Meta-analysis preprint on the efficacy and safety of semaglutide in the treatment of heart failure

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Abstract

Background Semaglutide' s multi-target effects make it a breakthrough drug for the management of diabetes and obesity, with comprehensive benefits especially in patients with concomitant cardiovascular disease. However, its efficacy and safety in patients with heart failure (HF) remain under exploration. 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 computerized search was conducted in the Cochrane Library, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP databases, from database inception to 2024-11-02. Randomized controlled trials of subcutaneous semaglutide for the treatment of HF were screened, in which the intervention group received subcutaneous semaglutide and the control group received placebo. Two researchers independently performed study selection, data extraction, and risk-of-bias assessment. Data on HF rehospitalization, cardiovascular mortality and all-cause mortality, serious adverse events, Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), and 6-minute walk distance (6-MWD) were collected and analyzed. Subgroup analyses were conducted based on comorbidities and different dosing regimens. Meta-analysis was performed using Review Manager 5.3 software. Results A total of 4 randomized controlled trials involving 6,109 patients were included, with 3,070 patients in the intervention group and 3,039 in the control group. Meta-analysis showed that, compared with placebo, subcutaneous semaglutide reduced the risk of cardiovascular death (RR = 0.75, 95% CI = 0.61-0.92, P = 0.005), all-cause death (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 in obese patients with heart failure with preserved ejection fraction (HFpEF), subcutaneous semaglutide improved KCCQ-CSS (MD = 7.58, 95% CI = 4.40-10.77, P $<$ 0.00001) and 6-MWD (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). 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). Similarly, in patients receiving 2.4 mg/week, compared with placebo, subcutaneous semaglutide reduced the risk of 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 efficacy of the 1.0 mg/week dose did not differ significantly from placebo. Conclusion Subcutaneous semaglutide can safely and effectively reduce the risks of cardiovascular death, all-cause death, and serious adverse events in patients with HF, improve quality of life and exercise capacity in obese patients with HFpEF, and lower the risk of HF rehospitalization. Given the limited number and population scope of the included studies, these findings require confirmation by further high-quality research.

Full Text

Abstract

Background: The multi-target effects of semaglutide have established it as a breakthrough therapy for diabetes and obesity management, offering comprehensive benefits particularly for patients with cardiovascular disease. However, its clinical applications for patients with heart failure (HF) are still under active investigation.

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

Methods: We systematically searched the Cochrane Library, PubMed, Embase, CNKI, Wanfang Data, and VIP databases from inception to November 2, 2024, for randomized controlled trials (RCTs) investigating subcutaneous semaglutide for HF treatment, with the experimental group receiving subcutaneous semaglutide and the control group receiving placebo. Two investigators independently screened studies, extracted data, and assessed risk of bias. Data on HF rehospitalization, cardiovascular death, all-cause death, serious adverse events, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), and 6-minute walk distance (6-MWD) were collected and analyzed. Subgroup analyses were performed based on comorbidities and different dosages, with meta-analysis conducted using Review Manager 5.3 software.

Results: Four RCTs involving 6,109 patients were included (3,070 in the experimental group and 3,039 in the control group). Meta-analysis showed that compared with placebo, subcutaneous semaglutide reduced the risk of cardiovascular death (RR=0.75, 95%CI=0.61~0.92, P=0.005), all-cause death (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 subcutaneous semaglutide increased KCCQ-CSS (MD=7.58, 95%CI=4.40~10.77, P<0.00001) and 6-MWD (MD=16.91, 95%CI=8.98~24.83, P<0.0001) while reducing HF rehospitalization risk (RR=0.41, 95%CI=0.26~0.65, P=0.0001) in obese patients with heart failure with preserved ejection fraction (HFpEF). In 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 death risk (RR=0.76, 95%CI=0.60~0.97, P=0.03). Similarly, in the 2.4 mg/week dosage group, subcutaneous semaglutide reduced HF rehospitalization (RR=0.29, 95%CI=0.14~0.58, P=0.0005) and cardiovascular death risk (RR=0.75, 95%CI=0.59~0.95, P=0.02) compared with placebo, but the 1.0 mg/week dosage group showed no significant difference from placebo.

Conclusion: Subcutaneous semaglutide can safely and effectively reduce cardiovascular death, all-cause death, and serious adverse events in HF patients, while improving quality of life and exercise tolerance and reducing HF rehospitalization risk in obese HFpEF patients. Due to limitations in the number and populations of included studies, these conclusions require verification through additional high-quality studies.

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

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by impaired ventricular filling or ejection resulting from structural or functional cardiac abnormalities. According to the latest classification based on left ventricular ejection fraction (LVEF), HF is categorized as HF with reduced EF (HFrEF; LVEF $\leq$ 40%), HF with preserved EF (HFpEF; LVEF $\geq$ 50%), HF with improved EF (HFimpEF; previously LVEF $\leq$ 40% with follow-up LVEF > 40%), and HF with mildly reduced EF (HFmrEF; LVEF 41%~49%) [1]. With population aging in China and rising incidence of chronic diseases such as coronary artery disease, hypertension, diabetes, and obesity—along with improved survival from cardiac conditions—the prevalence of HF continues to increase [2]. Studies have confirmed that coexisting HF with obesity or diabetes increases mortality risk [3-4], making tailored treatment strategies crucial for HF patients with cardiovascular risk factors or established disease.

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1 RA) that mimics endogenous intestinal GLP-1 to exert effects on receptors distributed across multiple organs, including the pancreas, gastrointestinal tract, and cardiac tissue [5]. GLP-1 RAs regulate glucose homeostasis by stimulating insulin secretion and suppressing glucagon release, while also delaying gastric emptying, enhancing satiety, and inducing central appetite suppression to reduce energy intake, thereby achieving dual benefits in glycemic control and weight reduction [6-7]. Initially approved for type 2 diabetes (T2DM) [8] and long-term weight management [9], semaglutide has demonstrated cardiovascular benefits. The MARSO study [10] found that subcutaneous semaglutide reduced major adverse cardiovascular events (MACE)—cardiovascular death, stroke, or myocardial infarction—in T2DM patients with high cardiovascular risk. Recent studies indicate subcutaneous semaglutide may benefit HF patients, particularly obese or T2DM patients with HFpEF, by reducing weight, improving exercise tolerance, and decreasing cardiovascular outcomes [11]. Although multiple studies have evaluated semaglutide' s efficacy and safety in HF, its comprehensive effects require clarification through systematic evidence-based evaluation. This meta-analysis aims to systematically assess the value of semaglutide in HF treatment to provide higher-level evidence for clinical decision-making. This study is registered with PROSPERO (CRD42024609866).

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

1.1 Search Strategy

We systematically searched the Cochrane Library, PubMed, Embase, CNKI, Wanfang Data, and VIP databases for RCTs on subcutaneous semaglutide for HF from inception to November 2, 2024. The search combined MeSH terms and free text, supplemented by screening reference lists and appendices of included studies. Chinese search terms included: 心力衰竭, 心衰, 司美格鲁肽. 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. No restrictions were placed on language, region, sample size, or intervention duration. The PubMed search strategy is detailed in Table 1 .

1.2 Inclusion Criteria

1.2.1 Study Type: RCTs of subcutaneous semaglutide for HF patients.

1.2.2 Participants: HF patients aged >18 years, regardless of obesity or T2DM status.

1.2.3 Intervention: Experimental group received subcutaneous semaglutide at 1 mg/week or 2.4 mg/week; control group received placebo.

1.2.4 Outcome Measures: (1) Primary adverse outcomes: HF rehospitalization, cardiovascular death, all-cause death; (2) Quality of life and exercise tolerance: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and 6-minute walk distance (6-MWD); (3) Safety outcomes: serious adverse events.

Figure 1

Figure 1: Figure 1

1.3 Exclusion Criteria

(1) Non-Chinese or non-English literature; (2) Non-RCTs or animal studies; (3) Conference abstracts, case reports, reviews, letters, or expert opinions; (4) Duplicate publications or studies with unavailable primary outcome data.

1.4 Data Extraction and Risk of Bias Assessment

Two investigators independently screened literature and extracted data, with disagreements resolved by a third investigator. Extracted data included trial name, first author, publication year, follow-up duration, dosage and frequency, participant numbers and characteristics, and outcome measures. Two investigators independently assessed risk of bias using the Cochrane Handbook 5.1.0 RCT tool, evaluating randomization, allocation concealment, blinding, outcome completeness, and selective reporting.

1.5 Statistical Analysis

We used Review Manager 5.3 for data analysis. Dichotomous outcomes were expressed as risk ratio (RR) with 95% confidence interval (CI); continuous outcomes as mean difference (MD) with 95%CI. Heterogeneity was assessed using I^2 and Q tests. Fixed-effects models were used when $P>0.1$ and $I^2<50\%$; otherwise, random-effects models were applied. Clinical heterogeneity was addressed through subgroup or sensitivity analyses. Given the limited number of included studies (n=4), traditional funnel plots or Egger' s tests were not performed. Instead, we searched clinical trial registries and used R 4.4.1 software to calculate fail-safe N tests, with Rosenthal' s threshold of 5k+10 (where k=number of studies). $P<0.05$ was considered statistically significant.

Results

2.1 Literature Search Results and Study Characteristics

The search identified 417 potentially relevant articles. After removing 105 duplicates, 312 articles remained. Following title and abstract screening, 293 were excluded, leaving 19 for full-text review. Ultimately, 4 studies [13-16] met inclusion criteria

. These 4 studies included 6,109 HF patients (3,070 experimental, 3,039 control), with 3,418 (56%) being overweight or obese HFpEF patients. Follow-up duration ranged from 52 weeks to 3.4 years. Study characteristics are summarized in Table 2 .

Figure 2

Figure 2: Figure 2

Figure 5

Figure 3: Figure 5

2.2 Risk of Bias Assessment

The 4 included studies [13-16] comprised mixed RCT evidence: 2 original RCTs [14-15], 1 prespecified subgroup analysis of the SELECT trial [16], and 1 post-hoc analysis of the FLOW trial [13]. All 4 studies [13-16] reported adequate randomization, allocation concealment, and blinding. No incomplete data were reported in 4 studies [13-16]; 1 study [13] had selective reporting; other bias sources were unclear in 4 studies [13-16]

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2.3 Efficacy Outcomes

2.3.1 HF Rehospitalization Risk: Three studies [13-15] reported HF rehospitalization events (n=1,823). Significant heterogeneity existed (P=0.02, I^2=75%). Subgroup analysis by maintenance dose (2.4 mg/week vs 1.0 mg/week) revealed reduced heterogeneity in the 2.4 mg/week group (P=0.35, I^2=0), with significant difference (RR=0.29, 95%CI=0.14~0.58, P=0.0005), indicating semaglutide 2.4 mg/week significantly reduced HF rehospitalization risk. The 1.0 mg/week group showed no significant difference [FIGURE:3].

2.3.2 Cardiovascular Death Risk: Four studies [13-16] reported cardiovascular death events (n=6,109). No heterogeneity was observed (P=0.73, I^2=0). Fixed-effects analysis showed semaglutide reduced cardiovascular death risk compared with placebo (RR=0.75, 95%CI=0.61~0.92, P=0.005) [FIGURE:4].

2.3.3 All-Cause Death Risk: Three studies [14-16] reported all-cause death events (n=5,431). No heterogeneity existed (P=0.81, I^2=0). Fixed-effects analysis demonstrated semaglutide reduced all-cause death risk (RR=0.81, 95%CI=0.67~0.98, P=0.03)

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2.4 Safety Outcomes

Two studies [14-15] reported serious adverse events (n=1,145). Semaglutide reduced serious adverse event risk compared with placebo (RR=0.53, 95%CI=0.41~0.68, P<0.00001). No significant differences were found for discontinuation due to serious adverse events (RR=0.62, 95%CI=0.31~1.22, P=0.17), arrhythmia (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,

Figure 6

Figure 4: Figure 6

Figure 8

Figure 5: Figure 8

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)

. One severe hypoglycemic event occurred in the semaglutide group in KOSIBOROD et al. [15].

2.5 Subgroup Analyses

2.5.1 HFpEF Subgroup Efficacy: Three studies [14-16] reported efficacy outcomes in HFpEF (n=3,418). Semaglutide reduced HF rehospitalization risk (RR=0.41, 95%CI=0.26~0.65, P=0.0001) but showed no significant difference in cardiovascular death (RR=0.80, 95%CI=0.54~1.21, P=0.30) or all-cause death (RR=0.80, 95%CI=0.59~1.09, P=0.15). Two studies [14-15] reported KCCQ-CSS and 6-MWD (n=1,145), showing semaglutide improved KCCQ-CSS (MD=7.58, 95%CI=4.40~10.77, P<0.00001) and 6-MWD (MD=16.91, 95%CI=8.98~24.83, P<0.0001) [FIGURE:7].

2.5.2 Obesity Subgroup Efficacy: Three studies [14-16] reported outcomes in obese HF patients (n=5,431). Semaglutide reduced cardiovascular death (RR=0.75, 95%CI=0.59~0.95, P=0.02) and all-cause death (RR=0.81, 95%CI=0.67~0.98, P=0.03)

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2.5.3 Dosage Subgroup Efficacy: Three studies [14-16] used 2.4 mg/week maintenance dose, while one study [13] used 1.0 mg/week. The 2.4 mg/week dose significantly reduced HF rehospitalization (RR=0.29, 95%CI=0.14~0.58, P=0.0005) and cardiovascular death risk (RR=0.75, 95%CI=0.59~0.95, P=0.02) compared with placebo, while 1.0 mg/week showed no significant difference [FIGURE:3, FIGURE:4].

2.5.4 T2DM Comorbidity Subgroup Efficacy: Two studies [13-14] included T2DM patients, while two [15-16] did not. In HF patients without T2DM, semaglutide reduced HF rehospitalization (RR=0.16, 95%CI=0.04~0.68, P=0.01) and cardiovascular death risk (RR=0.76, 95%CI=0.60~0.97, P=0.03). No significant difference was observed in HF patients with T2DM [FIGURE:9].

2.5.5 Sensitivity Analysis of Subgroup Analyses: Two studies (Deanfield 2024 [16] and Pratley 2024 [13]) lacked important baseline demographic data. Sensitivity analysis revealed that after excluding these studies, significant benefits in the 2.4 mg/week, obesity, and non-T2DM subgroups were reversed .

2.6 Publication Bias Analysis

No completed but unpublished studies were found in clinical trial registries. Rosenthal' s fail-safe N values were 5 for cardiovascular death and 2 for all-cause death, both below the threshold values of 30 and 25, respectively, suggesting that a few unpublished negative studies could affect conclusion robustness. Publication bias cannot be excluded.

Discussion

This meta-analysis of 6,109 HF patients receiving subcutaneous semaglutide suggests the therapy reduces cardiovascular death, all-cause death, and serious adverse events. Subgroup analyses further reveal that semaglutide improves health-related quality of life and exercise tolerance while reducing HF rehospitalization in overweight/obese HFpEF patients. Benefits were also observed in obese and non-T2DM subgroups. A dose-dependent trend was evident: 2.4 mg/week significantly reduced HF rehospitalization and cardiovascular death risk, while 1.0 mg/week showed no significant difference. Notably, 56% of included patients were overweight/obese HFpEF patients, suggesting the primary beneficiary population.

KOSIBOROD et al. [11] pooled analysis of semaglutide in HFmrEF/HFpEF demonstrated superior event risk reduction in subgroups with LVEF $\geq$ 50% or BMI $\geq$ 35 kg/m^2. Age subgroup analysis showed efficacy in both <65 and \$ \$65 year groups, primarily driven by obese patients. These findings suggest potential differential responses in specific populations, particularly regarding applicability to HFrEF and non-obese patients, which remains uncertain.

However, DEANFIELD et al. [16] compared efficacy between overweight/obese HFrEF and HFpEF patients, finding semaglutide superior to placebo in reducing MACE and HF composite events (cardiovascular death/hospitalization or urgent HF visit) regardless of HF subtype, with lower adverse event rates. PRATLEY et al. [13] also found no differential effects across HF subtypes. These findings support semaglutide' s potential applicability across HF subtypes, highlighting its therapeutic potential pending further validation.

Interpretation regarding HFrEF requires caution. Previous studies of liraglutide, another GLP-1 RA, provide important warnings. The LIVE [19] and FIGHT [20] trials in HFrEF patients found that despite weight and glucose reduction, liraglutide increased heart rate without improving LVEF or cardiac contractility, potentially increasing serious cardiac events. Although these trials had short intervention periods (<26 weeks), and differences exist between liraglutide and semaglutide in stability, half-life, and dosing frequency [21], the distinct pathophysiology of HFpEF and HFrEF [43] cautions against extrapolating semaglutide' s benefits to all GLP-1 RAs. The applicability of different GLP-1 RAs to various LVEF categories requires individual careful assessment.

Subgroup analyses by maintenance dose revealed that heterogeneity in HF rehospitalization risk decreased significantly in the 2.4 mg/week group, while the single-study 1.0 mg/week group precluded heterogeneity assessment, suggesting dosage may contribute to heterogeneity. The 2.4 mg/week dose demonstrated superior efficacy over placebo in reducing HF rehospitalization and cardiovascular death, while 1.0 mg/week showed no significant difference, indicating possible dose-dependency. However, the 1.0 mg/week study [13] had the longest follow-up (3.4 years) versus 1-2 years in others, which may influence outcome development. Whether semaglutide' s efficacy is dose-dependent requires future high-quality, long-term, head-to-head comparisons.

Subgroup analysis by T2DM comorbidity showed that semaglutide' s benefits were more pronounced in patients without T2DM. Possible explanations include: (1) The T2DM subgroup included PRATLEY et al. [13] with lower baseline BMI and dosage, potentially diminishing treatment effects despite longer follow-up; (2) The T2DM subgroup had substantially more SGLT-2 inhibitor use at baseline, whose prognostic benefits may confound semaglutide effects; (3) HUSAIN et al. [22] post-hoc analysis found semaglutide' s MACE reduction (HR=0.76, 95%CI=0.62~0.92) was driven primarily by fatal stroke (HR=0.65, 95%CI=0.43~0.97) rather than cardiovascular death. Additionally, a review of GLP-1 RA trials identified exposure time as the primary source of heterogeneity, with longer exposure associated with improved MACE outcomes [23]. Therefore, the non-significant MACE effect in the T2DM subgroup may relate to differential drug exposure across studies, despite using the same long-acting semaglutide formulation. These hypotheses require further validation.

Semaglutide's mechanisms in HF involve multi-target synergistic effects. Animal studies demonstrate reduced extracellular matrix components (Coll5a1, Lama4, Sparc), improved vascular endothelial function and permeability [24], and enhanced mitochondrial function with suppressed NLRP3 inflammasome activation, attenuating pressure overload-induced cardiac hypertrophy [25]. Human studies confirm semaglutide modulates epicardial adipose tissue endocrine activity, reducing circulating fatty acid binding protein 4 (FABP4) and upregulating neutrophil CD88 expression, exerting anti-inflammatory and anti-thrombotic effects [26]. These findings suggest benefits extend beyond obesity to atherosclerotic cardiovascular disease (ASCVD) patients, a major HF risk factor [1]. Key clinical trials [27] consistently show semaglutide reduces weight (primarily fat mass rather than muscle loss [28]), C-reactive protein, NT-proBNP, and systolic blood pressure, indicating anti-inflammatory, cardiac unloading, and hemodynamic benefits beyond weight reduction. Cardiac imaging confirms reversal of cardiac remodeling through reduced left atrial volume, improved left ventricular diastolic function, and decreased right heart load [29].

With increasing HF risk factors (obesity, diabetes, chronic kidney disease) [30-33] and multimorbidity [34], patient-centered individualized strategies are urgently needed. Inflammation, oxidative stress, and endothelial dysfunction contribute to HFpEF pathophysiology [35], with higher BMI and insulin resistance more strongly associated with HFpEF than HFrEF risk [36]. Semaglutide improves β-cell function and insulin secretion in T2DM [37], potentially benefiting HFpEF patients. A 2023 network meta-analysis comparing GLP-1 RAs for weight reduction in obesity found semaglutide had optimal efficacy with low-to-moderate adverse risk [38]. Chinese guidelines recommend GLP-1 RAs with ASCVD benefit evidence as first-line for T2DM patients with ASCVD or high risk [39]. KRISTENSEN et al. [40] meta-analysis of 56,004 T2DM patients across 7 RCTs confirmed GLP-1 RAs reduce cardiovascular outcomes, all-cause death, and renal composite endpoints. However, GLP-1 RA efficacy and safety in HF patients remain unclear, prompting this preliminary exploration.

Unlike HFrEF, which has evidence-based "quadruple therapy"(ARNI/ACEI/ARB, SGLT-2i, β-blocker, MRA) [41-42], HFpEF has limited therapeutic options due to complex pathophysiology [43], with management focusing primarily on comorbidities [44]. This study' s HFpEF subgroup findings suggest subcutaneous semaglutide may become a key therapeutic agent for obese HFpEF patients by improving quality of life, increasing 6-MWD, and reducing HF rehospitalization.

Limitations

(1) Limited number and sample size of included studies (n=4, total n=6,109), constrained by the current evidence base, potentially reducing statistical power and limiting exploration of confounding factors in subgroup analyses. Generalizability is limited, as 56% of participants were overweight/obese HFpEF patients. (2) Weight/BMI changes were not compared due to data extraction difficulties. (3) Variable follow-up duration may influence outcome development. (4) Sensitivity analyses revealed that conclusions for the 2.4 mg/week, obesity, and non-T2DM subgroups heavily depended on the large Deanfield 2024 [16] study with missing baseline data, warranting cautious interpretation. (5) Language bias may exist as only Chinese and English literature was searched.

Conclusion

Current evidence indicates that subcutaneous semaglutide added to standard therapy can effectively and safely reduce cardiovascular death, all-cause death, and serious adverse events in HF patients. It improves health-related quality of life and exercise tolerance while reducing HF rehospitalization in overweight/obese HFpEF patients. Subgroup analyses suggest better efficacy in non-T2DM patients and possible dose-dependency. Due to limited study numbers and populations, these conclusions require verification through larger, multicenter, high-quality studies. Future research should focus on other HF subtypes (e.g., HFrEF) and non-obese patients to explore additional indications.

Author Contributions: LI Xueni contributed to study conception, design, search strategy development, literature screening, data collection, risk of bias assessment, and manuscript writing. LIU Gejing contributed to search strategy development, literature screening, data collection, and risk of bias assessment. LIU Yongming was responsible for quality control, resolving disagreements, overall responsibility, and supervision.

Conflict of Interest: None declared.

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