THE EFFICIENCY SEMAGLUTIDE FOR OBESITY WITH DIABETES WOMAN : REVIEW

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ABSTRAK
Obesitas merupakan suatu kondisi yang terjadi ketika kuantitas jaringan lemak tubuh dibandingkan dengan berat tubuh total lebih baik dari standar, atau suatu kondisi di mana terjadi penumpukan lemak tubuh yang berlebih sehingga berat badan seseorang jauh di atas standar. Wanita lebih besar daripada pria, wanita memiliki komposisi lemak tubuh yang lebih tinggi daripada pria. Komposisi lemak tubuh lebih tinggi dibandingkan dengan pria, sehingga wanita lebih rentan terhadap obesitas, yang berhubungan dengan risiko obesitas dan diabetes. Dari masalah ini Semaglutide telah menunjukkan efikasi dalam mengurangi berat badan pada pasien dengan gagal jantung terkait obesitas dengan fraksi ejeksi terjaga (HFpEF), terutama pada wanita. Metode yang digunakan pada penelitian ini berupa review jurnal dengan menganalisis hasil review jurnal dengan kata kunci serta tahun terbit. Mendapatkan hasil semaglutide 2,4 mg, dibandingkan dengan plasebo, secara signifikan memperbaiki KCCQ-CSS dan mengurangi berat badan sebesar 9,6% pada wanita dan 7,2% pada pria. Kedua jenis kelamin mengalami peningkatan jarak tempuh berjalan kaki 6 menit dan titik akhir gabungan dari kematian karena sebab apa pun, kejadian gagal jantung, perubahan KCCQ-CSS, dan 6MWD, dengan lebih sedikit kejadian buruk serius yang dilaporkan dengan semaglutide. Temuan ini menggarisbawahi potensi manfaat semaglutide dalam mengelola HFpEF terkait obesitas, yang menunjukkan peran terapeutiknya tanpa memandang jenis kelamin.

Kata kunci : diabetes perempuan, obesitas, semaglutide

ABSTRACT
Obesity is a condition that occurs when the quantity of body fat tissue compared to total body weight is better than the standard, or a condition in which there is an accumulation of excess body fat so that a person's weight is far above the standard. Women are larger than men, women have a higher body fat composition than men. The composition of body fat is higher than that of men, so women are more susceptible to obesity, which is associated with the risk of obesity and diabetes. From this problem Semaglutide has shown efficacy in reducing body weight in patients with obesity-related heart failure with preserved ejection fraction (HFpEF), especially in women. The method used in this study was a journal review by analyzing the results of journal reviews with keywords and year of publication. Getting the results of semaglutide 2.4 mg, compared to placebo, significantly improved KCCQ-CSS and reduced body weight by 9.6% in women and 7.2% in men. Both sexes experienced improvements in 6-minute walk distance and the composite endpoint of all-cause death, heart failure events, KCCQ-CSS change, and 6MWD, with fewer serious adverse events reported with semaglutide. These findings underscore the potential benefit of semaglutide in managing obesity-associated HFpEF, suggesting its therapeutic role regardless of sex.

Keywords *: diabetes woman, obesity, semaglutide*

INTRODUCTION

Obesity is a condition that occurs when the quantity of body fat tissue compared to total body weight is better than standard, or a condition in which there is an accumulation of excess body fat so that a person's weight is far above standard (Jin et al., 2023). Obesity can occur because of an imbalance between energy from food intake higher greater than the energy used by the body (Septiyanti & Seniwati, 2020) Obesity is a widespread, chronic, and relapsing condition that necessitates long-term management. It has clinical complications that impact

nearly every organ system, leading to significant effects on morbidity, mortality, and healthcare costs is substantial. Lifestyle modification is the recommended cornerstone of treatment for individuals with overweight or obesity, but it generally results in only modest weight loss, which is then often regained (Wadden et al., 2020). This is caused by metabolic adaptations that encourage gradual weight regain, making it difficult to maintain the initial weight loss. Pharmacological treatments for obesity can be a valuable addition to lifestyle interventions (Wadden et al., 2020). However, until recently, available medications have only provided moderate weight loss beyond what is achieved through lifestyle changes alone (Hall et al., 2021)

Women are larger than men, women have a higher body fat composition than men. Body fat composition is higher compared with men, so women are more prone to obesity, which is associated with the risk of obesity and diabetes (komariah & Rahayu, 2020). Semaglutide is a powerful, long-acting glucagon-like peptide-1 (GLP-1) analog that is administered once weekly. Semaglutide treatment effect in people with obesity clinical trial program is assessing the efficacy of a weekly subcutaneous dose of 2.4 mg semaglutide in individuals with overweight or obesity (Kushner et al., 2021). The purpose of this review is to describe the study design and clinical outcomes of published clinical trials of the STEP program, discuss the clinical implications of the data and the practicality of using semaglutide 2.4 mg in individuals with obesity, and place the program in the context of the current and future landscape of obesity pharmacotherapy for women (Kim et al., 2022).

METHOD

The method used was a journal review following the PRISMA guidelines to identify studies to be included in our meta-analysis (Salameh et al., 2020). The study was conducted at the University of Lampung, with a processing time of June 20 to July 7, 2024. The data we used were searched by searching Sciendirect, Google Scholar, Wiley, PubMed, Cochrane Library, Embase databases, by classifying terms such as semaglutide, weight loss, overweight, and obesity. Using included articles that met the following criteria: (1) randomized trials with a placebo-controlled design for semaglutide treatment, (2) studies involving patients with overweight or obesity, and (3) studies involving adult humans without a diagnosis of diabetes. Data were reviewed for possible inclusion in the meta-analysis. We manually reviewed the references of the identified studies to find additional potential studies for inclusion. After identifying relevant studies, we extracted data related to our meta-analysis. This includes the study name, year of publication, study population, semaglutide dose, study duration, weight loss efficacy outcomes, and reported side effects/adverse events.

RESULT

Efficacy Parameters without Diabetes

This meta-analysis demonstrated significant improvements in various weight-related parameters with semaglutide. Compared to placebo, once weekly semaglutide resulted in a significant reduction in percentage body weight change, with a mean difference (MD) of -11.49% and a 95% confidence interval (CI) of -13.12 to -9.86 ($p < 0.0001$) (Kommu & Berg, 2024). Similarly, the reduction in body weight in kilograms was also significant, with an MD of -11.74 kg and a 95% CI of -13.53 to -9.94 ($p < 0.0001$). The pooled odds ratio (OR) for a body weight reduction of at least 5% with once-weekly semaglutide compared to placebo was 8.43 (95% CI of 5.17 to 13.75, $p < 0.0001$), for a 10% reduction was 11.13 (95% CI of 7.87 to 15.75, $p < 0.0001$), for a 15% reduction was 14.37 (95% CI of 8.79 to 23.50, $p < 0.0001$), and for a 20% reduction was 16.57 (95% CI of 9.33 to 29.42, $p < 0.0001$). Additionally, once

weekly semaglutide significantly reduced BMI and waist circumference, with MDs of -4.18 kg/m² (95% CI of -4.84 to -3.52, p < 0.0001) and -9.06 cm (95% CI of -10.33 to -7.79, p < 0.0001), respectively. These results indicate significant beneficial outcomes in these weight-related parameters with semaglutide use. Our study also showed improvements in other parameters with once weekly semaglutide compared to placebo. HbA1C levels showed a small improvement with a change of -0.30 (95% CI of -0.31 to -0.29, p < 0.0001). C-reactive protein (CRP) levels decreased by -38.33% (95% CI -48.22 to -28.45, p < 0.0001). Systolic and diastolic blood pressures also improved, with changes of -4.32 mmHg (95% CI -5.42 to -3.22, p < 0.0001) and -2.01 mmHg (95% CI -3.19 to -0.82, p = 0.0009), respectively. These improvements may confer additional benefits with semaglutide (Behzadmehr & Rezaie-Keikhaie, 2022).

We also analyzed changes in the lipid profile comparing once-weekly subcutaneous semaglutide to placebo. Semaglutide showed favorable changes in the lipid panel: total cholesterol decreased by -4.48% (95% CI -6.01 to -2.95), LDL cholesterol by -5.01% (95% CI -7.28 to -2.74), triglycerides by -16.77% (95% CI -18.93 to -14.61), VLDL by -16.67% (95% CI -17.70 to -15.65), and free fatty acids by -14.93% (95% CI -16.77 to -13.08), all statistically significant with p < 0.0001. The percentage change in HDL cholesterol was 1.39% (95% CI -0.60 to 3.38), which was not statistically significant (p = 0.17). The improvements seen in these parameters may provide additional benefits with semaglutide. Additionally, we analyzed changes in the lipid profile comparing once-weekly subcutaneous semaglutide to placebo, as shown in the supporting information (Davies et al., 2021) (Kommu & Berg, 2024). Semaglutide resulted in favorable changes in the lipid panel: the mean difference (MD) in the percentage change in total cholesterol was -4.48 (95% CI -6.01 to -2.95), LDL cholesterol was -5.01 (95% CI -7.28 to -2.74), triglycerides was -16.77 (95% CI -18.93 to -14.61), VLDL was -16.67 (95% CI -17.70 to -15.65), and free fatty acids was -14.93 (95% CI -16.77 to -13.08), all statistically significant with p < 0.0001. The percentage change in HDL cholesterol was 1.39 (95% CI -en et al., 2021)0.60 to 3.38), which was not statistically significant (p = 0.17).

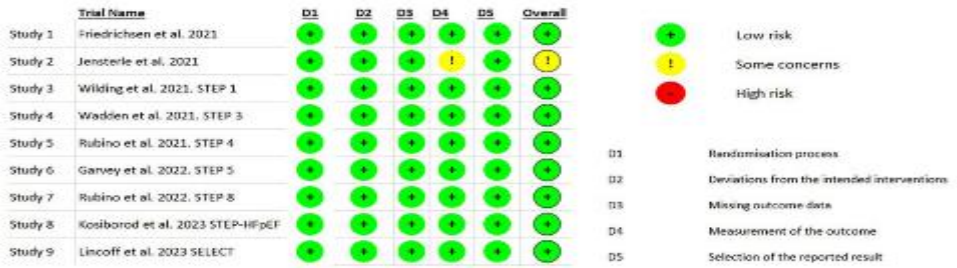


Figure 1. The Risk Of Bias For The Nine Studies Was Assessed Using Version 2 Of The Cochrane Risk-Of-Bias Tool (ROB2)

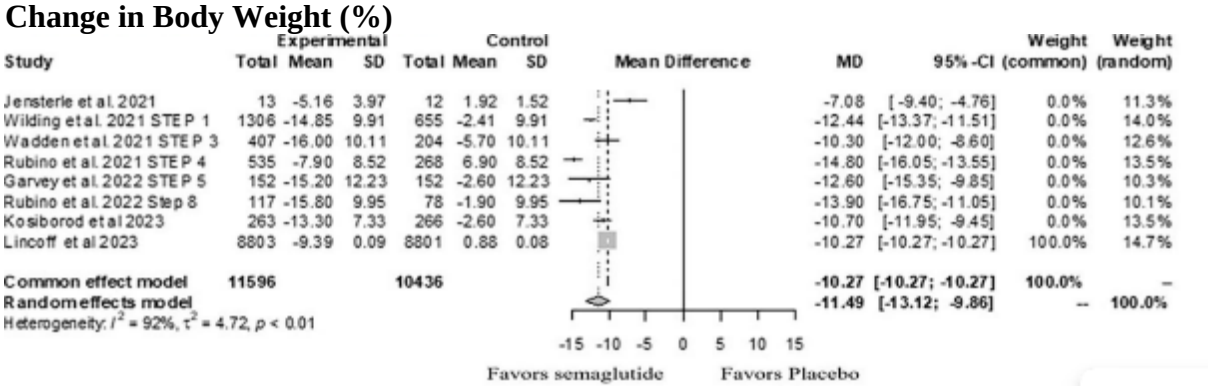


Figure 2. Forest Plots Illustrate The Change In Body Weight As A Percentage (A) And In Kilograms (B) In Patients With Overweight Or Obesity Without Diabetes Militus Treated With Once Weekly Semaglutide Compared To Placebo. SD Refers To Standard Deviation, MD To Mean Difference, And CI To Confidence Interval

While semaglutide showed significant improvements in weight loss parameters, a major limiting factor noted in most studies was gastrointestinal side effects (Quddos et al., 2023a). Our study found that, compared to placebo, the percentage of patients experiencing nausea and vomiting with once weekly semaglutide was significantly higher, with odds ratios (OR) of 4.06 (95% CI 3.43 to 4.81, p < 0.0001) for nausea and 4.43 (95% CI 3.48 to 5.63, p < 0.0001) for vomiting. The ORs for diarrhea and constipation were also significantly higher at 2.10 (95% CI 1.77 to 2.49, p < 0.0001) and 2.43 (95% CI 2.01 to 2.94, p < 0.0001), respectively. Additionally, the ORs for gallbladder disorders and cholelithiasis were elevated with semaglutide compared to placebo, at 1.26 (95% CI 1.06 to 1.50, p = 0.010) for gallbladder disorders and 2.06 (95% CI 1.04 to 4.08, p = 0.038) for cholelithiasis. Despite these side effects, the OR for a serious adverse event with once weekly semaglutide was 1.06 (95% CI 0.66 to 1.71, p = 0.82), which was not statistically significant (Garvey et al., 2022). However, the percentage of participants discontinuing semaglutide due to adverse events was significantly higher, with an OR of 2.22 (95% CI 2.03 to 2.43, p < 0.0001), and discontinuation due to gastrointestinal side effects was also significantly higher, with an OR of 3.77 (95% CI 2.25 to 6.33, p < 0.0001).

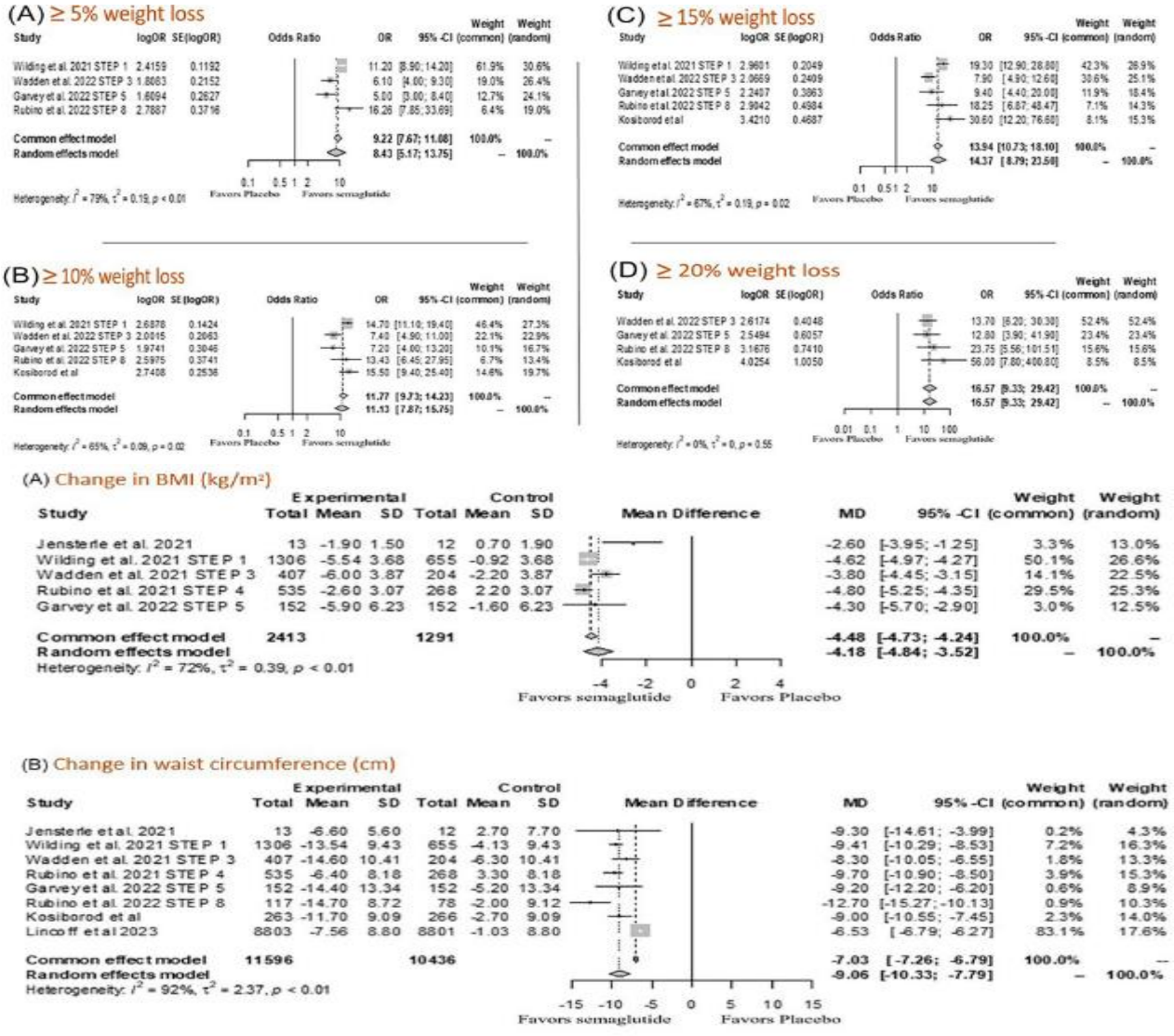


Figure 4. Forest Plots Illustrate The Change In BMI (A) And Waist Circumference (B) In Patients With Overweight Or Obesity Without Diabetes Mellitus Treated With Once Weekly Semaglutide Compared To Placebo. BMI Stands For Body Mass Index, SD For Standarddeviation, MD For Mean Difference, And CI For Confidence Interval

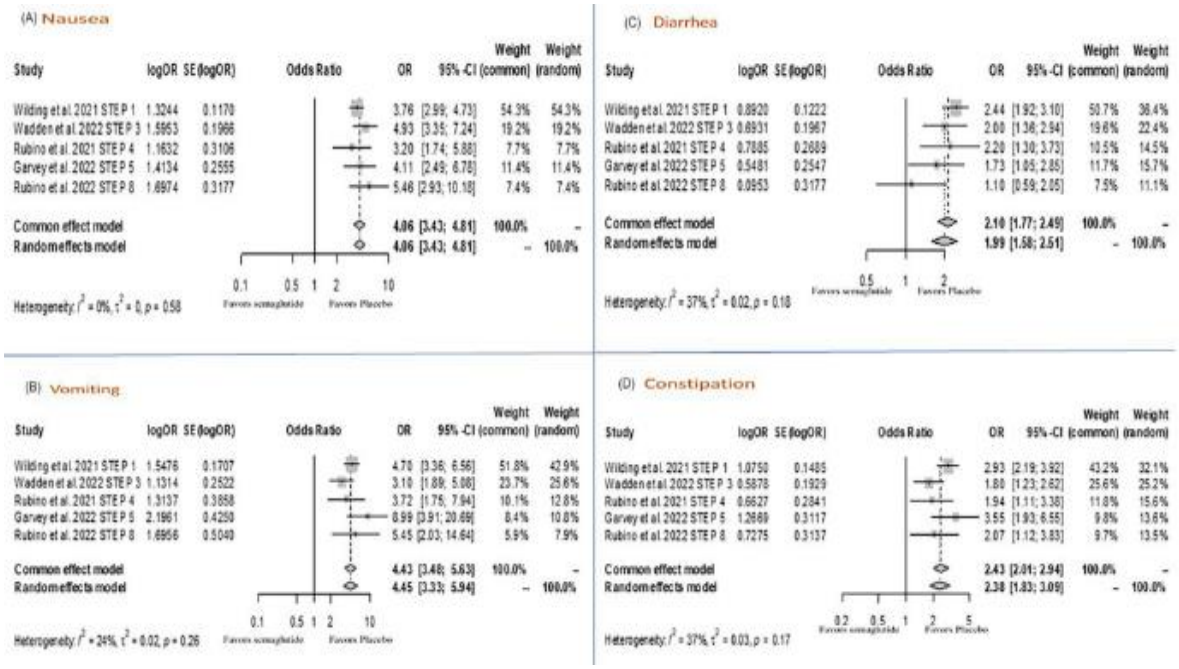


Figure 5. Forest Plots Illustrate The Gastrointestinal Side Effects Of Nausea (A), Vomiting (B), Diarrhea (C), And Constipation (D) In Patients With Overweight Or Obesity Without Diabetes Mellitus Treated With Once Weekly Semaglutide Compared To Placebo. OR Refers To Odds Ratio And CI To Confidence Interval

Various mechanisms contribute to the weight loss benefits of semaglutide. It activates GLP-1 receptors in the gut and pancreas, slowing gastric emptying and inhibiting glucagon release, which suppresses appetite (Newsome et al., 2021). Additionally, semaglutide activates GLP-1 receptors in the brain's hypothalamus, reducing hunger, curbing food cravings, and increasing satiety, thus helping to regulate food intake. Semaglutide stands out among GLP-1 receptor agonists for its notable weight loss effects, as demonstrated in several studies. The SUSTAIN 3 trial, conducted over 56 weeks, showed semaglutide's superiority over exenatide in reducing body weight. Similarly, the SUSTAIN 7 trial confirmed semaglutide's superiority to dulaglutide in weight reduction, while the SUSTAIN 10 trial demonstrated its superiority over liraglutide. These trials have made semaglutide a favorable option among GLP-1 receptor agonists for weight loss. Numerous other trials have consistently demonstrated semaglutide's weight-reducing effects in individuals with overweight or obesity, both with and without diabetes mellitus (DM).

As a result, the US Food and Drug Administration (FDA) approved semaglutide injections (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight, alongside at least one weight-related ailment such as high blood pressure, type 2 DM, or elevated cholesterol levels. This approval is accompanied by recommendations for use with a calorie-restricted diet and increased physical activity. Despite the weight loss benefits, gastrointestinal side effects are common with semaglutide. These side effects, while prevalent, generally range from mild to moderate in intensity. Considering these gastrointestinal side effects, the use of semaglutide in certain patients prone to these side effects remains a concern. A comprehensive analysis of the efficacy and side effects of once weekly semaglutide is needed to fully understand its benefits and risks. Previous meta-analyses have examined the impact of semaglutide on weight loss in patients without DM, providing valuable information but leaving certain aspects unexplored. For instance, Gao et al. provided insights into semaglutide's efficacy and safety for weight loss in patients without DM but included studies with both once-daily and once-weekly dosing regimens. Tan et al. explored semaglutide's role in weight loss among patients with overweight or obesity without DM but their meta-analysis was limited to

four studies and included a study with once-daily dosing. Included four studies and provided limited insights into major side effects. Additionally, (Wilding et al., 2022). investigated semaglutide's potential for weight loss but included studies involving patients with DM as well.

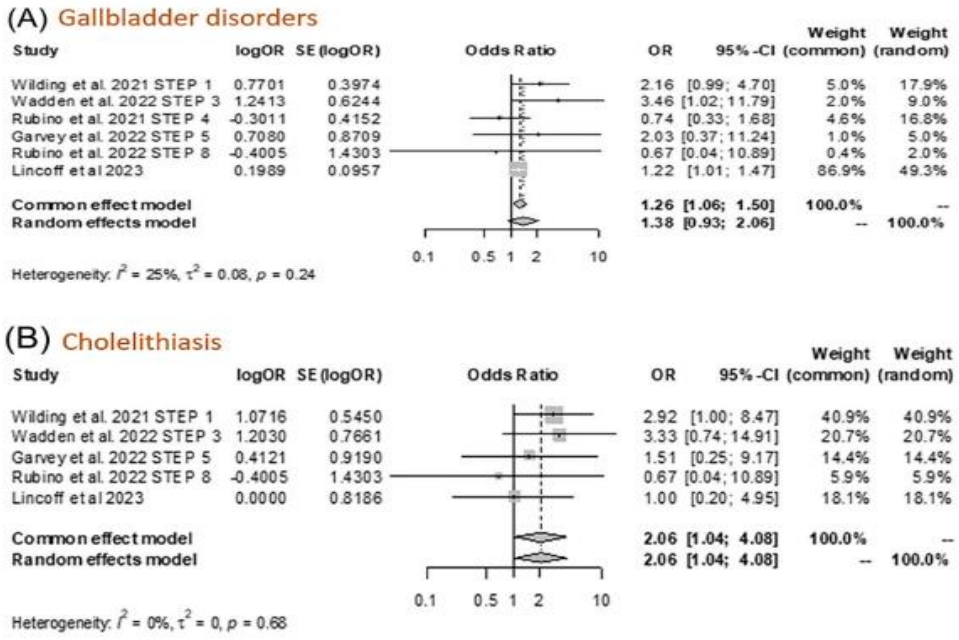


Figure 6. Forest Plots Depict The Odds Ratios For Additional Gastrointestinal Side Effects—Gallbladder Disorders (A) And Cholelithiasis (B)—In Patients With Overweight Or Obesity Without Diabetes Mellitus Treated With Once-Weekly Semaglutide Compared To Placebo. OR Refers To Odds Ratio And CI To Confidence Interval

The STEP trials, including recent additions like STEP-HFpEF and SELECT, form a significant part of our meta-analysis. The STEP-HFpEF trial by (Rehman et al., 2024) published in September 2023, focused on semaglutide in patients with preserved ejection fraction and obesity, excluding those who were merely overweight. In contrast, the SELECT trial by (Michael Lincoff et al., 2023) et al., published in November 2023, examined cardiovascular outcomes in a large cohort of 17,604 patients with obesity. Our meta-analysis distinguishes itself in several aspects compared to previous ones: Firstly, it exclusively incorporates studies using once-weekly dosing of semaglutide, providing a focused perspective. Secondly, our analysis is limited to patients without diabetes mellitus (DM), ensuring a more homogeneous study population. Thirdly, we conducted a comprehensive evaluation of semaglutide's efficacy, carefully examining major limitations and side effects that could affect its clinical utility. Fourthly, our study includes the recent STEP-HFpEF and SELECT trials, which offer significant data on individuals with overweight or obesity without DM. This thorough evaluation of all included studies positions our meta-analysis as a valuable update on semaglutide's role in weight management among individuals without DM.

Prior meta-analyses by Gao et al. and Tan et al. on patients without DM demonstrated weight reduction favoring semaglutide, with mean differences (MD) of approximately 10% and 11.85%, respectively. However, these analyses did not include data from the STEP-HFpEF and SELECT trials and had other limitations. In contrast, our study found that once weekly semaglutide significantly reduced body weight compared to placebo, with a pooled MD estimate of 11.49% (95% CI 9.86 to 13.12) (Figure 3A). Similarly, studies by Gao et al. and Arastu et al. reported absolute weight reductions favoring semaglutide, with MDs ranging from 10.54 kg to 11.62 kg. Our meta-analysis also demonstrated statistically significant benefits in favor of semaglutide, with an MD for change in absolute body weight of 11.74 kg (95% CI

9.94 to 13.53) (Figure 3B). Furthermore, our study highlighted that semaglutide significantly increased the odds of achieving weight reductions of at least 5%, 10%, 15%, and 20%, with odds ratios ranging from 8.43 to 16.57 (Figure 4). These findings underscore semaglutide's efficacy in promoting weight loss among individuals without DM, supported by robust data from recent trials not included in previous meta-analyses.

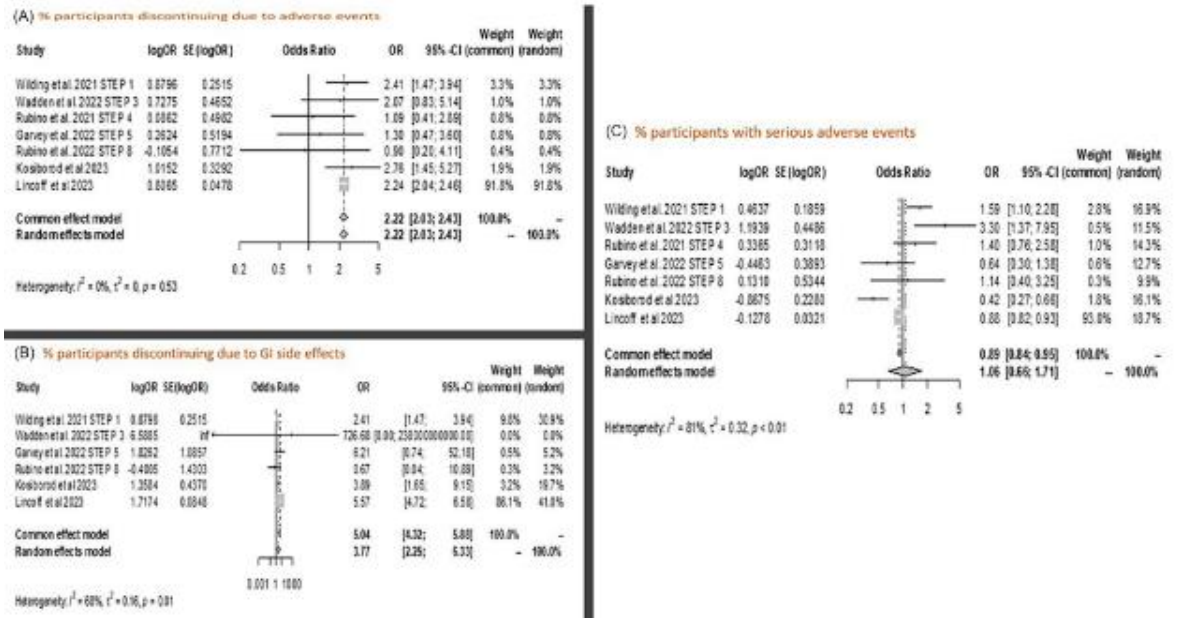


Figure 7. Forest Plots Showing The Participants Discontinuing Due To Adverse Events (A), Participants Discontinuing Due To Gi Side Effects (B), And Participants With Serious Adverse Reactions (C) In Patients With Overweight Or Obesity Without Diabetes Mellitus Treated With Once Weekly Semaglutide Versus Placebo. Or—Odds Ratio, Ci—Confidence Interval

Semaglutide's weight loss benefits stem from several mechanisms. It activates GLP-1 receptors in the gut and pancreas, slowing gastric emptying and inhibiting glucagon release, thus reducing appetite. Additionally, it activates GLP-1 receptors in the brain's hypothalamus, decreasing hunger, mitigating food cravings, and increasing satiety, thereby regulating food intake. Semaglutide is notable among GLP-1 receptor agonists (GLP-1 RAs) for its significant weight loss effects, as demonstrated in various studies. The SUSTAIN 3 trial showed semaglutide's superiority over exenatide in reducing body weight over 56 weeks. The SUSTAIN 7 trial found semaglutide more effective than dulaglutide, and the SUSTAIN 10 trial established its superiority over liraglutide. These trials, among others, have consistently shown semaglutide's weight-reducing effects in individuals with overweight or obesity, with or without diabetes mellitus (DM). Consequently, the US FDA approved semaglutide injections (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight, alongside at least one weight-related condition such as high blood pressure, type 2 DM, or elevated cholesterol levels, recommending its use with a calorie-restricted diet and increased physical activity (Wadden et al., 2020).

However, gastrointestinal side effects are a significant concern with semaglutide. While hypoglycemic events in patients without DM are low, gastrointestinal issues are prevalent, though typically mild to moderate. A comprehensive analysis of semaglutide's efficacy and side effects is necessary to understand its overall benefits and risks. Previous meta-analyses have explored semaglutide's impact on weight loss in patients without DM, but many included once-daily dosing regimens or patients with DM. Our meta-analysis stands out by exclusively including studies with once-weekly dosing of semaglutide and focusing on patients without DM (Quddos et al., 2023b). It includes recent trials like the STEP-HFpEF and SELECT trials,

offering significant data on patients with obesity. This comprehensive evaluation positions our study as a valuable contribution to understanding semaglutide's role in weight management among individuals without DM.

Previous meta-analyses by Gao et al. and Tan et al. demonstrated significant weight reduction with semaglutide. Our study also found that once weekly semaglutide significantly decreased body weight compared to placebo, with a pooled mean difference (MD) estimate of 11.49%. Additionally, our study showed significant increases in the odds of achieving at least 5%, 10%, 15%, and 20% weight loss with semaglutide compared to placebo. Despite its efficacy, semaglutide's gastrointestinal side effects, such as nausea, vomiting, diarrhea, constipation, gallbladder disorders, and cholelithiasis, can impact its clinical utility (Meier, 2021). Our study revealed a statistically significant increase in the odds of discontinuing semaglutide due to adverse events, especially gastrointestinal side effects. While there were some limitations in our study, such as variability in dosages and study durations, our findings contribute valuable insights into the efficacy and safety of once weekly semaglutide therapy for weight management in individuals without DM. Long-term studies focusing on the comprehensive side-effect profile of semaglutide are imperative to understand the potential risks associated with its prolonged use.

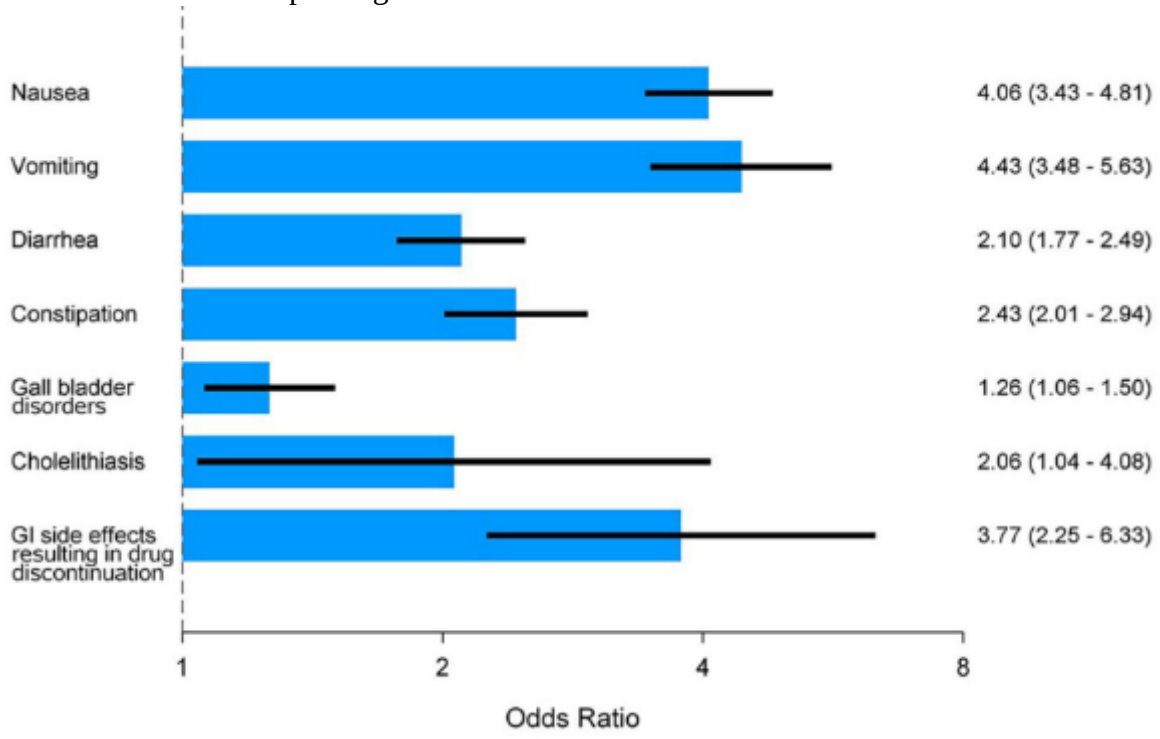


Figure 8. A Graph Illustrating The Odds Ratios (95% Confidence Intervals) For Gastrointestinal Side Effects In Overweight Or Obese Patients Without Diabetes Mellitus Treated With Once Weekly Semaglutide Compared To Placebo

The meta-analyses by Gao et al. and Tan et al. indicated a significant risk of serious adverse events with semaglutide, showing relative risks (RR) of 1.34 (95% CI: 1.10 to 1.65) and 1.60 (95% CI: 1.24 to 2.07) respectively. In contrast, our study did not find a statistically significant difference, showing a neutral effect on serious adverse events with semaglutide compared to placebo, with an odds ratio (OR) of 1.06 (95% CI: 0.66 to 1.71). Previous meta-analyses also showed a significant risk of adverse events leading to discontinuation with semaglutide (Gao et al.: RR of 2.29, 95% CI: 1.74 to 3.01; Tan et al.: RR of 2.19, 95% CI: 1.36 to 3.55). Our study corroborated this, showing significant odds of discontinuing semaglutide due to adverse events (OR of 2.22, 95% CI: 2.03 to 2.43). Additionally, our study found a statistically

significant increase in gastrointestinal side effects leading to discontinuation in patients without diabetes (OR of 3.77, 95% CI: 2.25 to 6.33).

Despite including studies with once-weekly dosing, most using 2.4 mg after gradual dose escalation, and one study by (Jensen et al., 2014). using 1 mg/week, the varying durations of the studies (mostly 68 weeks) may have introduced variability and heterogeneity in outcomes. We used a random-effects model to address detected heterogeneity. Despite these limitations, our study provides valuable insights into the efficacy and safety of once weekly semaglutide for weight management in individuals without diabetes. Our findings highlight the promising weight loss effects of semaglutide in non-diabetic patients. As its use increases, so do concerns about its side effects. Therefore, more long-term studies focusing on the comprehensive side-effect profile are necessary to understand the potential risks of long-term semaglutide use.

Efficacy Of Semaglutide Vs Placebo by Sex

Compared to the placebo, semaglutide similarly improved the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) in both men and women. At 52 weeks, the adjusted mean difference was +7.5 points (95% CI: 4.3-10.6 points) for men and +7.6 points (95% CI: 4.5-10.7 points) for women, with no significant interaction by sex (P = 0.944). The improvement in KCCQ-CSS was noticeable early after treatment began and continued to increase throughout the trial, with consistent patterns for both sexes. These benefits were observed across key subgroups based on age, BMI, left ventricular ejection fraction (LVEF), and C-reactive protein (CRP) levels. Semaglutide led to a significant reduction in body weight for both men and women, with women experiencing approximately 2.5% greater weight loss than men (P interaction = 0.006). Additionally, semaglutide improved the 6-minute walk distance (6MWD), resulted in more favorable outcomes for the hierarchical composite endpoint, and reduced CRP and NT-proBNP levels in both sexes, with no significant differences in treatment benefits between men and women.

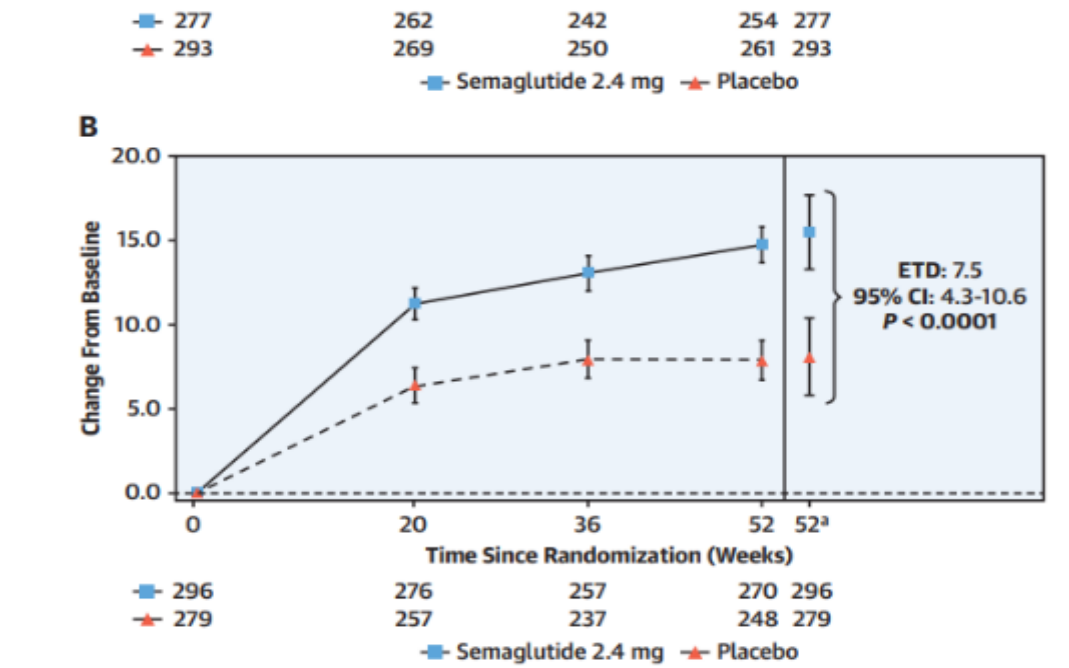
TABLE 1 Baseline Characteristics of Patients from the Pooled STEP-HFpEF and STEP-HFpEF DM Trials by Sex Characteristics

	Total (N = 1,145[a])	Women (n = 570)	Men (n = 575)	*P* Value
Age, y				
<65	368 (32.1)	172 (30.2)	196 (34.1)	
65-79	666 (58.2)	334 (58.6)	332 (57.7)	0.125
≥80	111 (9.7)	64 (11.2)	47 (8.2)	
Race[b]				
Asian	76 (6.6)	41 (7.2)	35 (6.1)	
Black or African American	39 (3.4)	24 (4.2)	15 (2.6)	0.397
Other	4 (0.3)	2 (0.4)	2 (0.3)	
White	1,026 (89.6)	503 (88.2)	523 (91.0)	
Body weight, kg	103.7 (91.3-119.0)	96.0 (86.0-108.6)	111.5 (99.6-125.4)	<0.001
BMI,[c] kg/m²	38.0 (34.6-42.6)	38.8 (35.3-43.7)	37.1 (34.0-41.8)	<0.001
Waist circumference, cm	120.0 (111.0-129.0)	115.4 (108.0-124.5)	123.8 (116.0-133.0)	<0.001
Systolic blood pressure, mm Hg	133.0 (123.0-144.0)	135.0 (123.0-144.0)	133.0 (122.0-144.0)	0.391
NYHA functional class				
II	785 (68.6)	360 (63.2)	425 (73.9)	
III	358 (31.3)	209 (36.7)	149 (25.9)	<0.001
IV	2 (0.2)	1 (0.2)	1 (0.2)	
LVEF, %	57.0 (50.0-60.0)	60.0 (54.0-61.0)	55.0 (50.0-60.0)	<0.001
KCCQ-CSS, points	58.9 (43.2-72.4)	54.7 (38.5-67.2)	63.0 (48.4-76.0)	<0.001
6MWD, m	294.8 (220.0-368.0)	270.5 (200.0-344.0)	322.1 (241.7-387.0)	<0.001
CRP, mg/L	3.7 (1.8-8.1)	4.4 (2.1-9.4)	3.0 (1.6-6.8)	0.002
NT-proBNP, pg/mL	477.8 (236.8-1,015.7)	436.4 (237.6-921.0)	522.6 (236.8-1,120.6)	0.36
Comorbidities at screening				
Hypertension	959 (83.8)	482 (84.6)	477 (83.0)	0.461
Atrial fibrillation	518 (45.2)	227 (39.8)	291 (50.6)	<0.001
Obstructive sleep apnea	119 (10.4)	48 (8.4)	71 (12.3)	0.029
Coronary artery disease	453 (39.6)	181 (31.8)	272 (47.3)	<0.001
Diabetes[d]	616 (53.8)	273 (47.9)	343 (59.7)	<0.001
Concomitant medications				
Diuretics	925 (80.8)	456 (80.0)	469 (81.6)	0.501
Loop diuretics	702 (61.3)	348 (61.1)	354 (61.6)	0.858
Thiazides	175 (15.3)	88 (15.4)	87 (15.1)	0.884
Beta-blockers	928 (81.0)	456 (80.0)	472 (82.1)	0.367
SGLT2i	221 (19.3)	83 (14.6)	138 (24.0)	<0.001
MRA	384 (33.5)	183 (32.1)	201 (35.0)	0.306
ACEI/ARB (ARNI)	899 (78.5)	428 (75.1)	471 (81.9)	0.004
ARNI	58 (5.1)	23 (4.0)	35 (6.1)	0.113
Insulin and analogues	128 (11.2)	58 (10.2)	70 (12.2)	0.283
Sulfonylureas	106 (9.3)	51 (8.9)	57 (9.9)	0.576
DPP-4 inhibitors	92 (8.0)	40 (7.0)	52 (9.0)	0.207

Over 52 weeks, semaglutide consistently improved all KCCQ summary and individual domains in both sexes, with no heterogeneity observed. The drug's effects on lowering systolic blood pressure and waist circumference were also similar between men and women. Logistic regression analysis indicated that patients treated with semaglutide had significantly lower odds of experiencing a deterioration of 5 points or more in KCCQ-CSS (OR: 0.49; 95% CI: 0.35-0.68; P < 0.001), with no sex-related differences. Furthermore, semaglutide-treated patients had significantly higher odds of achieving improvements of 5 points (OR: 2.10; 95% CI: 1.61-2.73; P < 0.001), 10 points (OR: 2.07; 95% CI: 1.61-2.69; P < 0.001), 15 points (OR: 2.03; 95% CI: 1.55-2.65; P < 0.001), and 20 points (OR: 2.36; 95% CI: 1.76-3.17; P < 0.001) in KCCQ-CSS in both sexes.

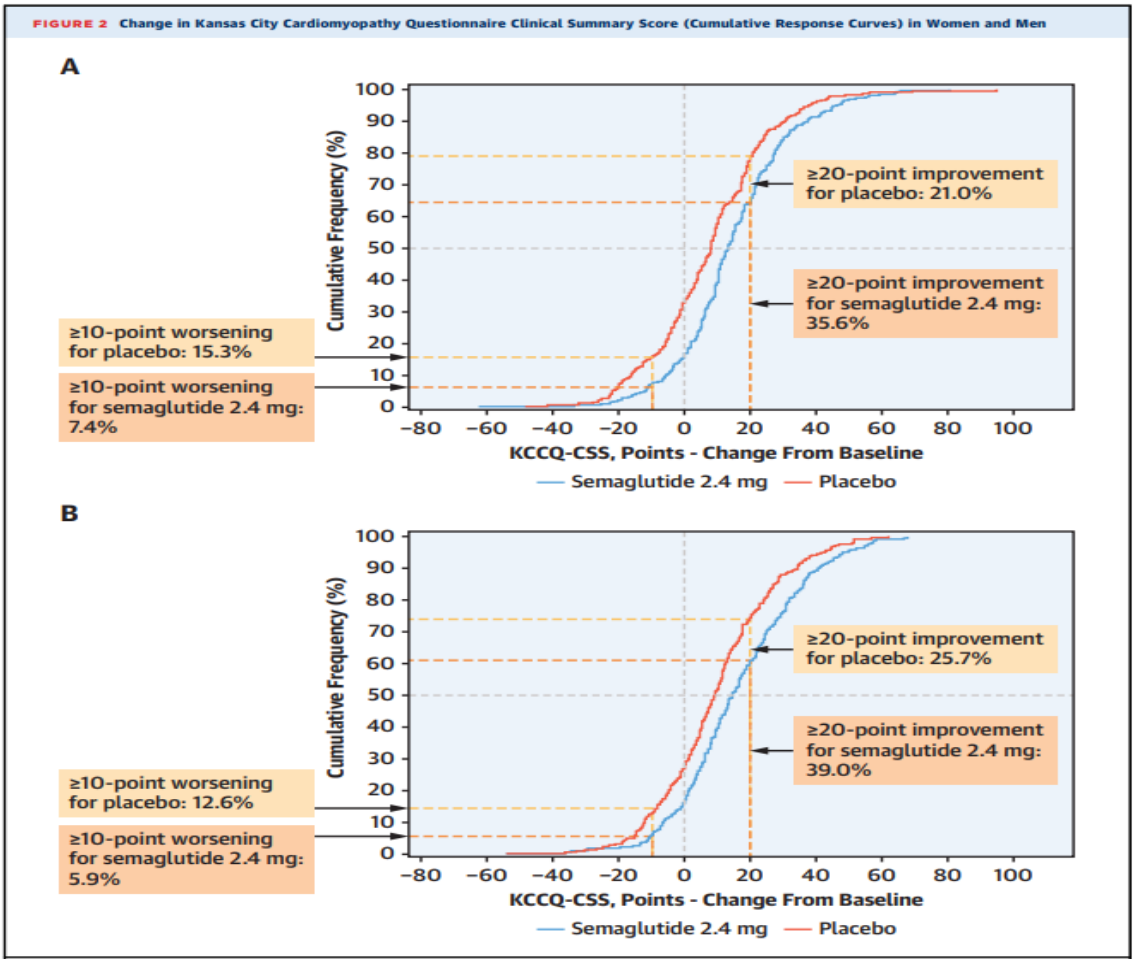
TABLE 2 Effect of Semaglutide Compared With Placebo on Outcomes by Sex

	Women (n = 570)		Men (n = 575)		
	Semaglutide 2.4 mg (n = 277)	Placebo (n = 293)	Semaglutide 2.4 mg (n = 296)	Placebo (n = 279)	P Value
Dual primary endpoints					
Change in KCCQ-CSS at 52 wks, points	n = 254 14.5 (12.2-16.7)	n = 261 6.9 (4.7-9.1)	n = 270 15.5 (13.3-17.7)	n = 248 8.1 (5.8-10.3)	
Adjusted mean difference, points	7.6 (4.5-10.7)		7.5 (4.3-10.6)		0.944
Change in body weight at 52 wks, %	n = 257 −12.6 (−13.5 to −11.7)	n = 268 −3.0 (−3.9 to −2.1)	n = 275 −10.2 (−11.1 to −9.3)	n = 252 −3.0 (−4.0 to −2.1)	
Adjusted mean difference, %	−9.6 (−10.9 to −8.4)		−7.2 (−8.4 to −6.0)		0.006
Confirmatory secondary endpoints					
Change in 6MWD at 52 wks, m	n = 252 12.0 (4.1-19.9)	n = 251 0.1 (−8.0 to 8.1)	n = 269 21.3 (13.5-29.1)	n = 239 −0.7 (−8.8 to 7.3)	
Adjusted mean difference, m	11.9 (0.7-23.1)		22.0 (11.0-33.1)		0.207
Hierarchical composite endpoint, win ratio	1.58 (1.27-1.98)		1.75 (1.40-2.18)		0.658
CRP ratio at 52 wks	n = 253 0.54 (0.48-0.62)	n = 268 0.92 (0.81-1.03)	n = 274 0.60 (0.53-0.69)	n = 252 0.88 (0.77-1.00)	
Treatment ratio	0.59 (0.50-0.70)		0.69 (0.57-0.82)		0.232
Supportive secondary and exploratory endpoints					
Change in systolic blood pressure at 52 wks, mm Hg	n = 257 −5.6 (−7.5 to −3.6)	n = 268 −1.7 (−3.7 to 0.4)	n = 275 −3.7 (−5.6 to −1.8)	n = 253 −1.8 (−4.0 to 0.4)	
Adjusted mean difference, mm Hg	−3.9 (−6.7 to −1.1)		−1.9 (−4.8 to 1.0)		0.335
Change in waist circumference at 52 wks, cm	n = 257 −11.8 (−12.8 to −10.8)	n = 266 −3.7 (−4.7 to −2.6)	n = 273 −8.8 (−9.8 to −7.8)	n = 251 −1.5 (−2.6 to −0.4)	
Adjusted mean difference, cm	−8.1 (−9.5 to −6.7)		−7.3 (−8.8 to −5.8)		0.445
Change in KCCQ Overall Summary Score at 52 wks, points	n = 254 14.3 (12.0-16.5)	n = 261 7.3 (5.1-9.5)	n = 270 15.5 (13.3-17.7)	n = 248 7.7 (5.5-9.9)	
Adjusted mean difference, points	7.0 (3.9-10.1)		7.8 (4.7-10.9)		0.707
NT-proBNP ratio at 52 wks	n = 255 0.76 (0.69-0.85)	n = 268 0.96 (0.86-1.07)	n = 274 0.79 (0.72-0.88)	n = 252 0.95 (0.84-1.06)	
Treatment ratio	0.80 (0.69-0.93)		0.84 (0.72-0.98)		0.662



The cumulative response analysis showed a continuous separation of KCCQ-CSS curves in favor of semaglutide versus placebo across the entire range of KCCQ changes from baseline

to week 52 for both men and women. Among women, 39.0% of those treated with semaglutide experienced a KCCQ-CSS increase of 20 points or more (Ghusn et al., 2022), compared to 25.7% in the placebo group. For men, these figures were 35.6% and 21.0%, respectively. Conversely, 5.9% of women treated with semaglutide experienced a decrease of 10 points or more in KCCQ-CSS compared to 12.6% in the placebo group. For men, these numbers were 7.4% and 15.3%, respectively. In terms of safety outcomes, there were fewer serious adverse events (SAEs) and serious cardiac disorders in both women and men treated The cumulative response analysis showed a continuous separation of KCCQ-CSS curves in favor of semaglutide versus placebo across the entire range of KCCQ changes from baseline to week 52 for both men and women. Among women, 39.0% of those treated with semaglutide experienced a KCCQ-CSS increase of 20 points or more (Ghusn et al., 2022), compared to 25.7% in the placebo group. For men, these figures were 35.6% and 21.0%, respectively. Conversely, 5.9% of women treated with semaglutide experienced a decrease of 10 points or more in KCCQ-CSS compared to 12.6% in the placebo group. For men, these numbers were 7.4% and 15.3%, respectively. In terms of safety outcomes, there were fewer serious adverse events (SAEs) and serious cardiac disorders in both women and men treated with semaglutide compared to the placebo. Gastrointestinal SAEs and SAEs leading to premature discontinuation was similar between the treatment groups for both sexes.



In this prespecified patient-level pooled analysis of STEP-HFpEF and STEP-HFpEF DM (the STEP-HFpEF program), notable differences between women and men with obesity-related HFpEF were observed. Women had a higher BMI and more severe heart failure-related symptoms, physical limitations, and reduced exercise tolerance compared to men, despite

having a higher left ventricular ejection fraction (LVEF). Inflammation levels, measured by CRP, were higher in women, although they had lower rates of comorbid conditions like atrial fibrillation and coronary artery disease compared to men(Haseeb et al., 2024). The lower KCCQ-CSS and higher CRP levels in women at baseline indicate a significant disparity, emphasizing the need to understand and address these differences better. Semaglutide resulted in greater weight loss in women than in men, but despite this differential weight loss and key baseline differences by sex, no significant treatment-by-sex interactions were found for any of the heart failure outcomes assessed. Semaglutide 2.4 mg once weekly, compared with placebo, demonstrated consistent and substantial improvements across all domains of KCCQ, increased 6MWD, and reduced CRP and NT-proBNP levels, regardless of sex. Responder analyses showed similar proportions of patients experiencing at least 5-, 10-, 15-, and 20-point improvements in KCCQ-CSS scores with semaglutide compared to placebo, regardless of sex. Improvements in KCCQ-CSS showed no treatment heterogeneity by age, BMI, LVEF, or CRP levels in either sex for semaglutide (Newsome et al., 2021).

Despite extensive research into sex-based differences in the epidemiology, pathophysiology, and clinical course of HFpEF, a significant gap remains in understanding these differences within the context of the obesity phenotype of HFpEF. Consistent with previous HFpEF trials, women with obesity-related HFpEF experienced more severe heart failure-related symptoms compared to men (Smits & Van Raalte, 2021). The mechanisms underlying these differences are complex and likely multifactorial. One explanation is that increased adiposity in women serves as a critical causal factor. Prior studies have shown that women with obesity-related HFpEF exhibit significantly higher levels of visceral adiposity, which can disproportionately impact exercise hemodynamics and exacerbate heart failure symptoms compared to men. Visceral adiposity acts as a reservoir for the synthesis and release of various adipocytokines and neurohormones, promoting local and systemic inflammation, sodium retention, and plasma volume expansion. It is theorized that the higher symptom burden in women may stem from a more pronounced increase in exercise pulmonary capillary wedge pressure with elevated plasma and blood volume compared to men.

Visceral adiposity is also implicated as a key driver of heightened inflammation and microvascular endothelial dysfunction, both prevalent in women with HFpEF (Xie et al., 2022). The findings of greater inflammation in women with obesity-related HFpEF suggest a potentially important sex-difference in pathophysiology. Systemic inflammation was reduced to a similar extent in both women and men, but because women had higher CRP at baseline, they may have greater residual inflammation even after treatment. Increased inflammation is believed to contribute to oxidative stress and impair myocardial energetics, potentially explaining the exacerbated symptoms observed in women. Excessive adiposity in women, as opposed to men, may impose greater extrinsic constraints on the heart, hindering venous return and predisposing individuals to hemodynamic deterioration.

The sex-based differences in baseline demographics observed in the STEP program exhibit both similarities and differences compared with previous HFpEF trials. Notably, the proportion of women enrolled (approximately 50%) aligns with recent trials investigating SGLT2i in HFpEF. Unlike earlier HFpEF studies where women tended to be older than men, this study found no such age disparity. This may relate to the fact that patients with the obesity phenotype of HFpEF are, on average, a decade younger than those with HFpEF without obesity. Consistent with prior HFpEF studies, women had lower rates of coronary artery disease. However, unlike previous studies, women had similar rates of hypertension and diuretic use and less atrial fibrillation compared to men. The lower rates of atrial fibrillation despite higher BMI in women is an interesting and unexpected finding. Because atrial fibrillation is a marker of left atrial myopathy, these data may indicate that more female participants had a more typical isolated obesity phenotype, whereas more male participants had left atrial myopathy HFpEF

complicated by an increase in BMI. Interestingly, women were also less likely to receive an SGLT2i or inhibitors of the renin-angiotensin system than men (Tucker et al., 2021). Similarly, in line with previous HFpEF trials, women in this study presented with more severe symptoms despite having higher LVEF. One proposed explanation is that because women typically have lower left ventricular volumes than men, they may rely more heavily on a higher ejection fraction to maintain stroke volume and cardiac output, potentially explaining the observed higher LVEF (Gove & Hughes, 1979). Ventricular volume contraction in this setting may further exacerbate elevation in cardiac filling pressures with higher LVEF, especially because volume expansion is greater in women with HFpEF and more visceral adiposity. The BMI among women in the STEP-HFpEF program was markedly higher than that reported in recently completed HFpEF trials. For instance, in the EMPEROR-Preserved trial, women had a BMI of approximately 30 kg/m^2, compared with 39 kg/m^2 noted in the present study. This difference in BMI levels may contribute to the lower levels of NT-proBNP observed relative to previous HFpEF trials, as there is an inverse relationship between BMI and NT-proBNP levels.

Previous pharmacologic studies in HFpEF have suggested potential interactions between sex and treatment efficacy. For instance, in the PARAGON-HF trial, a subgroup analysis indicated that women responded more favorably to sacubitril/valsartan than men. Similarly, a post hoc analysis of the TOPCAT trial suggested that spironolactone therapy reduced all-cause mortality in women with HFpEF but not in men. However, no such sex-treatment interaction has been observed with empagliflozin or dapagliflozin in patients with HFpEF, although the obesity-related HFpEF phenotype was not specifically targeted in these trials. The consistency and magnitude of benefit observed with semaglutide in the STEP-HFpEF program, regardless of sex, are notable. Although direct comparisons between trials can be challenging, improvements in KCCQ-CSS of nearly 8 points at 52 weeks were noted in both men and women. In contrast, in the EMPEROR-Preserved trial, empagliflozin improved KCCQ-CSS by approximately 2.5 points in women and 2.2 points in men. Similar results were observed in the DELIVER trial with dapagliflozin, though KCCQ benefits were greater in patients with higher BMI. Furthermore, neither SGLT2i nor mineralocorticoid receptor antagonists have demonstrated significant reductions in CRP in HFpEF, unlike the observations made in the STEP-HFpEF program. SGLT2i cause a modest but similar reduction in weight in men and women of approximately 1.5 kg. In STEP-HFpEF, although clinically meaningful, significant reductions in weight with semaglutide were observed in both sexes, women had an augmented response. This is consistent with what has been demonstrated previously with semaglutide (and other incretin-based therapies) in other trials. The exact mechanism for this remains unclear. Notably, the impact of semaglutide on HF outcomes was similar between men and women despite greater weight loss in women, suggesting that mechanisms beyond weight loss may play a role in mediating the effects of semaglutide in obesity-related HFpEF. The results of this analysis must be interpreted within the context of potential limitations: The key objectives of the STEP-HFpEF program were to evaluate the effects of semaglutide on HF-related symptoms, physical limitations, and exercise function. It was not designed to assess heart failure events, although fewer adjudicated events were reported with semaglutide than placebo in the program.

Alternative anthropometric assessments of visceral adiposity were not available. Additionally, sex- and ethnicity-based thresholds for adiposity were not employed, potentially limiting the generalizability of these data. Few Non-White patients were enrolled, which also limits broad generalizability. There was an imbalance in SGLT2i use between women and men; however, the effects of semaglutide versus placebo on KCCQ-CSS were consistent regardless of background SGLT2i use. Mechanistic insights regarding body composition, skeletal/visceral fat, microvascular function, and extracardiac adiposity were not available. Finally, analyses were confined to biological sex and did not characterize the impact of gender.

CONCLUSION

In individuals with obesity-related heart failure with preserved ejection fraction (HFpEF), women exhibit more pronounced symptom severity, exercise limitations, and systemic inflammation compared to men. Semaglutide treatment led to reductions in body weight in both genders, with women experiencing greater weight loss. Despite the differential weight loss, semaglutide demonstrated comparable and clinically significant improvements in heart failure symptoms, physical limitations, and exercise capacity across sexes. Additionally, it reduced inflammation markers and natriuretic peptides similarly in both men and women

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