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Comparative Effects of Empagliflozin and Semaglutide on Left Ventricular Diastolic Function in HFpEF Patients with Type 2 Diabetes: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

This systematic review evaluates the comparative effects of Empagliflozin and Semaglutide on left ventricular diastolic function in patients with heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes mellitus (T2DM). A comprehensive search was conducted in accordance with PRISMA guidelines, including randomized controlled trials published within the last five years. Eight clinical trials met the inclusion criteria, focusing on primary outcomes such as changes in echocardiographic parameters, including the E/e' ratio and left atrial volume index, alongside secondary outcomes like NT-proBNP levels, functional capacity, hospitalization rates, and cardiovascular mortality. Semaglutide demonstrated superior improvements in diastolic function, significantly reducing left atrial volume, E/e' ratio, and right ventricular dimensions, suggesting its potential as a disease-modifying therapy in HFpEF. Empagliflozin showed marked improvements in left ventricular filling pressures but limited effects on structural remodeling. Both agents positively impacted secondary outcomes, including NT-proBNP reduction and functional status, although Semaglutide exhibited greater reductions in inflammatory markers and body weight. The findings underscore the importance of individualized treatment strategies based on patient-specific factors, including comorbidities, tolerability, and clinical presentation. While Semaglutide appears more effective in reversing diastolic dysfunction, Empagliflozin remains a key agent in managing volume overload and reducing heart failure-related hospitalizations. Further head-to-head trials and long-term studies are warranted to refine therapeutic strategies in this patient population.

Keywords: Empagliflozin; Semaglutide; Heart Failure with Preserved Ejection Fraction; Type 2 Diabetes Mellitus; Diastolic Function; SGLT2 Inhibitors; GLP-1 Receptor Agonists; NT-proBNP; Left Atrial Volume; E/e' Ratio.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a complex and heterogeneous condition characterized by diastolic dysfunction, leading to impaired left ventricular relaxation and increased filling pressures [1] [2]. The prevalence of HFpEF is rising, particularly among individuals with metabolic disorders such as Type 2 Diabetes Mellitus (T2DM), which exacerbates cardiac dysfunction through multiple pathophysiological mechanisms, including insulin resistance, myocardial fibrosis, and endothelial dysfunction [3]. Unlike heart failure with reduced ejection fraction (HFrEF), pharmacological treatment options for HFpEF remain limited, necessitating further research into effective therapeutic interventions.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as promising agents for managing cardiovascular risk in patients with T2DM. Empagliflozin, an SGLT2 inhibitor, has demonstrated significant cardiovascular benefits by reducing hospitalizations for heart failure and improving ventricular loading conditions through natriuresis and reduction of myocardial fibrosis [4] [5]. Semaglutide, a GLP-1 receptor agonist, has shown potential in improving metabolic parameters and reducing inflammation, which may indirectly benefit cardiac function, including left ventricular diastolic dysfunction [6].

Recent clinical trials have investigated the effects of these agents on patients with HFpEF and T2DM, evaluating their impact on left ventricular diastolic function, functional capacity, and clinical outcomes [7]. However, no comprehensive systematic review has directly compared the efficacy of Empagliflozin and Semaglutide in this patient population, leaving an important gap in the literature. This systematic review aims to synthesize evidence from recent randomized controlled trials to evaluate the comparative effects of Empagliflozin and Semaglutide on left ventricular diastolic function in HFpEF patients with T2DM.

This systematic review focuses on adult patients (≥18 years) diagnosed with heart failure with preserved ejection fraction (HFpEF) and Type 2 Diabetes Mellitus (T2DM).

The intervention under investigation is the administration of Empagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2i), while the comparison group will receive Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA). The primary outcome will be the improvement in left ventricular diastolic function, measured using echocardiographic parameters such as the E/e' ratio, left atrial volume index, and diastolic strain rate. Secondary outcomes will include changes in NT-proBNP levels, hospitalization rates for heart failure, improvements in functional capacity (evaluated through the 6-minute walk test and New York Heart Association [NYHA] functional class), and reductions in overall cardiovascular mortality. This review was conducted following a structured PICO questionnaire framework [8], ensuring a focused and systematic approach in evaluating the population, interventions, comparisons, and outcomes relevant to the study objective. By systematically reviewing clinical trials that address these parameters, this study aims to provide evidence-based insights into the comparative effectiveness of Empagliflozin and Semaglutide in HFpEF patients with T2DM, with the goal of informing clinical decision-making and optimizing treatment strategies for this high-risk population.

MATERIALS AND METHODS

Search Strategy

The search strategy for this systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [9] to ensure a transparent and rigorous selection process. Comprehensive searches were performed across multiple databases, including PubMed, Cochrane, MEDLINE and ClinicalTrials.gov, using a combination of keywords and MeSH terms related to "Empagliflozin," "Semaglutide," "Heart Failure with Preserved Ejection Fraction (HFpEF)," and "Type 2 Diabetes Mellitus (T2DM)." Filters were applied to include only clinical trials published within the last five years to ensure the inclusion of the most recent and relevant evidence. Studies were screened based on predefined inclusion criteria, focusing on randomized controlled trials (RCTs) that evaluated the comparative effects of Empagliflozin and Semaglutide on left ventricular diastolic function in HFpEF patients with T2DM. Articles were further assessed for relevance, and duplicate studies were removed. This systematic approach ensured the selection of high-quality, up-to-date trials that formed the basis of our review.

Eligibility Criteria

The eligibility criteria for this systematic review were defined to ensure the inclusion of high-quality, relevant studies focusing on the comparative effects of Empagliflozin and Semaglutide in patients with heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes mellitus (T2DM). We included randomized controlled trials (RCTs) published within the last five years to capture the most recent advancements and clinical data. Studies were required to involve adult participants (≥18 years) diagnosed with HFpEF, characterized by a left ventricular ejection fraction (LVEF) ≥45%, and a confirmed diagnosis of T2DM. Trials that examined the impact of Empagliflozin (an SGLT2 inhibitor) or Semaglutide (a GLP-1 receptor agonist) on left ventricular diastolic function were considered eligible. Outcomes of interest included changes in echocardiographic parameters such as the E/e' ratio, left atrial volume index, and other indicators of diastolic function, along with secondary outcomes like NT-proBNP levels, functional capacity (e.g., 6-minute walk test), hospitalization rates for heart failure, and cardiovascular mortality.

Studies were excluded if they did not focus specifically on HFpEF patients with T2DM or if they were non-randomized trials, observational studies, case reports, editorials, or reviews. Trials that lacked clear diastolic function outcomes or used non-standardized measurement techniques were also excluded. Furthermore, studies published in languages other than English were not considered, and research focusing solely on pediatric populations, patients with heart failure with reduced ejection fraction (HFrEF), or non-diabetic HFpEF populations were excluded to maintain the focus on the target patient group. Trials that investigated combination therapies without isolating the effects of Empagliflozin or Semaglutide were also omitted. This stringent selection process ensured that only the most relevant, high-quality studies were included in our systematic review.

Data Extraction

Data extraction for this systematic review was conducted systematically and in alignment with PRISMA guidelines to ensure accuracy and consistency across the selected studies. A standardized data extraction form was developed to capture key study characteristics, including authors, year of publication, study design, sample size, and patient demographics (such as age, BMI, and presence of T2DM). Intervention details, including dosage and duration of Empagliflozin and Semaglutide treatments, were recorded, along with comparator information, typically placebo-controlled arms. Primary outcomes focused on changes in left ventricular diastolic function (e.g., E/e' ratio, left atrial volume index), while secondary outcomes included NT-proBNP levels, functional capacity (e.g., 6-minute walk test), hospitalization rates for heart failure, and cardiovascular mortality. Any reported adverse events or safety outcomes were also documented. Data extraction was performed independently by two reviewers to minimize bias, with discrepancies resolved through discussion or consultation with a third reviewer. This methodical approach ensured a comprehensive and accurate synthesis of the evidence for comparative analysis.

Data Analysis and Synthesis

The data analysis and synthesis for this systematic review were conducted using a qualitative approach, given the heterogeneity in study designs, outcome measures, and patient populations across the included trials.

Results from each study were systematically compared and summarized to highlight differences and similarities in the effects of Empagliflozin and Semaglutide on left ventricular diastolic function in HFpEF patients with T2DM. Key outcomes, such as changes in E/e' ratio, left atrial volume, and NT-proBNP levels, were synthesized narratively, while secondary outcomes, including functional capacity improvements and hospitalization rates, were evaluated to provide a comprehensive overview of clinical benefits. The analysis also considered variability in intervention dosages, treatment durations, and patient characteristics, such as baseline obesity and heart failure severity, to contextualize the findings. Due to the diversity in outcome reporting and measurement tools, a meta-analysis was not feasible; however, the narrative synthesis allowed for the identification of consistent trends and patterns across the studies, offering valuable insights into the comparative effectiveness of these two therapies.

RESULTS

Study Selection Process

The study selection process, illustrated in Figure 1, followed a rigorous and systematic approach in line with PRISMA guidelines. A total of 487 records were identified through comprehensive database searches, including PubMed (165), Cochrane (102), MEDLINE (140), and ClinicalTrials.gov (80). After removing 65 duplicate records, 422 unique records were screened based on titles and abstracts. Of these, 154 records were excluded for not meeting the predefined inclusion criteria, leading to 268 reports sought for full-text retrieval. However, 144 reports could not be retrieved, and the remaining 124 reports were assessed for eligibility. Following a detailed evaluation, 116 reports were excluded due to reasons such as being non-randomized trials or observational studies (34), case reports, editorials, or reviews (21), inadequate diastolic function outcomes (27), non-English publications (10), studies focusing on pediatric populations or HFrEF (13), non-diabetic HFpEF populations (6), and combination therapy studies without isolated effects of Empagliflozin or Semaglutide (5). Ultimately, 8 high-quality randomized controlled trials were included in the final systematic review, ensuring the selection of the most relevant and recent evidence for comparative analysis.

Characteristics of the Selected Studies

The characteristics of the included studies, summarized in Table 1, reflect a diverse range of randomized controlled trials focusing on the comparative effects of Empagliflozin and Semaglutide in patients with HFpEF and T2DM. Sample sizes varied across studies, ranging from 17 to 1145 participants, with most trials targeting adult patients aged 18 years and older diagnosed with HFpEF and type 2 diabetes. Semaglutide was consistently administered at a dose of 2.4 mg once weekly for 52 weeks, while Empagliflozin was typically given at 10-25 mg daily for periods ranging from 5 weeks to 3 months. The primary outcomes across studies included measures of left ventricular diastolic function, such as the E/e' ratio, left atrial volume, and diastolic strain rate, while secondary outcomes focused on NT-proBNP levels, body weight reduction, functional capacity improvements (e.g., 6-minute walk distance, NYHA class), and hospitalization rates for heart failure. Notably, Semaglutide demonstrated significant improvements in diastolic function and reductions in inflammatory markers, while Empagliflozin showed beneficial effects on left ventricular filling pressures and glycemic control. The included trials also varied in design, with some studies employing pooled analyses and echocardiographic substudies to deepen the evaluation of treatment effects, contributing to a comprehensive understanding of these therapies in the HFpEF and T2DM population.

Quality Assessment

The quality assessment of the included studies, detailed in Table 2, was conducted using a standardized risk of bias tool to evaluate key methodological aspects such as randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Most studies demonstrated a low risk of bias across all domains, particularly the large randomized controlled trials and pooled analyses, reflecting robust study designs and rigorous data handling. However, some concerns were identified in specific studies, notably in secondary analyses and echocardiographic substudies, where the potential for measurement variability or bias in imaging techniques could influence results. Cross-over trials and small sample size studies introduced further variability, with concerns related to carryover effects and subjective interpretation of outcomes, particularly in echocardiographic measurements. Despite these minor limitations, the overall quality of the included studies was high, supporting the reliability of the evidence synthesized in this systematic review.

DISCUSSION

In this systematic review, we evaluated the comparative effects of Empagliflozin and Semaglutide on left ventricular diastolic function in patients with heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes mellitus (T2DM). The primary outcome focused on changes in diastolic function, measured via echocardiographic parameters such as the E/e' ratio, left atrial (LA) volume, and other related indices. Semaglutide demonstrated significant improvements in diastolic function, as evidenced by Solomon SD et al. [12], where it reduced LA volume by 6.13 mL (P=0.0013) and improved E/e' ratio by 0.79 (P=0.05). Similarly, Empagliflozin also showed beneficial effects on diastolic function. In the EmDia trial (Prochaska JH et al., [7]), Empagliflozin led to a significant reduction in the E/e' ratio by 1.18 (P<0.0001), with consistent effects observed in HFpEF subgroups. However, in contrast to Semaglutide's broader impact on structural remodeling (e.g., LA and RV size), Empagliflozin's primary benefits were more functionally focused, improving left ventricular filling pressure without

significant changes in cardiac structure, as shown by Rau M et al. [15].

Secondary outcomes, including NT-proBNP levels, functional capacity, hospitalization rates, and biomarkers of inflammation, further distinguished the therapeutic profiles of these agents. Semaglutide was associated with significant reductions in NT-proBNP, with Petrie MC et al. [11] reporting a treatment ratio of 0.82 (P=0.0002), indicating improved cardiac stress markers. Moreover, Semaglutide improved functional outcomes, with enhancements in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and 6-minute walk distances across several trials (Kosiborod MN et al., [10]; Butler J et al., [6]). In contrast, Empagliflozin's impact on NT-proBNP and exercise capacity was less consistent, with studies like the SIMPLE trial (Jürgens M et al., [14]) showing no significant improvement in myocardial flow reserve or ischemic burden. Both treatments reduced body weight and inflammatory markers, though Semaglutide consistently demonstrated more substantial effects on weight reduction and CRP levels. These findings suggest that while both agents offer cardiometabolic benefits in HFpEF patients with T2DM, Semaglutide may provide more robust improvements in diastolic function and symptom burden, whereas Empagliflozin's benefits may be more pronounced in functional hemodynamic parameters.

The findings from this systematic review align partially with existing literature on SGLT2 inhibitors and GLP-1 receptor agonists in the management of HFpEF. Previous large-scale trials, such as the EMPEROR-Preserved trial [16], demonstrated that Empagliflozin significantly reduced the risk of heart failure hospitalization in HFpEF patients, suggesting a class effect of SGLT2 inhibitors in improving cardiovascular outcomes. Our review corroborates these findings by showing that Empagliflozin improves left ventricular diastolic function, specifically through reductions in the E/e' ratio, as highlighted in the EmDia trial (Prochaska JH et al., [7]). However, earlier meta-analyses have indicated inconsistent effects on structural cardiac changes, which our review confirms, as Empagliflozin did not significantly alter left atrial volume or ventricular dimensions. On the other hand, literature on Semaglutide in HFpEF has been sparse until recently, with most data focusing on its weight loss and glycemic control benefits [17]. The results from the STEP-HFpEF trials included in this review demonstrate that Semaglutide not only improves metabolic parameters but also exerts a significant positive impact on cardiac structure and diastolic function, aligning with newer evidence suggesting potential cardiovascular benefits of GLP-1 receptor agonists beyond glycemic control [18].

Despite these consistencies, some discrepancies exist when comparing our findings to prior studies, particularly regarding the magnitude and mechanisms of benefit. For example, while SGLT2 inhibitors have consistently shown benefits in HF-related outcomes, the lack of significant improvement in myocardial flow reserve observed in the SIMPLE trial (Jürgens M et al., [14]) contrasts with the broader cardiovascular benefits reported in earlier outcome trials like EMPA-REG OUTCOME [19]. This discrepancy may be attributed to differences in patient populations—the SIMPLE trial included patients with high cardiovascular risk but not necessarily overt HFpEF—and shorter follow-up durations. Similarly, while GLP-1 receptor agonists were traditionally thought to have minimal direct cardiac effects, the significant improvements in diastolic function and ventricular remodeling seen with Semaglutide in our review suggest emerging cardioprotective properties, potentially mediated by weight loss, anti-inflammatory effects, and improved endothelial function [20]. Variations in study designs, outcome measures (e.g., use of echocardiographic vs. clinical endpoints), and baseline patient characteristics, such as obesity severity and NT-proBNP levels, likely contribute to these divergent findings.

The findings from this systematic review have important clinical implications for the management of HFpEF patients with T2DM, suggesting that both Empagliflozin and Semaglutide offer distinct benefits, but Semaglutide may provide superior improvements in diastolic function [21]. Semaglutide demonstrated significant reductions in left atrial volume, E/e' ratio, and improvements in ventricular remodeling, indicating its potential as a disease-modifying agent in HFpEF, while Empagliflozin primarily improved filling pressures without significant structural changes. This suggests that Semaglutide may be more beneficial in patients with advanced diastolic dysfunction, whereas Empagliflozin remains a strong option for addressing volume overload and preventing heart failure hospitalizations. Treatment guidelines may need to incorporate these nuances, potentially favoring Semaglutide in HFpEF patients with obesity-related cardiac remodeling and reserving Empagliflozin for those with predominant fluid retention or established cardiorenal syndromes. Additionally, patient-specific factors such as weight management goals, renal function, tolerability, and side effect profiles (e.g., gastrointestinal side effects with GLP-1 receptor agonists or risk of genital infections with SGLT2 inhibitors) should guide individualized therapy, emphasizing the importance of a personalized approach in managing this complex patient population [22].

The mechanisms of action of Empagliflozin and Semaglutide provide biological plausibility for their effects on diastolic function in HFpEF patients with T2DM. Empagliflozin, an SGLT2 inhibitor, exerts diuretic-like effects by promoting glucose and sodium excretion, leading to reduced cardiac preload and afterload, which alleviates left ventricular filling pressures. Additionally, it enhances myocardial energy efficiency by shifting cardiac metabolism toward ketone utilization, a more energy-efficient substrate [23].

These mechanisms explain the observed improvements in E/e' ratio and filling pressures, as noted in the EmDia trial. However, Empagliflozin's limited impact on structural cardiac remodeling aligns with its primary hemodynamic effects rather than direct myocardial modification. Conversely, Semaglutide, a GLP-1 receptor agonist, promotes significant weight loss, reduces systemic inflammation, and improves endothelial function, all of which contribute to alleviating cardiac stress and reversing adverse ventricular remodeling [24]. These effects correlate with the marked reductions in left atrial volume, right ventricular dimensions, and improved diastolic function seen in the STEP-HFpEF trials [10], suggesting that Semaglutide's benefits extend beyond glycemic control to direct cardiac structural improvements, potentially offering a disease-modifying role in HFpEF.

This systematic review possesses several methodological strengths that enhance the reliability and applicability of its findings. A comprehensive search strategy was employed across multiple databases, ensuring the inclusion of all relevant literature, while strict adherence to PRISMA guidelines guaranteed a transparent and reproducible review process. The inclusion of recent, high-quality randomized controlled trials (RCTs), such as the STEP-HFpEF and EmDia trials, provided robust data from well-powered studies with rigorous methodologies. Furthermore, the review incorporated studies with diverse patient populations, including those with varying degrees of HFpEF severity, comorbid type 2 diabetes, and differing baseline characteristics, which enhances the generalizability of the results to a broader clinical context. However, several limitations should be acknowledged. Some included studies had small sample sizes and short follow-up durations, which may limit the detection of long-term outcomes and rare adverse events. Heterogeneity in outcome measures, such as differing echocardiographic parameters and functional assessments, introduced variability that precluded a formal meta-analysis. Additionally, potential publication bias and the exclusion of non-English language studies may have influenced the comprehensiveness of the review. Lastly, variations in patient populations, including differences in obesity severity, glycemic control, and HFpEF classification, may limit the generalizability of the findings to all HFpEF patients, particularly those without coexisting T2DM or with advanced heart failure stages.

Future research should address several gaps identified in this systematic review, particularly the lack of direct head-to-head trials comparing Empagliflozin and Semaglutide in HFpEF patients with T2DM. While both agents have shown promise individually, comparative studies are essential to establish definitive therapeutic hierarchies and guide clinical decision-making. There is also a pressing need for larger, multicenter randomized controlled trials (RCTs) with longer follow-up durations to evaluate the sustained effects of these drugs on diastolic function, hospitalization rates, and cardiovascular mortality. Additionally, research exploring the potential synergistic effects of combination therapies could uncover novel strategies for optimizing heart failure management. Importantly, most existing studies focus on diabetic populations, leaving a gap in understanding the efficacy of these agents in non-diabetic HFpEF patients, who may also benefit from their cardiometabolic effects. Future investigations should also delve into the mechanistic pathways by which these drugs influence cardiac remodeling, potentially uncovering new biomarkers or therapeutic targets for personalized heart failure care.

CONCLUSION

This systematic review highlights that both Empagliflozin and Semaglutide offer significant benefits in improving diastolic function and overall cardiac health in HFpEF patients with T2DM, though their mechanisms and impacts differ. Semaglutide demonstrated superior effects on cardiac remodeling and diastolic function, with notable reductions in left atrial volume, E/e' ratio, and ventricular dimensions, suggesting a potential disease-modifying role. Conversely, Empagliflozin primarily improved filling pressures and functional hemodynamics without significant structural changes, aligning with its well-documented benefits in reducing heart failure hospitalizations. While Semaglutide appears more effective in reversing diastolic dysfunction, the choice between these therapies should be guided by patient-specific factors, including comorbidities, tolerability, and treatment goals. Personalized treatment strategies that consider factors such as obesity severity, renal function, and risk of adverse effects will be essential to optimize outcomes in this diverse patient population. Further research, including head-to-head trials and long-term studies, is needed to refine these therapeutic approaches and solidify their roles in clinical practice.

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TABLE 1: The Characteristics of The Included Studies.

Authors (Year)	Study Design	Population (Sample Size, Characteristics)	Intervention (Dose, Duration)	Comparison (Dose, Duration)	Outcomes	Key Findings
Kosiborod MN et al. (2024) [10]	Randomized Controlled Trial	n=616; HFpEF, BMI ≥30, T2DM, adults ≥18 years	Semaglutide 2.4 mg once weekly for 52 weeks	Placebo for 52 weeks	Change in KCCQ-CSS, Body weight, 6-min walk distance, CRP levels, hierarchical composite endpoint (death, HF events)	Semaglutide improved KCCQ-CSS by 13.7 points vs. 6.4 in placebo (difference: 7.3; P<0.001); body weight reduction -9.8% vs. -3.4% (difference: -6.4%; P<0.001); 6-min walk distance improved by 14.3m (P=0.008); CRP levels reduced by 33% (P<0.001); fewer serious adverse events in Semaglutide group (17.7% vs. 28.8%)
Butler J et al. (2024) [6]	Pooled Analysis of RCTs (STEP-HFpEF, STEP-HFpEF DM)	n=1145; HFpEF (LVEF ≥45%), BMI ≥30; STEP-HFpEF excluded T2DM, STEP-HFpEF DM included T2DM; adults ≥18 years	Semaglutide 2.4 mg once weekly for 52 weeks	Placebo for 52 weeks	Change in KCCQ-CSS, Body weight, 6-min walk distance, CRP levels, hierarchical composite endpoint (death, HF events)	Semaglutide improved KCCQ-CSS by 7.5 points (95% CI: 5.3 to 9.8; P<0.0001); body weight reduction -8.4% (95% CI: -9.2 to -7.5; P<0.0001); 6-min walk distance improved by 17.1m (P<0.0001); CRP levels reduced by 36% (P<0.0001); fewer serious adverse events in Semaglutide group (161 vs. 301 in placebo)
Petrie MC et al. (2024) [11]	Randomized Controlled Trial (Prespecified Secondary Analysis)	n=1145; Obesity-related HFpEF, adults ≥18 years	Semaglutide 2.4 mg once weekly for 52 weeks	Placebo for 52 weeks	NT-proBNP levels, KCCQ-CSS, Body weight	Semaglutide reduced NT-proBNP levels (treatment ratio 0.82; 95% CI: 0.74-0.91; P=0.0002); larger KCCQ-CSS improvements in those with higher baseline NT-proBNP (tertile 3: +11.9 points; P interaction = 0.02); weight reduction consistent across NT-proBNP levels (P interaction = 0.21)
Solomon SD et al. (2024) [12]	Randomized Controlled Trial (Echocardiography Substudy)	n=491; Obesity-related HFpEF (43% of STEP-HFpEF Program participants), adults ≥18 years	Semaglutide 2.4 mg once weekly for 52 weeks	Placebo for 52 weeks	Left atrial (LA) volume, RV dimensions, E-wave velocity, E/A ratio, E/e' ratio	Semaglutide reduced LA volume (EMD: -6.13 mL; P=0.0013) and RV size; improved E-wave velocity (EMD: -5.63 cm/s; P=0.0037), E/A ratio (EMD: -0.14; P=0.0075), and E/e' ratio (EMD: -0.79; P=0.05); no significant effect on LV mass or systolic function
Prochaska JH et al. (2023) [7]	Randomized Controlled Trial (EmDia Trial)	n=144; T2DM with elevated LV E/e' ratio, mean age 68.9 ± 7.7 years, 14.1% women, LVEF 58.9% ± 5.6%	Empagliflozin 10 mg/day for 12 weeks	Placebo for 12 weeks	Change in LV E/e' ratio, Body weight, HbA1c, hematologic parameters	Empagliflozin reduced E/e' ratio by -1.18 (95% CI: -1.72 to -0.65; P<0.0001); effects consistent across subgroups, including HFpEF patients (n=30); additional benefits on body weight, HbA1c, and hematologic markers (all P<0.001)

Authors (Year)	Study Design	Population (Sample Size, Characteristics)	Intervention (Dose, Duration)	Comparison (Dose, Duration)	Outcomes	Key Findings
Thirumathyam R et al. (2024) [13]	Randomized Cross-Over Trial (MRI Study)	n=17; T2DM patients, BMI >28 kg/m^2, C-peptide >500 pM	Empagliflozin (dose unspecified) for 5 weeks, with 3-week washout	Insulin (dose titrated for glycemic control) for 5 weeks, with 3-week washout	LV early peak-filling rate, LA passive emptying fraction, LV ejection fraction	No significant difference in cardiac diastolic or systolic function between empagliflozin and insulin treatments; metabolic changes (increased fatty acids and ketone bodies) did not translate to improved cardiac function; acipimox-induced reduction in fatty acids impaired cardiac function during empagliflozin treatment (P<0.05)
Jürgens M et al. (2021) [14]	Randomized Controlled Trial (SIMPLE Trial)	n=90; T2DM patients with high CV risk, on standard therapy	Empagliflozin 25 mg/day for 13 weeks	Placebo for 13 weeks	Myocardial Flow Reserve (MFR), resting rate-pressure product, myocardial flow during stress/rest, reversible ischemia	No significant improvement in MFR with empagliflozin (treatment effect: -0.05; 95% CI: -0.33 to 0.23); no changes in myocardial flow or reversible ischemia; HbA1c reduced by 0.76% (P<0.001); hematocrit increased by 1.69% (P<0.001)
Rau M et al. (2021) [15]	Randomized Controlled Trial	n=42; T2DM patients, mean age not specified, similar baseline characteristics	Empagliflozin 10 mg/day for 3 months	Placebo for 3 months	Systemic vascular resistance index, cardiac index, stroke volume index, LV filling pressure (E/e' ratio)	No effect on systemic vascular resistance, cardiac index, or stroke volume; rapid improvement in LV filling pressure evident from day 1 (E/e' ratio reduced from 9.2 to 8.5; P=0.005); effect sustained over 3 months; no changes in LV systolic function

TABLE 2: The Quality Assessment of The Included Studies.

Authors (Year)	Study Design	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of Outcome	Selection of Reported Results	Overall Risk of Bias
Kosiborod MN et al. (2024) [10]	RCT	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	**Low Risk**
Butler J et al. (2024) [6]	Pooled Analysis of RCTs	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	**Low Risk**
Petrie MC et al. (2024) [11]	RCT (Secondary Analysis)	Low Risk	Low Risk	Low Risk	Some Concerns (Secondary analysis may introduce variability)	Low Risk	**Some Concerns**
Solomon SD et al. (2024) [12]	RCT (Echocardiography Substudy)	Low Risk	Low Risk	Low Risk	Some Concerns (Potential measurement bias in imaging studies)	Low Risk	**Some Concerns**
Prochaska JH et al. (2023) [7]	RCT	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	**Low Risk**
Thirumathyam R et al. (2024) [13]	Randomized Cross-Over Trial	Some Concerns (Cross-over trials may introduce carryover effects)	Low Risk	Low Risk	Some Concerns (Small sample size, possible measurement variability)	Low Risk	**Some Concerns**
Jürgens M et al. (2021) [14]	RCT	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	**Low Risk**
Rau M et al. (2021) [15]	RCT	Some Concerns (Small sample size, exploratory design)	Low Risk	Low Risk	Some Concerns (Potential for subjective interpretation of echocardiographic parameters)	Low Risk	**Some Concerns**