 diabetes (T2D), and overweight or obesity have been shown to reduce the risk of cardiovascular events in patients with T2D who are at high cardiovascular risk[8]. Treatment with tirzepatide in patients with HFpEF and obesity produced a broad spectrum of important and clinically significant benefits in the evolution of HF, evident in multiple domains, including improved health status and well-being, increased functional capacity and exercise tolerance, a reduction in symptoms and medication burden, and the prevention of worsening HF events[9]. Therefore, the objective of this systematic review and meta-analysis is to evaluate the efficacy of GLP-1 agonists in reducing mortality and the number of hospitalizations due to exacerbation of HF in patients with preserved ejection fraction and obesity.

Material and methods

The study selection criteria were as follows: (1) patients with HF and at least 40% preserved ejection fraction, (2) patients with functional class II-IV, (3) patients with obesity and a body mass index > 30 kg/m^2, (4) use of GLP-1 agonists, (5) use of optimal medical therapy guided by international guidelines for HF.

Search strategy

This systematic review and meta-analysis was integrated by searching PubMed, Scopus and Web of Science for studies published up to March 23, 2025, with the adaptation of descriptors (DeCS/MeSH): ("GLP-1 receptor agonists" OR "GLP-1 analogs" OR "incretins" OR "semaglutide" OR "tirzepatide" OR "liraglutide") AND ("heart failure with preserved ejection fraction" OR "HFpEF" OR "preserved ejection fraction heart failure" OR "heart failure with normal ejection fraction") AND ("obesity" OR "overweight" OR "high BMI" OR "body mass index elevated") AND ("mortality" OR "hospitalization" OR "hospital admissions" OR "death" OR "cardiovascular events"). In accordance with PRISMA guidelines[10].

Bias risk assessment

Bias and quality assessment for randomized clinical trials and cohort studies were using the RoB 2 tool and ROBINS-E of the Cochrane risk assessment[11,12].

Data extraction process

A standardized form was designed for the extraction and capture of data from the selected studies, which included detailed information on the following aspects; main author, year of publication, title, type of study, population, description of the control and experimental group, as well as primary and secondary outcomes; mortality and number of hospitalizations due to exacerbation of HF. The data extraction process was carried out by two independent reviewers, and in the case of discrepancies, they were resolved by consensus of all authors (Table 1).

Statistical analysis

The statistical analysis for meta-analysis was performed using Review Manager 5.4.1 software. The effect measure variable of the pooled analysis was using the odds ratio (OR), which was calculated by extracting the number of events and non-events of each study, with a calculated confidence interval (CI) of 95%, while the heterogeneity of the results was performed using the I2 statistic, considering values > 35% as indicative of significant heterogeneity. The analysis method used random-effects, using the Mantel-Haenszel model for calculations.

Results

From the search in PubMed, Scopus and Web of Science, using the search matrix described in the

Table 1. Studies included in the review

Author and year	Type of study	Population	Intervention	Results
Kosiborod et al.[15] 2023	Randomized clinical trial	529 patients with HFpEF and obesity, without DM2; semaglutide group n = 263 and placebo group 266	Semaglutide 2.4 mg administration once a week, for 52 weeks	All-cause mortality in the semaglutide group n = 3, while the placebo group n = 4 Hospitalizations due to HF exacerbation, semaglutide group n = 1, while in the placebo group n = 12
Kosiborod et al.[14] 2024	Randomized clinical trial	616 patients with HFpEF, obesity and DM2, semaglutide group n = 310 and placebo group n = 306	Semaglutide 2.4 mg administration once a week, for 52 weeks	All-cause mortality in the semaglutide group n = 4, while the placebo group n = 15 Hospitalizations due to HF exacerbation, semaglutide group n = 7, while in the placebo group n = 18
Packer et al.[13] 2025	Randomized clinical trial	731 patients with HFpEF, obesity and DM2, semaglutide group n = 364 and placebo group n = 367	Administration of tirzepatide 2.5 mg up to 15 mg, for 52 weeks	All-cause mortality in the semaglutide group n = 8, while the placebo group n = 5 Hospitalizations due to HF exacerbation, semaglutide group n = 29, while in the placebo group n = 52
Rehman et al.[16] 2023	Retrospective cohort study	318 patients with HFpEF and obesity, semaglutide group n = 104 and placebo group n = 214	Semaglutide 2.4 mg administration once a week, for 52 weeks	All-cause mortality in the semaglutide n = 3 group, while the placebo group n = 5 Hospitalizations due to HF exacerbation, semaglutide group n = 2, while in the placebo group n = 9

The previous table shows the included studies, with author's data, type of study, population and division of the experimental and control groups, intervention and primary and secondary outcomes.
HFpEF: heart failure with preserved ejection fraction; DM2: Type 2 diabetes mellitus.

methodology, 180 articles were identified. Subsequently, by reading the titles and abstracts, 15 articles were chosen for full reading, of which 11 articles were excluded due to the presence of duplicate populations, patients, non-reporting of mortality data and hospitalization data due to exacerbation of HF, finally including 4 studies in this review (Fig. 1).

Risk of bias in the included studies

The risk of bias assessment for randomized clinical trials was performed using the RoB 2 tool, where a low and moderate risk was obtained in these studies, mainly due to the presence of biases in patient randomization, measurement, and reporting of results (Figs. 2 and 3). While the risk of bias for cohort studies was performed with the ROBINS-E tool, where the cohort study obtained moderate biases due to biases in the selection of study participants, classification of exposure, bias of missing data, and in the presentation of results (Figs. 4 and 5).

Population studied

This review includes four original articles, three randomized clinical trials, and one cohort study, with a total of 2,194 HF patients with preserved LVEF and obesity, of whom 1,041 patients received GLP-1 agonists and 1,553 placebo, over a period > 50 weeks[13-16].

All-cause mortality associated with GLP-1 agonist use

The use of GLP-1 agonists showed a non-significant decrease in mortality (OR 0.77; 95% CI [0.31-1.89], p = 0.56), with heterogeneity calculated by I2 = 50% (Fig. 6).

Number of emergency room hospitalizations due to exacerbated HF

On the other hand, the number of hospitalizations associated with the use of GLP-1 compared to patients who used a placebo showed a significant decrease in the number of hospitalizations due to exacerbation of

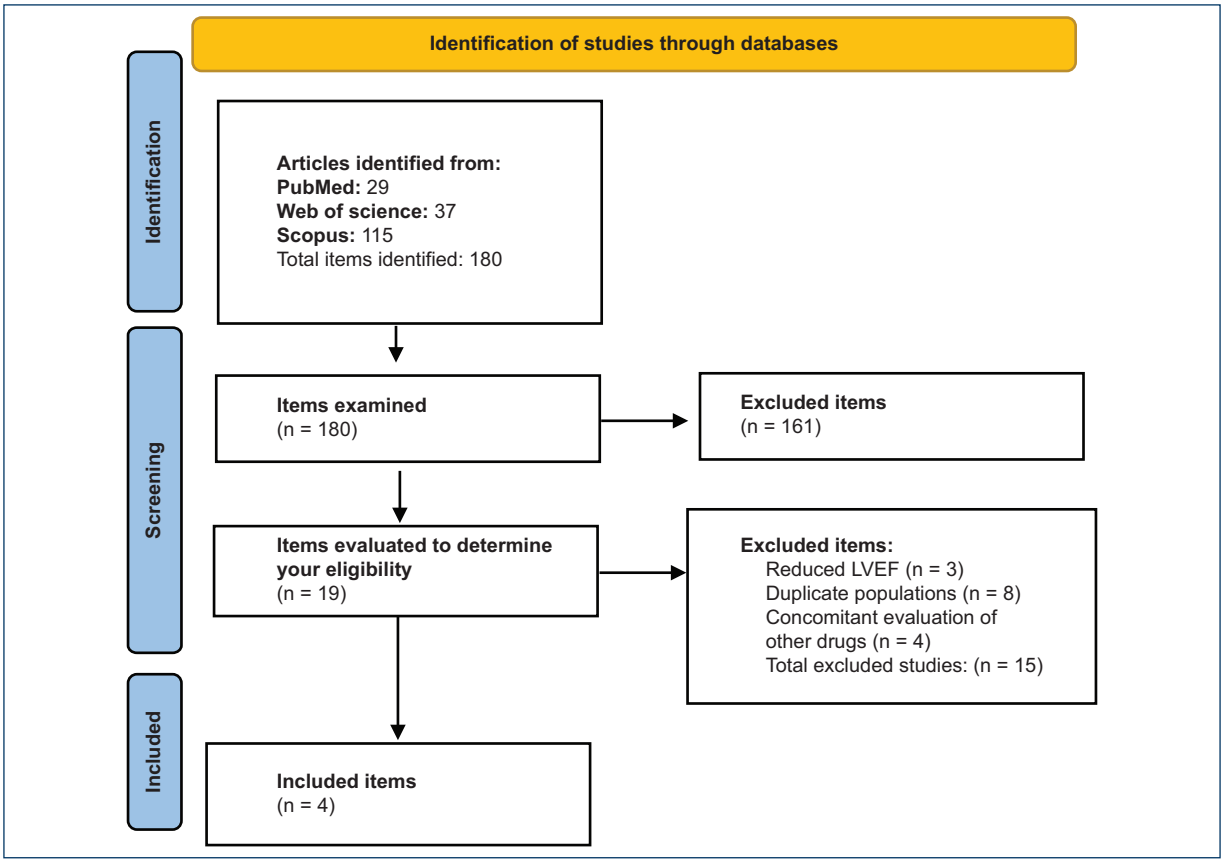


Figure 1. PRISMA diagram. The previous diagram shows the process by which, when performing the search with the search matrix described in the methodology in the different digital libraries, the initial number of articles was obtained, then by reading titles and abstracts, 161 articles were excluded, and consequently 19 articles were obtained for complete reading, with subsequent use of the inclusion criteria, 15 articles were excluded for not meeting the selection criteria and finally four articles were selected to be included in the review.

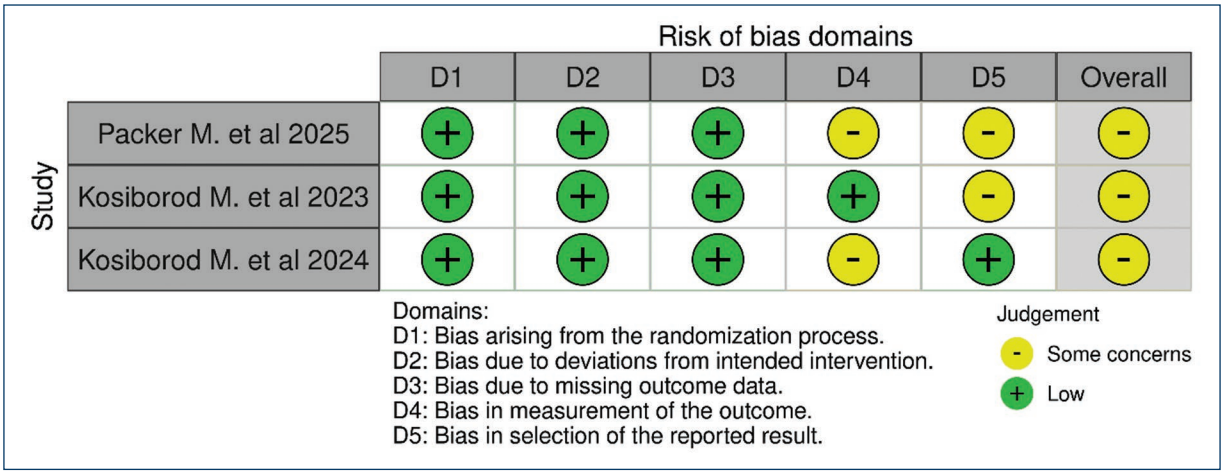


Figure 2. Global bias risk according to RoB 2 tool.

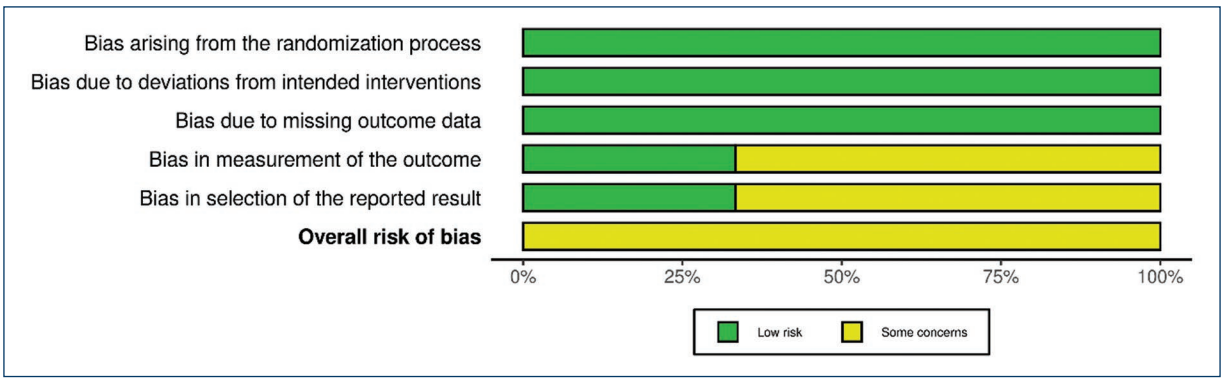


Figure 3. Risk of bias according to each domain of the RoB 2 tool.

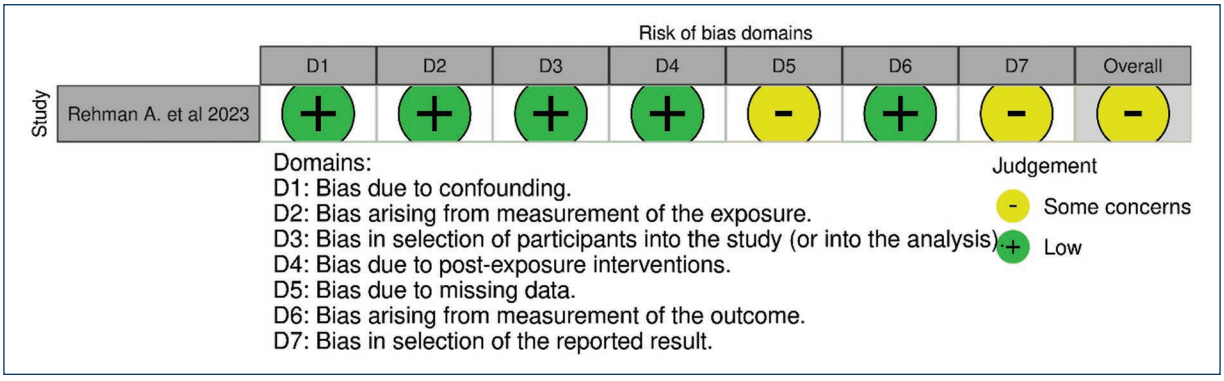


Figure 4. Risk of bias according to each domain of the ROBINS-E tool.

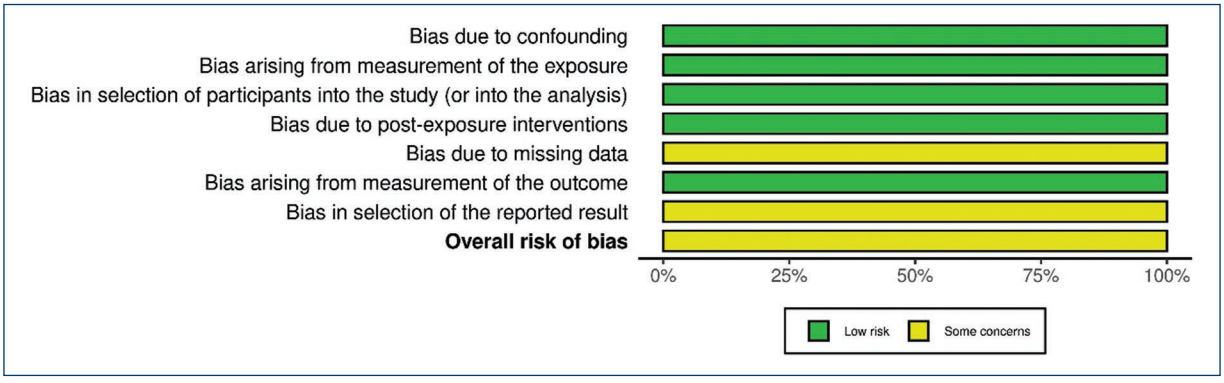


Figure 5. Risk of bias according to each domain of the ROBINS-E tool.

HF (OR 0.43; 95% CI [0.27-0.69], p = 0.0005), with heterogeneity calculated by I2 = 11% (Fig. 7).

Discussion

This systematic review and meta-analysis, which included 2,194 patients from 4 studies, found the following results; (1) the use of GLP-1 agonists and the glucose-dependent insulinotropic polypeptide (GIP) receptor did not significantly reduce all-cause mortality, and (2) the use of these therapies was associated with a significant decrease in hospital admission due to HF exacerbation. While the findings of our systematic review and meta-analysis, the use of GLP-1 agonists

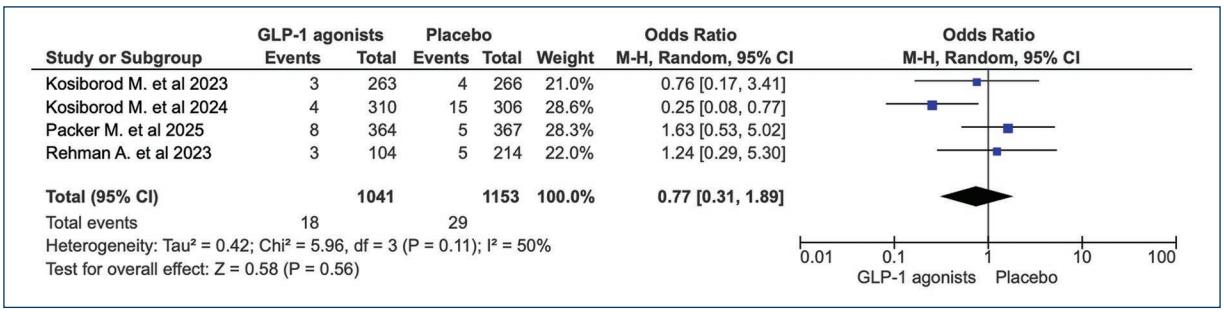


Figure 6. Forest plot (all-cause mortality variable).

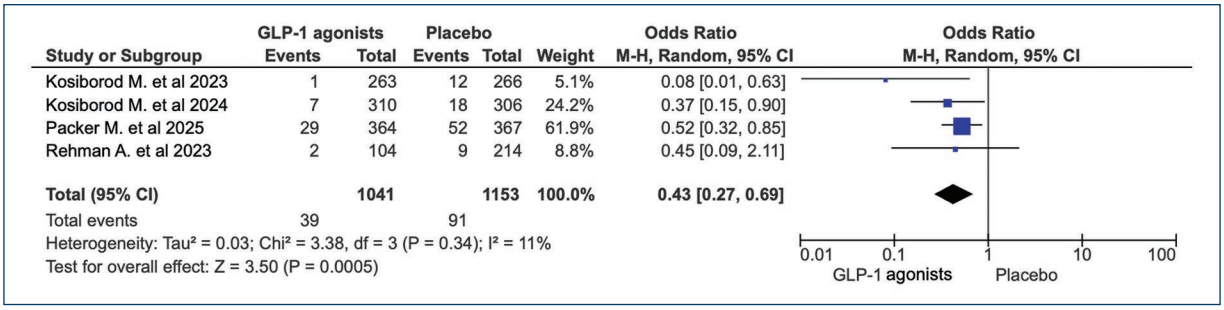


Figure 7. Forest plot (variable: number of hospitalizations due to exacerbation of heart failure).

and GIP significantly reduced hospital admission for HF exacerbation compared to placebo in patients with HFpEF and obesity, this was influenced by the homogeneity of the STEP-HFpEF, STEP-HFpEF DM2, SUMMIT studies, and the retrospective cohort study published by Rehman et al., because patients with HFpEF, a body mass index > 30 kg/m^2 and a proportion of patients with type 3 phenotype postulated in the TOPCAT trial were included. On the other hand, with regard to the decrease in all-cause mortality, a non-significant decrease was observed because although most studies used GLP-1 agonists, such as semaglutide, in the SUMMMIT trial GIP agonists, such as tirzepadide, were used, finding a non-significant increase in cardiovascular mortality in patients who received this drug (OR 1.58 95% CI [0.52-4.83]). However, these results may be due to accelerated weight loss and sarcopenia, which in patients with established cardiovascular disease, excessive or rapid weight loss could contribute to sarcopenia, frailty, and increased adverse events[13-16].

A systematic review and meta-analysis published by Waqas et al. in 2025, which included 8,788 patients, from 8 studies comparing the use of GLP-1/GIP agonists compared to placebo with rHFrEF and HFpEF in patients with obesity or diabetes, where a significant decrease in HF worsening events was observed (OR 0.56; 95% CI [0.38-0.82], p = 0.003), while no significant decrease in mortality reduction was observed (OR 0.86; 95% CI [0.67-1.12], p = 0.27)[17]. The study published by Zhao et al. in 2023 a meta-analysis evaluating the use of GLP-1 receptor agonists in patients with HF and DM2, which included 8,920 from 9 studies, where no significant reduction in mortality was observed (OR 0.99; 95% CI [0.84-1.15]) or a reduction in HF hospitalization (OR 1.04; 95% CI [0.89-1.22], these results could be due to the presence of patients with different LVEF and the heterogeneity of the studies[18]. A systematic review published in Al-Shudifat et al. in 2025, which included 16,011 patients from 13 studies, which included patients > 18 years of age with HFpEF and Type 2 diabetes mellitus with the aim of evaluating the use of GLP-1 agonists and/or SGLT2 inhibitors against placebo, where both treatments showed a non-significant reduction in major clinical events and hospitalization[19].

Limitations

This systematic review and meta-analysis presents some limitations that must be taken into account when

interpreting its results, among which are: a small sample of 2,194 patients, the heterogeneity considerably in the context of the all-cause mortality variable, and the scant number of randomized clinical trials currently available on the subject.

Conclusion

In addition to the quantitative findings, the information obtained in this review has significant practical utility. Since patients with HFpEF and obesity constitute a specific phenotype with peculiar clinical and prognostic characteristics, the evidence on the efficacy of GLP-1 agonists provides a solid basis for considering them as a complementary therapeutic strategy. These findings can guide individualized clinical decisions, encourage the development of specific protocols for this subgroup, and stimulate new lines of research aimed at the specific phenotypes of HF. In particular, GLP-1 agonists and GIP in patients with HFpEF and obesity, which correspond to phenotype 3 described by the TOPCAT trial, were associated with a reduction in hospitalizations, although without a significant impact on a reduction in all-cause mortality. This suggests that their incorporation in phenotypically similar patients could optimize therapeutic management and improve clinical outcomes.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

References

1. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. Circulation. 2022;145:e895-1032.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599-726.
3. Sotomi Y, Hikoso S, Nakatani D, Okada K, Dohi T, Sunaga A, et al. Medications for specific phenotypes of heart failure with preserved ejection fraction classified by a machine learning-based clustering model. Heart. 2023;109:1231-40.
4. Shah SJ, Kitzman DW, Borlaug BA, Van Heerebeek L, Zile MR, Kass DA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation. 2016;134:73-90.
5. Anker SD, Usman M, Anker MS, Butler J, Böhm M, Abraham WT, et al. Patient phenotype profiling in heart failure with preserved ejection fraction to guide therapeutic decision making. A scientific statement of the heart failure association, the European heart rhythm association of the European society of cardiology, and the European society of hypertension. Eur J Heart Fail. 2023;25:936-55.
6. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, et al. Clinical phenogroups in heart failure with preserved ejection fraction: detailed phenotypes, prognosis, and response to spironolactone. JACC Heart failure. 2020;8:172-84.
7. Bonfioli GB, Pagnesi M, Calò L, Metra M. Towards a phenotype profiling of the patients with heart failure and preserved ejection fraction. Eur Heart J Suppl. 2025;27 Suppl 1:i115-21.
8. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389:2221-32.
9. Zile MR, Borlaug BA, Kramer CM, Baum SJ, Litwin SE, Menon V, et al. Effects of tirzepatide on the clinical trajectory of patients with heart failure, preserved ejection fraction, and obesity. Circulation. 2025;151:656-68.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
11. Risk of Bias Tools - RoB 2 Tool; 2019. Available from: https://www.riskofbias.info/welcome/rob-2-0-tool
12. Risk of Bias Tools - ROBINS-E Tool. Available from: https://www.riskofbias.info/welcome/robins-e-tool
13. Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med. 2025;392:427-37.
14. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med. 2024;390:1394-407.
15. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies MJ, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389:1069-84.
16. Rehman A, Saidullah S, Asad M, Gondal UR, Ashraf A, Khan MF, et al. Efficacy and safety of semaglutide in patients with heart failure with preserved ejection fraction and obesity. Clin Cardiol. 2024;47:e24283.
17. Waqas SA, Sohail MU, Saad M, Minhas AM, Greene SJ, Fudim M, et al. Efficacy of GLP-1 receptor agonists in patients with heart failure and mildly reduced or preserved ejection fraction: a systematic review and meta-analysis. J Card Fail. 2025;31:1076-80.
18. Zhao H, Liu Y, Liu M, Xu Y, Ling Q, Lin W, et al. Clinical outcomes with GLP-1 receptor agonists in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. Drugs. 2023;83:1293-307.
19. Al-Shudifat M, Sumra B, Kocherry C, Shamim H, Jhakri K, Khan S, et al. Comparing glucagon-like peptide-1 receptor agonists to sodium-glucose cotransporter-2 inhibitors in heart failure with preserved ejection fraction: a systematic review. Cureus. 2025;17:e78570.