Precision Medication 2 (2025) 100064

Contents lists available at ScienceDirect

Precision Medication

journal homepage: www.keaipublishing.com/en/journals/precision-medication/

# Efficacy and safety of semaglutide in patients with heart failure: A meta-analysis

Xueni Li[a], Gejing Liu[b], Yongming Liu[b,c,*]

[a] The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China
[b] Geriatric Cardiovascular Department, the First Hospital of Lanzhou University, Lanzhou 730000, China
[c] Gansu Clinical Research Center for Geriatric Disease, the First Hospital of Lanzhou University, Lanzhou 730000, China

ARTICLE INFO

*Keywords:*
Semaglutide
Heart failure
Efficacy
Safety
Meta-analysis

ABSTRACT

*Background:* The pleiotropic effects of semaglutide make it a breakthrough therapy for managing diabetes and obesity, particularly in patients with comorbid cardiovascular diseases. However, its clinical application in heart failure (HF) remains under investigation.

*Objective:* To systematically evaluate the efficacy and safety of subcutaneous semaglutide in the treatment of HF, irrespective of obesity status or the presence of type 2 diabetes mellitus (T2DM).

*Methods:* A comprehensive search of the Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang, and VIP databases was conducted to identify randomized controlled trials (RCTs) of subcutaneous semaglutide in HF patients, from inception to November 2, 2024. RevMan 5.3 software was used for statistical analysis.

*Results:* A total of 4 RCTs involving 6109 patients were included. Four RCTs involving 6109 patients were included. Meta-analysis showed that, compared with placebo, subcutaneous semaglutide reduced the risks of cardiovascular death (*RR* = 0.75, 95 % *CI*: 0.61–0.92, *P* = 0.005), all-cause mortality (*RR* = 0.81, 95 % *CI*: 0.67–0.98, *P* = 0.03), and serious adverse events (*RR* = 0.53, 95 % *CI*: 0.41–0.68, *P* < 0.00001). Subgroup analysis revealed that semaglutide improved Kansas City Cardiomyopathy Questionnaire clinical summary scores (KCCQ-CSS) (*MD* = 7.58, 95 % *CI*: 4.40–10.77, *P* < 0.00001) and 6-minute walk test (6-MWT) distances (*MD* = 16.91, 95 % *CI*: 8.98–24.83, *P* < 0.0001), and reduced the risk of HF rehospitalization (*RR* = 0.41, 95 % *CI*: 0.26–0.65, *P* = 0.0001) in obese patients with HFpEF. Among patients without T2DM, semaglutide was superior to placebo in reducing HF rehospitalization (*RR* = 0.16, 95 % *CI*: 0.04–0.68, *P* = 0.01) and cardiovascular mortality (*RR* = 0.76, 95 % *CI*: 0.60–0.97, *P* = 0.03). Furthermore, at a dose of 2.4 mg weekly, semaglutide reduced HF rehospitalization (*RR* = 0.29, 95 % *CI*: 0.14–0.58, *P* = 0.0005) and cardiovascular mortality (*RR* = 0.75, 95 % *CI*: 0.59–0.95, *P* = 0.02) compared with placebo, whereas no significant benefit was observed at a dose of 1.0 mg weekly.

*Conclusion:* Current evidence suggests that subcutaneous semaglutide safely and effectively reduces cardiovascular mortality, all-cause mortality, and serious adverse events in patients with HF, improves quality of life and exercise tolerance in obese HFpEF patients, and lowers the risk of HF rehospitalization. Nevertheless, given the limited number of included trials and patient populations, further high-quality studies are warranted to confirm these findings.

## Introduction

Heart failure (HF) is a complex clinical syndrome characterized by impaired ventricular filling or ejection due to structural or functional abnormalities of the heart. According to the most recent classification based on left ventricular ejection fraction (LVEF), HF is categorized into heart failure with reduced ejection fraction (HFrEF; LVEF ≤40 %), heart failure with preserved ejection fraction (HFpEF; LVEF ≥50 %), heart failure with improved ejection fraction (HFimpEF; previous LVEF ≤40 % and LVEF > 40 % during the follow-up period), and heart

* Corresponding author.
*E-mail address:* cardtonm@263.net (Y. Liu).

https://doi.org/10.1016/j.prmedi.2025.100064
Received 6 June 2024; Received in revised form 26 August 2024; Accepted 9 September 2024
Available online 19 December 2025

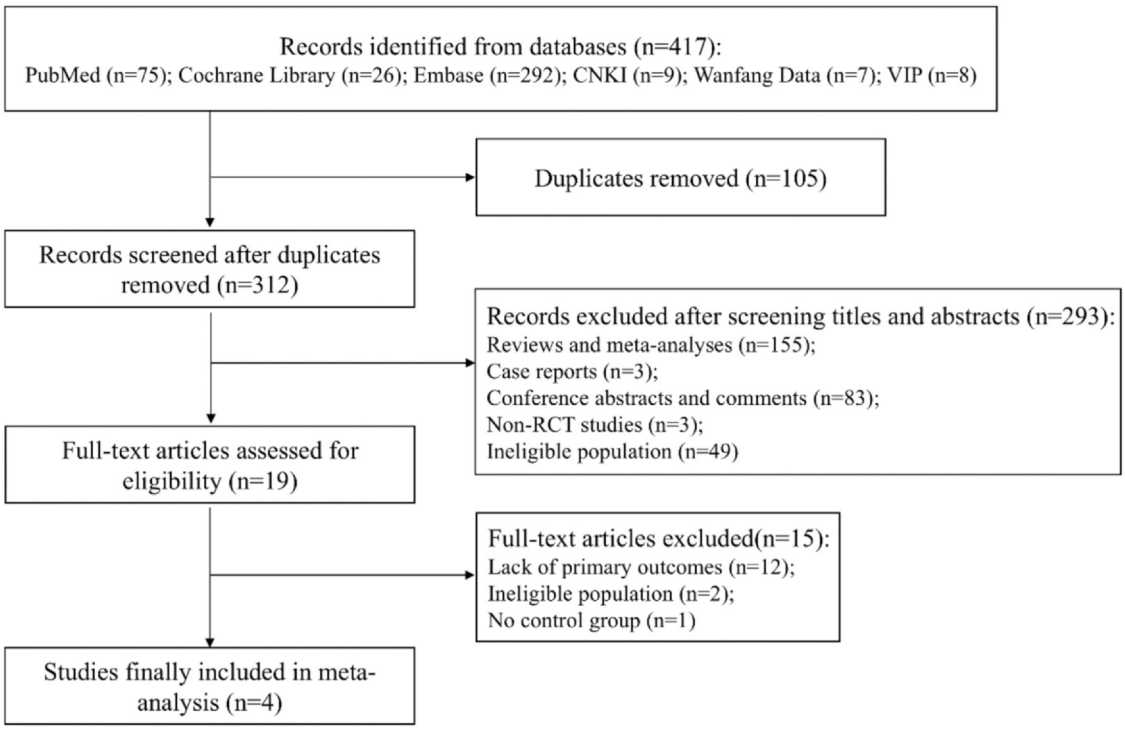



**Fig. 1.** Flowchart of the identification of eligible studies.

failure with mildly reduced ejection fraction (HFmrEF; LVEF 41–49 %).[1] In China, the prevalence of HF continues to rise due to population aging, the increasing incidence of chronic diseases such as coronary artery disease, hypertension, diabetes, and obesity, as well as the prolonged survival of patients with cardiovascular conditions owing to advances in medical care.[2] Existing studies have confirmed that the coexistence of HF with obesity or diabetes further increases mortality risk among HF patients.[3,4] Therefore, it is of great importance to develop more targeted and individualized treatment strategies for HF patients with cardiovascular risk factors or comorbid cardiovascular diseases.

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that mimics the physiological actions of endogenous GLP-1 and exerts effects through receptors distributed in multiple organs, including the pancreas, gastrointestinal tract, and cardiac tissues.[5] GLP-1 RAs regulate glucose homeostasis by stimulating insulin secretion and suppressing glucagon release, while also reducing energy intake by delaying gastric emptying, enhancing satiety, and inducing central appetite suppression. These mechanisms confer dual benefits of glycemic control and weight reduction.[6,7] Accordingly, semaglutide was initially approved for the treatment of type 2 diabetes mellitus (T2DM)[8] and for long-term weight management.[9] MARSO et al.[10] demonstrated that subcutaneous semaglutide reduced the risk of major adverse cardiovascular events (MACEs), including cardiovascular death, stroke, or myocardial infarction, in patients with T2DM at high cardiovascular risk. More recent studies[11] have shown that subcutaneous semaglutide is also effective in patients with HF, particularly those with HFpEF accompanied by obesity or T2DM, where it was superior to placebo in reducing body weight, improving exercise capacity, and lowering the risk of adverse cardiovascular outcomes. Although several clinical trials have evaluated the efficacy and safety of subcutaneous semaglutide in HF patients, systematic evidence-based analyses remain lacking. Therefore, the present study conducted a meta-analysis to assess the efficacy and safety of subcutaneous semaglutide in the treatment of HF, aiming to provide additional evidence for clinical practice. The study has been registered in PROSPERO (registration number CRD42024609866).

## Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

### *Search strategy*

Two researchers independently conducted the literature search, and disagreements were resolved by consultation with a third researcher. Electronic databases including The Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP were systematically searched for randomized controlled trials (RCTs) investigating subcutaneous semaglutide for the treatment of HF, from inception to November 2, 2024. Both subject terms and free-text terms were applied. References and supplementary materials of eligible studies were also screened to capture additional data. Chinese search terms equivalent to "heart failure" and "semaglutide" were used. English search terms included "Heart Failure", "Cardiac Failure", "Heart Decompensation", "Congestive Heart Failure", "Heart failure with reduced ejection fraction", "HFrEF", "Heart failure with preserved ejection fraction", "HFpEF", "semaglutide", "Ozempic", "Rybelsus", "Wegovy", "Randomized Controlled Trial", "RCT". Language was restricted to English or Chinese, and no restrictions were applied regarding region, sample size, or duration of intervention.

### *Inclusion and exclusion criteria*

Inclusion criteria: (1) study type: RCTs of subcutaneous semaglutide in HF patients; (2) participants: HF patients aged > 18 years, with or without obesity or T2DM; (3) interventions: the experimental group received subcutaneous semaglutide once weekly, with a maximum dose of 2.4 mg, and the control group received placebo.(4) outcomes: (i) cardiovascular outcomes: risk of HF rehospitalization, cardiovascular death, and all-cause mortality; (ii) quality of life and exercise capacity: KCCQ-CSS and 6-MWT; (iii) safety outcomes: serious adverse events.

**Table 1**
Basic characteristics of included studies.

| First author (Year) | Original study name | Trial registration | Phase | Therapeutic regimen | Sample size (n) | Age (years) | Female (%) | BMI (kg/m²) | LVEF (%) | Population characteristics | Follow-up duration | Outcomes* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pratley,[13] 2024 | FLOW | NCT03819153 | III | Semaglutide (1.0 mg/w)/ Placebo | 342/336 | 68 (63–73) | 247 (36.7) | 33.3 (28.9–38.0) | NA | HF + T2DM + CKD | 3.4 years | ①② |
| Kosiborod,[14] 2024 | STEP-HFpEF DM | NCT04916470 | III | Semaglutide (2.4 mg/w)/ Placebo | 310/306 | 69 (62–74) / 70 (63–75) | 128 (41.3) / 145 (47.4) | 36.9 (33.6–41.5) / 36.9 (33.5–41.1) | 57 (50–61) / 55 (50–60) | HFpEF + Obesity + T2DM | 52 weeks | ①②③④ |
| Kosiborod,[15] 2023 | STEP-HFpEF | NCT04788511 | III | Semaglutide (2.4 mg/w)/ Placebo | 263/266 | 70 (62–75) / 69 (62–75) | 149 (56.7) / 148 (55.6) | 37.2 (33.9–41.1) / 36.9 (33.3–41.6) | 57 (50–60) / 57 (50–60) | HFpEF + Obesity | 52 weeks | ①②③④ |
| Deanfield,[16] 2024 | SELECT | NCT03574597 | III | Semaglutide (2.4 mg/w)/ Placebo | 2155/2131 | 61.9 ± 8.7 | 1183 (26.6) | 33.9 ± 5.3 | NA | HF + Overweight/ Obesity | 104 weeks | ②③ |

Note: Pratley 2024 was a post hoc analysis based on the original RCT FLOW; Deanfield 2024 was a prespecified subgroup analysis of the original RCT SELECT. Baseline characteristics shown are for HF patients at study entry. BMI, body mass index; LVEF, left ventricular ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; CKD, chronic kidney disease; NA, not available. Outcomes: ① HF re-hospitalization; ② cardiovascular death; ③ all-cause mortality; ④ serious adverse events.

Exclusion criteria: (1) non-English or non-Chinese publications; (2) non-RCTs or animal experiments; (3) conference abstracts, case reports, reviews, letters, or expert opinions; (4) duplicate publications, or studies lacking extractable primary outcome data.

### *Data extraction and bias risk assessment*

Two investigators independently performed literature screening and data extraction, with discrepancies resolved by a third investigator. Extracted data included study name, first author, publication year, follow-up duration, dosing regimen, sample size and clinical characteristics of participants, and outcomes of interest. Risk of bias for included RCTs was independently assessed by two investigators, with disagreements adjudicated by a third. The Cochrane Handbook 5.1.0 risk of bias tool was applied, with assessment covering domains such as randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and other sources of bias. Each domain was rated as low, unclear, or high risk of bias.

### *Statistical analysis*

Data were analyzed using RevMan 5.3 software. For dichotomous outcomes, risk ratios (RRs) with 95 % confidence intervals (CIs) were calculated; for continuous outcomes, mean differences (MDs) with 95 % CIs were used. A $P$ value $< 0.05$ was considered statistically significant. Heterogeneity was assessed using the $I^2$ and Q statistics. A fixed-effect model was applied if no significant heterogeneity was present ($P > 0.1$ and $I^2 < 50\,\%$); otherwise, a random-effects model was used. Where substantial clinical heterogeneity existed, subgroup or sensitivity analyses were performed, or results were narratively described. Given the limited number of included studies, traditional assessments of publication bias, such as funnel plots, Egger's test were not conducted. Instead, a comprehensive search of clinical trial registries was undertaken, and potential bias risk was evaluated using the fail-safe N test implemented in R software (version 4.4.1).

## Results

### *Literature search and baseline characteristics of included studies*

According to the search strategy, a total of 417 potentially relevant articles were initially identified across the databases mentioned above. After removing 105 duplicates, 19 articles remained based on title and abstract screening. Full-text assessment further excluded ineligible studies, leaving 4 studies that met the inclusion criteria. The detailed screening process is presented in Fig. 1. The four included studies[13–16] enrolled a total of 6109 HF patients. Among them, 3418 were overweight or obese patients with HFpEF and accounted for 56 % of the study population. 3070 patients received subcutaneous semaglutide, and 3039 received placebo. The follow-up duration ranged from 52 weeks to 3.4 years. The baseline characteristics of the included studies are summarized in Table 1.

### *Bias risk assessment*

Of the four included studies, two were original RCTs,[14,15] one was a prespecified subgroup analysis of the SELECT trial,[16,17] and one was a post hoc analysis[13] based on the FLOW trial.[18] All four studies reported methods of randomization, allocation concealment, and blinding, and explicitly stated that no incomplete outcome data were present. One study[13] showed selective reporting, while other potential sources of bias were unclear in all four studies. The results of the risk of bias assessment are shown in Fig. 2.

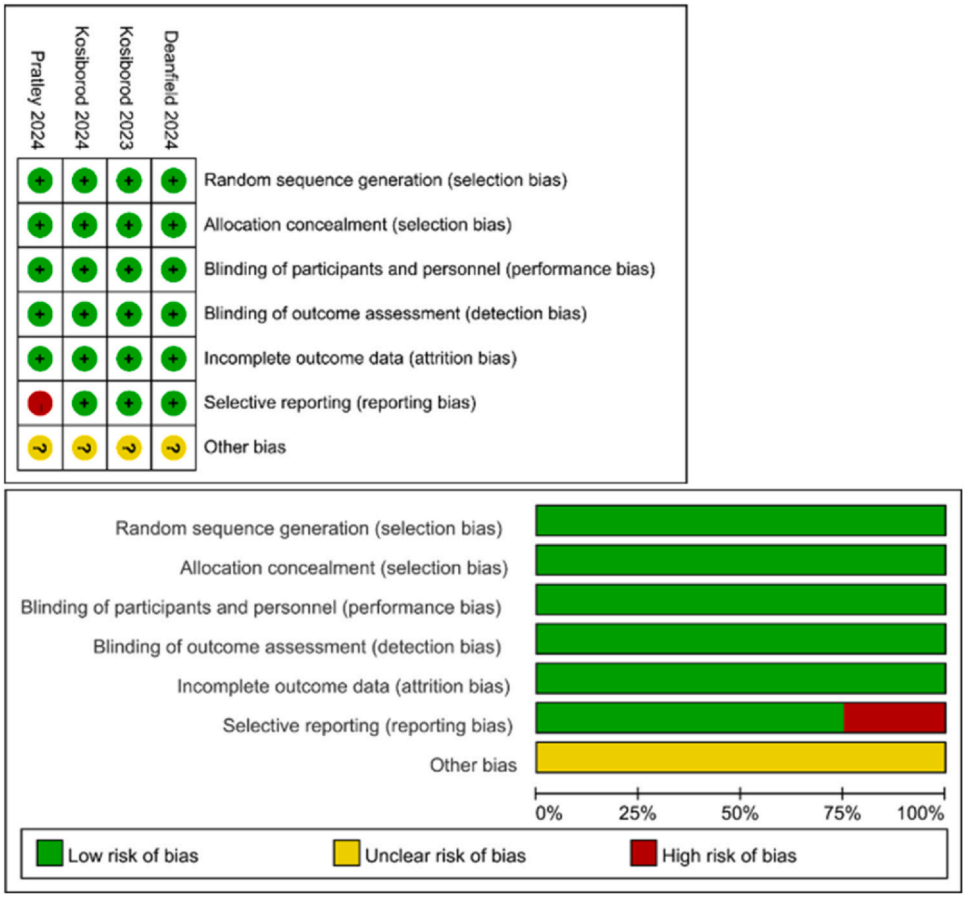



**Fig. 2.** Risk of bias summary for included studies. Deanfield 2024 was a prespecified subgroup analysis of the original RCT SELECT, and Pratley 2024 was a post hoc analysis based on the original RCT FLOW.

*Efficacy outcomes*

(1) Risk of HF rehospitalization
Three studies[13–15] reported HF rehospitalization events, including 1823 patients. Significant heterogeneity was observed among studies ($P = 0.02$, $I^2 = 75\%$). Subgroup analysis based on maintenance dosing (2.4 mg/week vs. 1.0 mg/week) suggested that heterogeneity markedly decreased in the 2.4 mg/week subgroup ($P = 0.35$, $I^2 = 0$). Pooled analysis showed that 2.4 mg weekly significantly reduced the risk of HF rehospitalization compared with placebo (*RR* = 0.29, 95 % *CI*: 0.14–0.58, $P = 0.0005$). In contrast, the 1.0 mg/week subgroup showed no statistically significant difference. Detailed results are presented in Fig. 3.

(2) Risk of cardiovascular death
Four studies[13–16] reported cardiovascular death events, including 6109 patients. No heterogeneity was observed ($P = 0.73$, $I^2 = 0$). Fixed-effect model analysis indicated that subcutaneous semaglutide significantly reduced the risk of cardiovascular death compared with placebo (*RR* = 0.75, 95 % *CI*: 0.61–0.92, $P = 0.005$). Results are shown in Fig. 4.

(3) Risk of all-cause mortality

Three studies[14–16] reported all-cause mortality events, including 5431 patients. No heterogeneity was observed among studies ($P = 0.81$, $I^2 = 0$). Fixed-effect model analysis demonstrated that subcutaneous semaglutide significantly reduced the risk of all-cause mortality compared with placebo (*RR* = 0.81, 95 % *CI*: 0.67–0.98, $P = 0.03$). Results are shown in Fig. 5.

*Safety outcomes*

Two studies[14,15] reported serious adverse events, involving 1145 patients. Compared with placebo, subcutaneous semaglutide significantly reduced the risk of serious adverse events (*RR* = 0.53, 95 % *CI*: 0.41–0.68, $P < 0.00001$). However, there were no statistically significant differences in treatment discontinuation due to serious adverse events (*RR* = 0.62, 95 % *CI*: 0.31–1.22, $P = 0.17$), arrhythmias (*RR* = 0.46, 95 % *CI*: 0.08–2.76, $P = 0.40$), acute pancreatitis (*RR* = 1.50, 95 % *CI*: 0.25–8.99, $P = 0.66$), acute cholelithiasis (*RR* = 1.25, 95 % *CI*: 0.50–3.13, $P = 0.64$), or acute renal failure (*RR* = 0.92, 95 % *CI*: 0.09–9.45, $P = 0.94$). Detailed results are shown in Fig. 6. Only one severe hypoglycemia event was reported, occurring in the semaglutide group in the study by Kosiborod et al.[15]

*Subgroup analyses*

(1) Efficacy in HFpEF patients
Three studies[14–16] reported efficacy outcomes, including 3418 patients with HFpEF. Compared with placebo, subcutaneous semaglutide reduced the risk of HF rehospitalization (*RR* = 0.41, 95 % *CI*: 0.26–0.65, $P = 0.0001$), but did not significantly reduce cardiovascular death (*RR* = 0.80, 95 % *CI*: 0.54–1.21, $P = 0.30$) or all-cause mortality (*RR* = 0.80, 95 % *CI*: 0.59–1.09, $P = 0.15$). Two of these studies[14,15] also reported quality of life and functional outcomes, including 1145 HFpEF patients. Semaglutide significantly improved KCCQ-CSS scores (*MD* = 7.58, 95 % *CI*: 4.40–10.77, $P < 0.00001$) and 6-MWT distance (*MD* = 16.91,

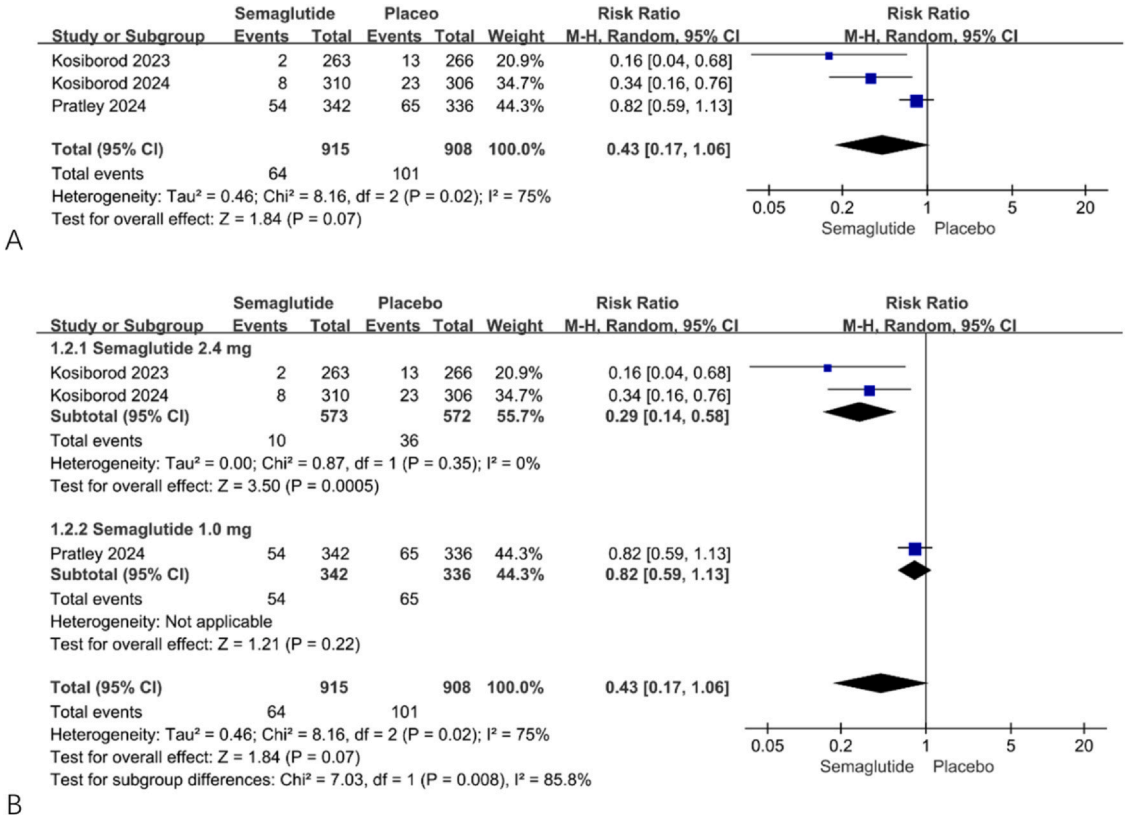



**Fig. 3.** Forest plot comparing the risk of rehospitalization for heart failure between the two groups. (A) all studies; (B) subgroup analysis by different maintenance doses.

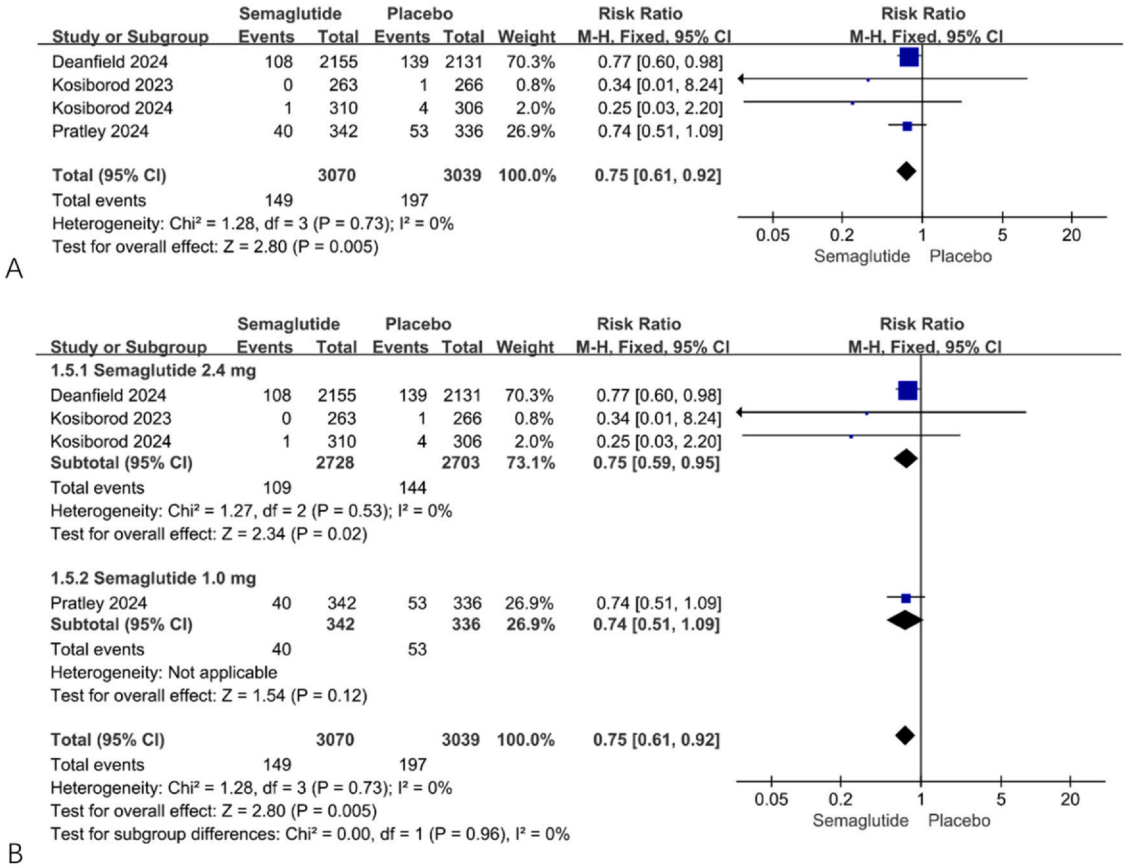



**Fig. 4.** Forest plot comparing the risk of cardiovascular death between the two groups. (A) all studies; (B) subgroup analysis by different maintenance doses.

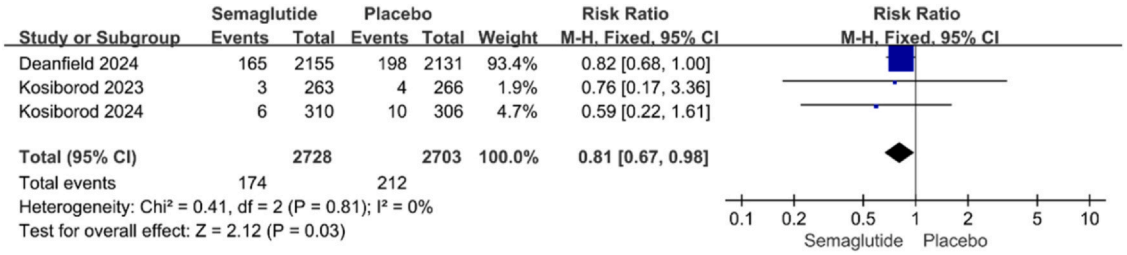



**Fig. 5.** Forest plot comparing the risk of all-cause death between the two groups.

95 % *CI*: 8.98–24.83, $P < 0.0001$), suggesting improved quality of life and exercise tolerance (Fig. 7).

(2) Efficacy in obese patients
Three studies[14–16] reported outcomes, comprising 5431 HF patients with obesity. Compared with placebo, subcutaneous semaglutide reduced the risk of cardiovascular death (*RR* = 0.75, 95 % *CI*: 0.59–0.95, $P = 0.02$) and all-cause mortality (*RR* = 0.81, 95 % *CI*: 0.67–0.98, $P = 0.03$) (Fig. 8).

(3) Efficacy by maintenance dose
Three studies[14–16] administered semaglutide at a maintenance dose of 2.4 mg weekly, while one study[13] used a dose of 1.0 mg weekly. Subgroup analysis showed that the 2.4 mg weekly dose was superior to placebo in reducing HF rehospitalization (RR = 0.29, 95 % CI: 0.14–0.58, P = 0.0005) and cardiovascular death (RR = 0.75, 95 % CI: 0.59–0.95, P = 0.02), whereas the 1.0 mg weekly dose showed no significant benefit (Figs. 3 and 4).

(4) Efficacy by T2DM comorbidity

Two studies[13,14] included patients with T2DM, while two studies[15,16] included patients without T2DM. In non-T2DM patients, subcutaneous semaglutide significantly reduced the risk of HF rehospitalization (*RR* = 0.16, 95 % *CI*: 0.04–0.68, $P = 0.01$) and cardiovascular death (*RR* = 0.76, 95 % *CI*: 0.60–0.97, $P = 0.03$). In patients with T2DM, semaglutide also showed a trend toward reducing these adverse outcomes, but the differences were not statistically significant (Fig. 9).

*Publication bias*

A search of clinical trial registries did not identify any completed but unpublished relevant studies. For the primary outcomes, Rosenthal's fail-safe N values (5 for cardiovascular death and 2 for all-cause mortality) were below the empirical threshold of 5k + 10 (30 for cardiovascular death and 25 for all-cause mortality), suggesting that even a small number of unpublished negative studies could potentially affect the robustness of current conclusions. Publication bias cannot be completely ruled out in this study.

## Discussion

We performed a meta-analysis to evaluate the efficacy and safety of subcutaneous semaglutide in 6109 patients with HF. Based on mixed RCT evidence, our preliminary findings suggest that subcutaneous semaglutide reduces the risks of cardiovascular death, all-cause mortality, and serious adverse events in HF patients. Subgroup analyses further indicated that semaglutide improved health-related life quality and exercise tolerance, and reduced the risk of HF rehospitalization in overweight or obese patients with HFpEF. In addition, beneficial effects on major adverse outcomes were also observed in obese patients and in those without T2DM. Moreover, our study suggested a potential dose-dependent effect: semaglutide at 2.4 mg/week was superior to placebo in reducing the risks of HF rehospitalization and cardiovascular death, whereas no significant benefit was observed with the 1.0 mg weekly dose. It is noteworthy that this meta-analysis included 3418 overweight or obese HFpEF patients, accounting for 56 % of the study population, which suggests that the observed benefits may primarily apply to overweight or obese HFpEF patients. Similarly, in a pooled analysis of semaglutide for HFmrEF and HFpEF, Kosiborod et al.[11] reported that semaglutide reduced the risk of first occurrence of cardiovascular death or worsening HF. Subgroup analyses by LVEF, BMI, and age demonstrated that patients with LVEF ≥ 50 % or BMI ≥ 35 kg/m$^2$ derived greater benefit compared with placebo. The effect was consistent across age subgroups (< 65 years and ≥65 years), with no significant difference in the magnitude of benefit between age groups; importantly, these findings were largely observed in obese patients. Collectively, these observations highlight the possibility that patient-specific factors may influence responsiveness to semaglutide, and raise uncertainty regarding its applicability in HFrEF or non-obese patients. However, Deanfield et al.[16] compared outcomes in overweight or obese patients with HFrEF and HFpEF, and found that semaglutide consistently reduced the risk of MACEs and composite HF outcomes (cardiovascular death, hospitalization, or urgent HF visits), regardless of HF subtype. Furthermore, adverse event rates were lower in the semaglutide group than in the placebo group. Similarly, Pratley et al.[13] did not identify differential effects of semaglutide across HF subtypes. These findings support the potential applicability of semaglutide across different HF phenotypes, underscoring its therapeutic promise. Future studies are needed to validate these results through rigorous evidence, and to enable more eligible patients to benefit from semaglutide in clinical practice under the premise of clarifying adverse event incidence.

However, caution is warranted when interpreting the above findings in HFrEF. Prior studies of another GLP-1 receptor agonist, liraglutide, are instructive. The LIVE[19] and FIGHT[20] trials in patients with HFrEF show that, although liraglutide reduced body weight and glucose levels, it increased heart rate and failed to improve LVEF or systolic function, and may even have increased the risk of serious cardiac events and other adverse reactions. These two studies had relatively short intervention periods (< 26 weeks), leaving long-term effects uncertain. Differences between liraglutide and semaglutide in drug stability, half-life, and dosing frequency,[21] together with the distinct pathophysiology of HFpEF versus HFrEF, argue against extrapolating the favorable results of semaglutide to all GLP-1 RAs. The suitability of individual GLP-1 RAs across LVEF phenotypes should be assessed cautiously.

Regarding the subgroup analyses, stratification by maintenance dose of semaglutide showed that heterogeneity in the risk of HF rehospitalization decreased substantially in the 2.4 mg/week group. The 1.0 mg/week group included only one study,[13] making it difficult to determine whether heterogeneity was affected. This suggests that different dosing regimens may be one of the main sources of heterogeneity. In terms of reducing both HF rehospitalization and cardiovascular death, semaglutide 2.4 mg/week was superior to placebo, whereas 1.0 mg/week showed no significant difference compared with placebo, which implies a potential dose-dependent effect of semaglutide in HF. It is noteworthy that the trial using 1.0 mg/week[13] had the longest follow-up (3.4 years), whereas the other studies had follow-up durations of approximately 1–2 years. The length of follow-up may influence the progression of adverse outcomes, and thus whether the efficacy of semaglutide in HF truly exhibits a dose-dependent effect

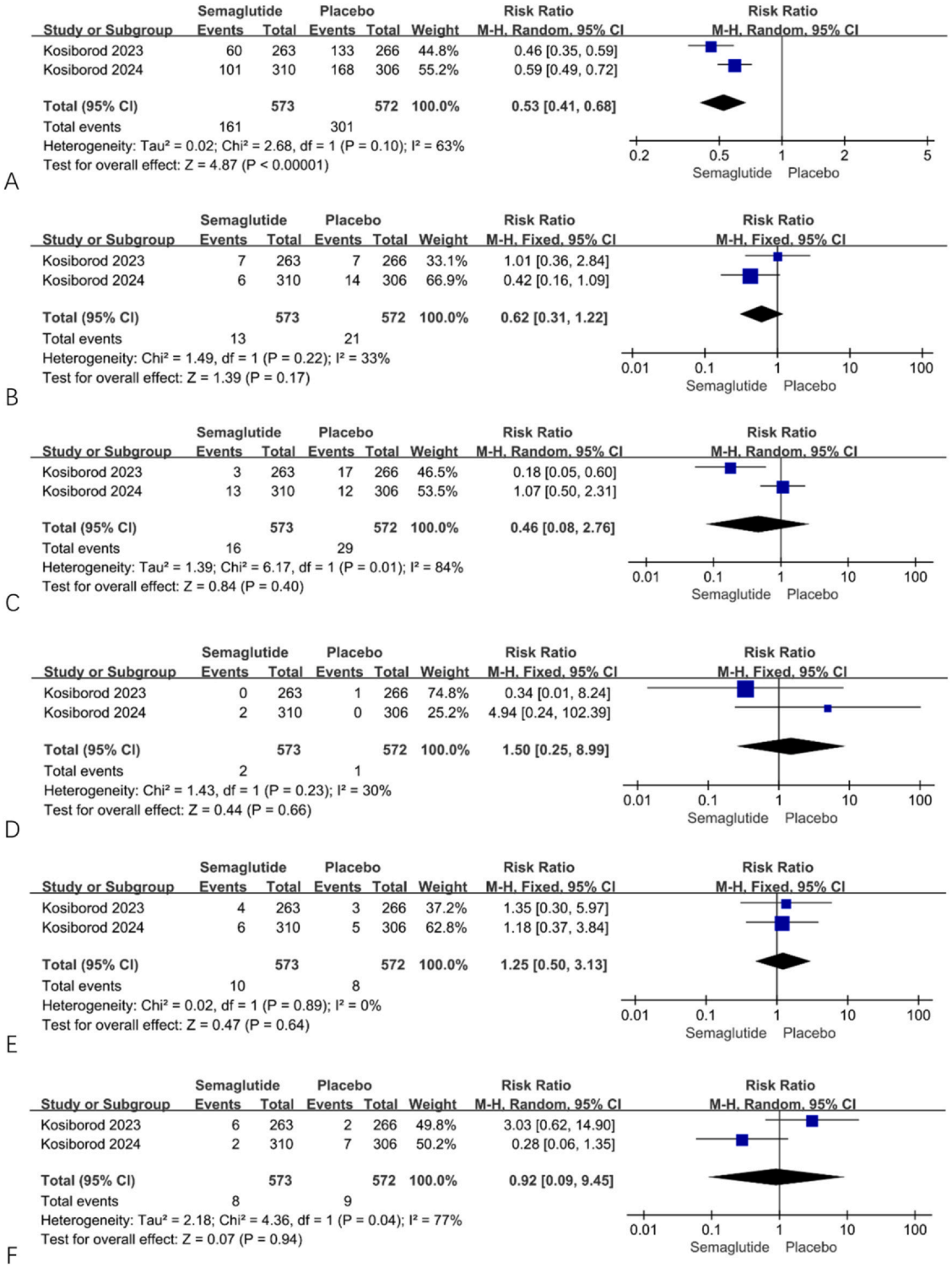



**Fig. 6.** Forest plot comparing the risk of serious adverse events between the two groups. (A) serious adverse events; (B) discontinuation due to serious adverse events; (C) arrhythmias; (D) acute pancreatitis; (E) acute cholelithiasis; (F) acute renal failure.

requires confirmation from future high-quality studies with longer follow-up and direct head-to-head comparisons.

Subgroup analysis by with or without T2DM comorbidity showed that, unlike in non-T2DM patients, adverse cardiovascular outcomes in patients with T2DM did not differ significantly between semaglutide and placebo. Several factors may account for this. First, the T2DM subgroup included Pratley 2024,[13] which recruited patients with lower baseline BMI, used the lowest semaglutide dose compared with the other three studies,[14–16] and may have had attenuated weight-loss effects and dose-dependent efficacy despite the longest follow-up. It may weaken outcome improvements. Second, baseline use of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) was far more common in the two T2DM studies[13,14] than in the non-T2DM subgroup, which may have produced synergistic prognostic benefits and reduced the detectable efficacy of semaglutide. Third, a post hoc analysis by Husain et al.[22] evaluating cardiovascular safety of semaglutide in T2DM patients found that its effect on MACEs (*HR* = 0.76, 95 % *CI*: 0.62–0.92) was primarily driven by fatal stroke (*HR* = 0.65, 95 % *CI*: 0.43–0.97),

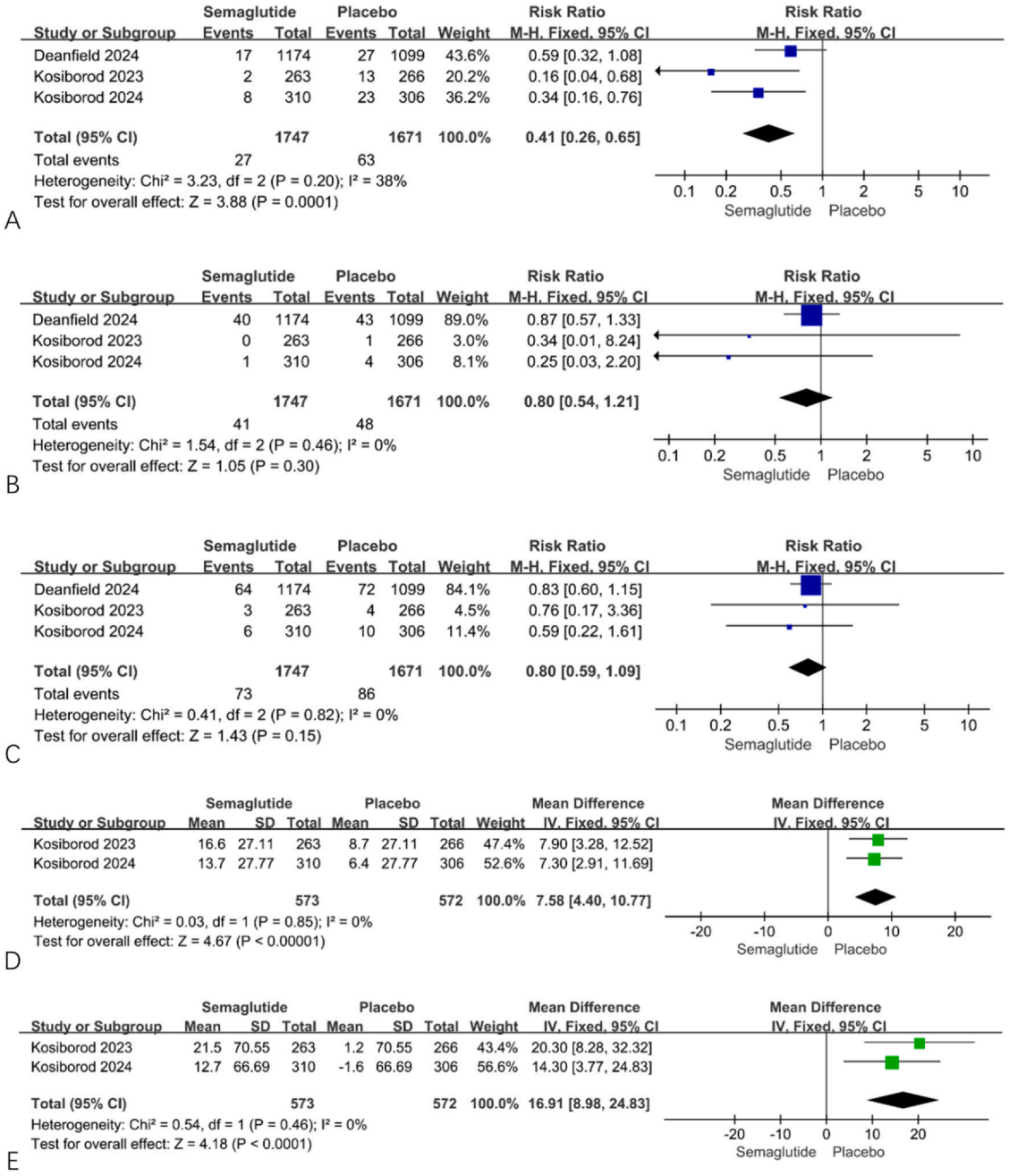



**Fig. 7.** Forest plot comparing the effectiveness outcomes in the HFpEF subgroup. (A) rehospitalization for heart failure; (B) cardiovascular death; (C) all-cause mortality; (D) KCCQ-CSS score; (E) 6-minute walk distance.

whereas the HR for cardiovascular death was not statistically significant. Furthermore, a review analysis of GLP-1 RAs suggested that drug exposure time was the most important factor contributing to heterogeneity, with longer exposure associated with greater MACEs risk reduction.[23] Taken together, we speculate that the lack of significant benefit in adverse cardiovascular outcomes among the T2DM subgroup may be related to differences in exposure time. Even with the same long-acting injectable semaglutide formulation and identical half-life, variations in study design, patient tolerance, adherence, and discontinuation rates could result in differential drug exposure durations. Ultimately, these interpretations require confirmation in future studies.

The mechanisms by which semaglutide improves HF outcomes are likely attributable to its multi-target synergistic effects. Animal studies have shown that semaglutide reduces key extracellular matrix components such as Coll5a1, Lama4, and Sparc, thereby improving endothelial function and vascular permeability.[24] It also alleviates pathological cardiac hypertrophy by enhancing mitochondrial function and inhibiting NLRP3 inflammasome activation in cardiomyocytes.[25] Human studies further demonstrated that semaglutide modulates the endocrine activity of epicardial adipose tissue, reduces circulating levels of the obesity marker FABP4, upregulates neutrophil CD88 expression, and exerts anti-inflammatory and antithrombotic effects.[26] These findings suggest that the benefits of semaglutide extend not only to obese patients but also to those with atherosclerotic cardiovascular disease (ASCVD), a major risk factor for HF.[1] Pivotal clinical trials[27] consistently showed that semaglutide significantly reduces body weight in HF patients and improves quality of life and exercise tolerance. Bioelectrical impedance analysis revealed that weight loss was primarily attributable to reductions in fat mass rather than muscle mass.[28] In addition, semaglutide lowered levels of C-reactive protein, NT-proBNP, and systolic blood pressure, indicating

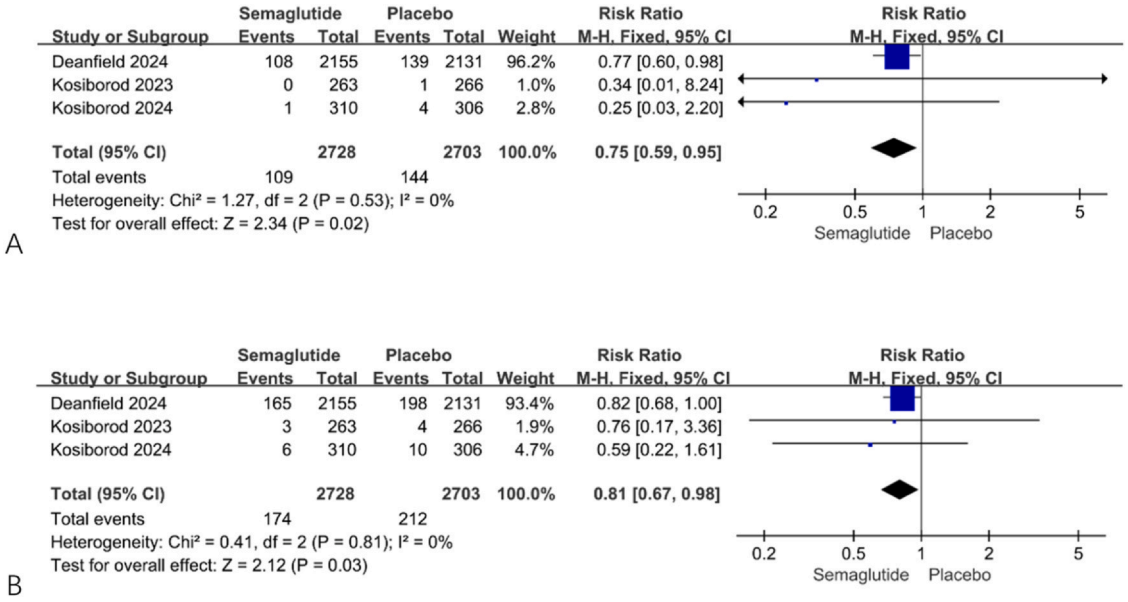



**Fig. 8.** Forest plot comparing the effectiveness outcomes in the obesity subgroup. (A) cardiovascular death; (B) all-cause mortality.

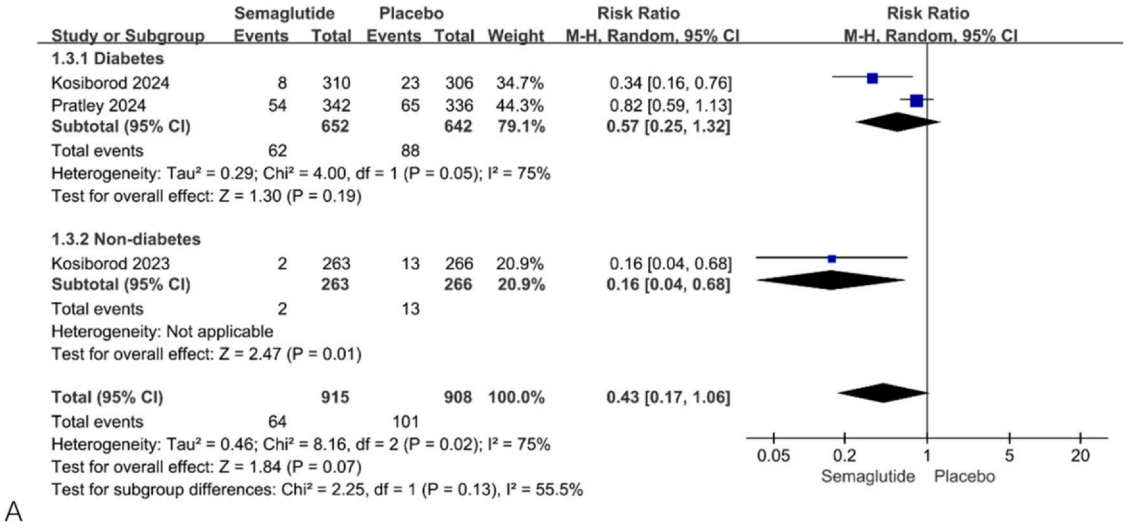
benefits beyond weight loss, including potential anti-inflammatory effects, attenuation of cardiac load, and favorable hemodynamic modulation. Cardiac imaging evidence further demonstrated that semaglutide effectively reverses cardiac remodeling in HF patients, characterized by reduced left atrial volume, improved left ventricular diastolic function, and decreased right heart load.[29]

On the one hand, with the rising prevalence of HF risk in patients with obesity, diabetes, or chronic kidney disease,[30–33] multimorbidity has become increasingly common.[34] To alleviate the challenges of complex therapeutic regimens and increased medication management burden in HF patients with multimorbidity, patient-centered and tailored treatment strategies are urgently needed. Systemic inflammation, oxidative stress, and endothelial dysfunction ultimately contribute to structural and functional abnormalities in patients with HFpEF.[35] Compared with HFrEF, higher BMI and insulin resistance are strongly associated with increased HFpEF risk.[36] Semaglutide has been shown to improve β-cell function and promote insulin secretion in patients with T2DM,[37] a mechanism that may also be beneficial for HFpEF. A network meta-analysis in 2023 compared the weight loss efficacy and safety of different GLP-1 RAs in obese patients and found that semaglutide provided the most pronounced weight loss benefit with a low-to-moderate risk of adverse events.[38] For T2DM patients with ASCVD or at high cardiovascular risk, the most recent Chinese guideline recommends GLP-1 RAs with proven cardiovascular benefit as the preferred choice.[39] Furthermore, a meta-analysis of seven RCTs involving 56,004 T2DM patients, including six GLP-1 RAs, confirmed that GLP-1 RAs reduce cardiovascular outcomes, all-cause mortality, and renal composite outcomes in this population.[40] However, the efficacy and safety of GLP-1 RAs in HF remain uncertain. Therefore, based on recently published RCTs, we evaluated the prognostic impact of subcutaneous semaglutide in patients with HF.

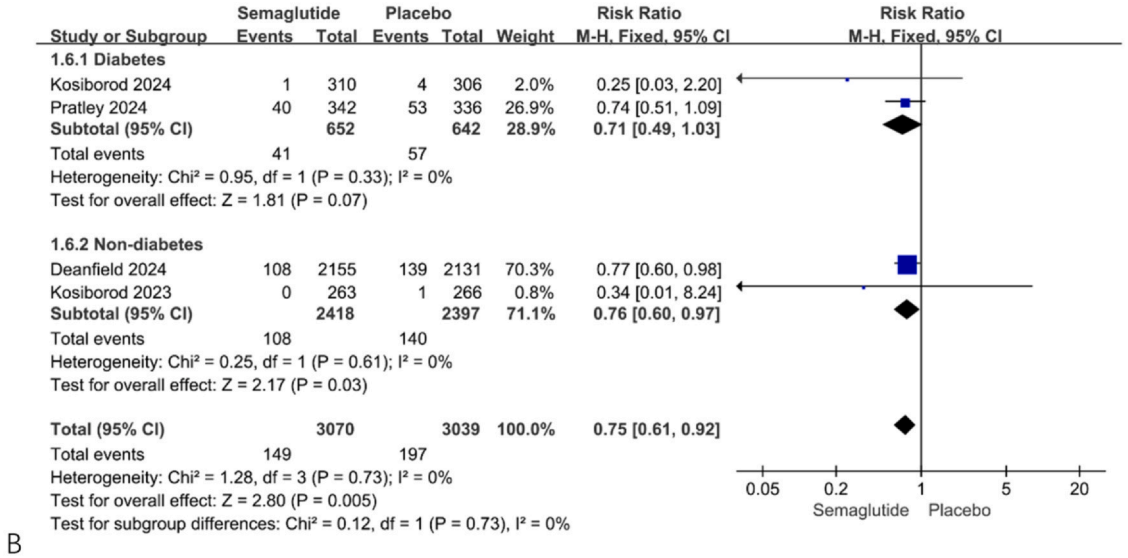
On the other hand, it is well established that only HFrEF currently has evidence-based pharmacologic therapies with robust prognostic benefits,[41] namely the "quadri-combination therapy" consisting of angiotensin receptor-neprilysin inhibitors (ARNIs) or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, SGLT-2 inhibitors, β-blockers, and mineralocorticoid receptor antagonists.[42] In contrast, HFpEF is characterized by complex pathophysiological mechanisms that are still being elucidated,[43] and therapeutic options with proven prognostic benefits remain limited. As a result, clinical management of HFpEF has long focused on addressing comorbidities.[44] However, our meta-analysis demonstrated that in the HFpEF subgroup, subcutaneous semaglutide improved health-related life quality, increased 6-MWT performance, and reduced the risk of HF rehospitalization in obese patients. These findings suggest that subcutaneous semaglutide may represent a promising therapeutic option that could provide meaningful clinical benefit for obese patients with HFpEF.

In conclusion, current evidence suggests that, when added to standard therapy, subcutaneous semaglutide is effective and safe in reducing cardiovascular mortality, all-cause mortality, and serious adverse events in patients with HF. In overweight or obese patients with HFpEF, semaglutide also improves health-related life quality and exercise tolerance, while reducing the risk of HF rehospitalization. Subgroup analyses further revealed that semaglutide is more effective in non-T2DM patients compared with those with T2DM, and that its efficacy may be dose-dependent. However, given the limited number and scope of included studies, these conclusions require confirmation in large-scale, multicenter, high-quality trials. Future research should also place greater emphasis on other HF phenotypes (such as HFrEF) and non-obese populations, to further explore the therapeutic potential of semaglutide and provide guidance for clinical practice.

This study has several limitations. (1) The number of included studies and the sample size were relatively small (only four studies with a total of 6109 patients), mainly constrained by the limited availability of high-quality evidence in this field. Although we systematically searched to capture all relevant studies, the small sample size may have reduced statistical power and limited the ability to adequately explore confounding factors (e.g., population characteristics, dosing regimens, comorbidities) in subgroup analyses, which restricts the generalizability of the findings. Notably, 56 % of the included patients were overweight or obese with HFpEF, which calls for caution when extrapolating to broader populations or real-world settings. (2) Due to difficulties in data extraction, we did not compare changes in weight or BMI across patients. (3) Differences in follow-up duration may have influenced the trajectory of outcomes. (4) Baseline demographic data were missing in half of the included studies, specifically Deanfield 2024[16] and Pratley 2024,[13] including sex, age, and BMI. Deanfield 2024[16] was a large study (n = 4286). Sensitivity analyses assessing the influence of these two studies on subgroup outcomes demonstrated that upon exclusion of the Deanfield 2024 study, the




A

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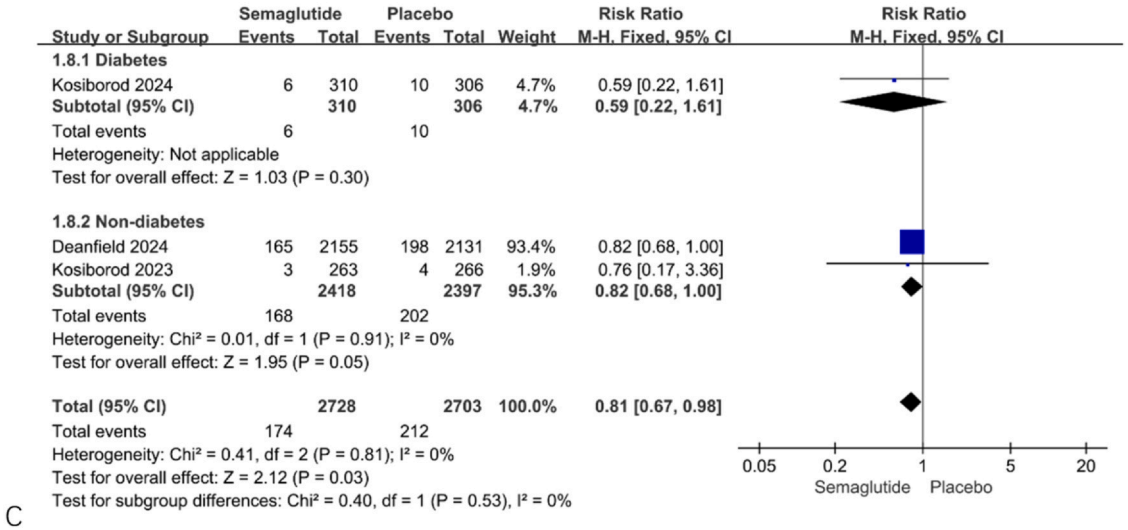


C

**Fig. 9.** Forest plot comparing the effectiveness outcomes between subgroups with and without T2DM. (A) rehospitalization for heart failure; (B) cardiovascular death; (C) all-cause mortality.

**Table 2**
Sensitivity analysis of subgroup analysis based on the exclusion of Deanfield 2024 and Pratley 2024 due to incomplete baseline data.

| Subgroup | Analysis type | No. of studies | Effect size (95 % CI) | Standardized weight | Effect size (95 % CI) | Standardized weight | Effect size (95 % CI) | Standardized weight |
|---|---|---|---|---|---|---|---|---|
| | | | HF rehospitalization | | Cardiovascular death | | All-cause mortality | |
| HFpEF | Main analysis | 3 | 0.41 (0.26–0.65) | 100 % | 0.80 (0.54–1.21) | 100 % | 0.80 (0.59–1.09) | 100 % |
| | After exclusion | 2 | 0.28 (0.14–0.55) | 65.40 % | 0.27 (0.04–1.64) | 11.10 % | 0.64 (0.28–1.46) | 15.90 % |
| Obesity | Main analysis | 3 | - | - | 0.75 (0.59–0.95) | 100 % | 0.81 (0.67–0.98) | 100 % |
| | After exclusion | 2 | - | - | 0.27 (0.04–1.64) | 3.80 % | 0.64 (0.28–1.46) | 6.60 % |
| 2.4 mg dose | Main analysis | 3 | - | - | 0.75 (0.59–0.95) | 100 % | - | - |
| | After exclusion | 2 | - | - | 0.27 (0.04–1.64) | 3.83 % | - | - |
| With T2DM | Main analysis | 2 | 0.57 (0.25–1.32) | 100 % | 0.71 (0.49–1.03) | 100 % | - | - |
| | After exclusion | 1 | 0.34 (0.16–0.76) | 43.87 % | 0.25 (0.03–2.20) | 6.92 % | - | - |
| Without T2DM | Main analysis | 2 | - | - | 0.76 (0.60–0.97) | 100 % | 0.82 (0.68–1.00) | 100 % |
| | After exclusion | 1 | - | - | 0.34 (0.01–8.24) | 1.13 % | 0.76 (0.17–3.36) | 1.99 % |

Note: Standardized weight was calculated using the actual weights from the main subgroup analysis as the reference (set to 100 %). Formula:
Standardized weight = (Sum of actual weights of remaining studies / Sum of actual weights in the original subgroup analysis) × 100 %.

conclusion of significant benefit was reversed in the 2.4 mg dose, obesity, and non-T2DM subgroups (Table 2). This suggests that the conclusions for these subgroups are highly dependent on this single large study. Thus, these findings should be interpreted with caution and require confirmation from future studies. (5) Only publications in Chinese or English were included, which may have introduced language bias.

## Declarations

Not applicable.

## Authors' contributions

**Xueni Li:** Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing-Original Draft. Gejing Liu: Methodology, Investigation, Data Curation, Formal Analysis. **Yongming Liu:** Supervision, Project Administration, Validation, Writing-Review & Editing. All authors contributed to the article and approved the submitted version.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

Not applicable.

## Funding

This study was supported by the Gansu Provincial Science and Technology Plan Project (No. 20YF8FA079) and the 2023 Lanzhou Municipal Science and Technology Development Guidance Plan Project (No. 2023-ZD-96).

## Declarations of Competing Interests

The authors declare no competing interests.

## Acknowledgements

Not applicable.

## Authors' other information

Not applicable.

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