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Review Article

Efficacy and Safety of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight and Cardiometabolic Parameters in Individuals With Obesity and Without Diabetes: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially for type 2 diabetes mellitus, show promise in promoting weight loss and improving heart health in obese individuals without diabetes. Our goal was to examine existing research for conclusive evidence on various types of GLP-1 RAs for weight loss and cardiometabolic benefits in obesity without diabetes.
Methods: We conducted an electronic search on PubMed, Scopus, and Cochrane Central using keywords, such as "GLP-1 RA," "obesity," and "weight loss." We considered all available global GLP-1 RAs for inclusion. Our analysis focused on weight loss, blood pressure (BP) changes (systolic and diastolic BPs), and lipid profile effects (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triacylglycerol). We used a random-effects meta-analysis with the standardized mean difference (SMD), mean difference (MD), odds ratio, and relative risk to present the results.
Results: Our search yielded a total of 7535 articles. We included 15 trials in our study. GLP-1 RAs led to significant weight loss (MD, −8.77 kg; P <.01) in obese individuals. GLP-1 RAs also improved the systolic BP (MD, −4.13 mm Hg; P <.01), diastolic BP (MD, −1.39 mm Hg; P <.01), and lipid profiles, including improved levels of triacylglycerol (SMD, −0.99 mg/dL; P <.01), total cholesterol (SMD, −0.73 mg/dL; P <.01), very low-density lipoprotein (SMD, −1.11 mg/dL; P <.01), and low-density lipoprotein (SMD, −0.27 mg/dL; P <.01), and significantly increased high-density lipoprotein levels (SMD, 0.11 mg/dL; P <.01). However, GLP-1 RAs were associated with an increased risk of gastrointestinal adverse events.
Conclusion: GLP-1 RAs were found to be beneficial for not only weight loss but also reduction in risk factors for cardiovascular disease such as BP and lipid profile. Consistent beneficial results were observed across the various subtypes of GLP-1 RAs.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SMD, standardized mean difference; TAG, triacylglycerol; TC, total cholesterol; T2DM, type 2 diabetes mellitus; VLDL, very-low-density lipoprotein.

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Introduction

Throughout the past few decades, the prevalence of obesity has been gradually increasing worldwide, and the trend is expected to further increase in the upcoming years.[1] Obesity significantly increases the risk of certain comorbidities, all of which contribute to a decline in both quality of life and life expectancy.[2] Obesity has been reported to cause a chronic inflammatory state that, in turn, increases the risk of oxidation of low-density lipoprotein (LDL) cholesterol and, hence, atherogenesis.[2] Additionally, obesity could lead to an altered lipid profile, type 2 diabetes mellitus (T2DM), and hypertension, all of which contribute to atherogenesis and, thus, increase the risk of developing cardiovascular disease. On the other hand, weight loss and chronic weight control are related to reductions in the overall risk of morbidity and mortality.[3] Although the core of most weight loss strategies is lifestyle adjustment, including dietary changes and exercise,[4] due to physiologic factors that limit weight loss and encourage weight return,[5] lifestyle adjustment alone is frequently insufficient to produce clinically meaningful weight loss. Given the risk that obesity poses to public health and the difficulties of adopting consistent lifestyle modifications, pharmaceutical treatments for weight loss in some individuals are required.[6]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as liraglutide and semaglutide, produce several times the amount of GLP-1 receptor agonism as natural GLP-1.[7] These drugs, although initially introduced to treat T2DM, were found to be successful in lowering not only the blood glucose levels but also body weight.[8] As a result, a once-daily subcutaneous dosage of 3.0-mg liraglutide and 2.4-mg semaglutide for the treatment of obesity was established.[9] These medications function by stimulating the pancreatic GLP-1 receptors, which results in increased insulin release and decreased glucagon release, both of which are glucose-dependent responses.[10] GLP-1 RAs have also shown an effect in delaying gastric emptying, reducing hunger, and prospective food consumption. This leads to reduced appetite and increased energy expenditure, which helps control weight in individuals with obesity.[11-13]

Alongside their impact on weight loss, GLP-1 RAs have demonstrated significant therapeutic effects on cardiometabolic parameters.[14] Cardiometabolic health encompasses a range of factors, including those related to the cardiovascular system, such as blood pressure (BP), and metabolic regulatory mechanisms, such as effects on body weight, body mass index (BMI), and lipid profile.[15] Notably, GLP-1 RAs have shown efficacy in lowering the BP levels and have also demonstrated efficacy in alleviating symptoms of heart failure in patients with preserved ejection.[16] The results of the LEADER and SUSTAIN-6 trials also confirm the noninferiority of liraglutide and semaglutide on their impact on cardiovascular outcomes in a population with diabetes.[17,18]

Previous studies on GLP-1 RAs analyzed their efficacy in improving glycemic index and weight loss in individuals with diabetes.[19,20] However, there are a limited number of studies collectively analyzing all available GLP-1 RAs regarding their efficacy in obese individuals but without diabetes. Therefore, we aimed to conduct this meta-analysis to consolidate data from various trials involving Food and Drug Administration–approved GLP-1 RAs, such as semaglutide, liraglutide, and exenatide, as well as forthcoming potential medications, such as tirzepatide, as a dual incretin, and orforglipron to determine whether different GLP-1 RAs result in improvement in obesity and cardiometabolic parameters and assess their safety in individuals with obesity without diabetes. In addition, we intended to analyze any differences in efficacy between various subtypes of GLP-1 RAs.

Highlights

- We reviewed past literature on GLP-1 RAs efficacy in obese, non-diabetic people
- Our analysis show all GLP-1 RAs lead to significant reduction in weight and BMI
- We observed tirzepatide as the most potent agent for inducing weight loss
- GLP-1 RAs lead to significant improvement in systolic and diastolic blood pressures
- Our results show a decrease in all lipid profile values with GLP-1 RA's use

Clinical Relevance

Lifestyle changes alone often fall short in achieving significant weight loss, necessitating medication intervention. GLP-1 RAs show promise in managing obesity and its complications. They promote weight loss and protect against deteriorating cardiometabolic risk factors, offering potential in obesity management.

Methods

Data Sources and Search Strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21] An electronic search of Scopus, PubMed, and Cochrane Central was conducted for clinically published articles from January 2000 to September 2023, without any language restrictions using the following search string: "(glucagon-like peptide-1 receptor agonist OR Semaglutide OR Liraglutide OR Tirzepatide OR Exenatide OR Orforglipron) AND (Obesity OR Obese OR Weightloss OR Weight OR Bodyweight)." Furthermore, we used the pharmaceutical, generic, and trade names of all GLP-1 RAs to search for additional published and unpublished trials on ClinicalTrials.gov. Lastly, we screened previous meta-analyses to identify any suitable studies matching our inclusion and exclusion criteria.

Study Selection

Studies were selected based on the following inclusion criteria. First, a GLP-1 RA(s) was compared with a placebo. The drugs were included irrespective of their Food and Drug Administration approval. Second, the studies included participants without diabetes. For the determination of the status of diabetes, a cutoff of hemoglobin A1c of 6.5% was used. However, because few studies did not report the hemoglobin A1c level, we included the study if it mentioned individuals without diabetes in its trial population. Third, all studies reported that individuals with a BMI of >30 kg/m^2 were considered obese and included. Fourth, all participants were aged ≥18 years. Fifth, only randomized controlled trials (RCTs) were included.

We included both single and dual incretin medications. Dual incretins, possessing both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor activities, were included only if the study adhered to the established inclusion criteria.

The articles retrieved from the systematic search were exported to EndNote Reference Library X7 software where duplicates were screened for and removed. The remaining articles were carefully assessed by 2 independent reviewers (Q.S.U. and H.U.H.A.), and

only those trials that met the previously defined criteria were selected. All trials were initially short-listed based on title and abstract, after which the full article was reviewed to affirm relevance. All discrepancies were resolved by a third reviewer (F.S.).

Outcome Measures

From the finalized trials, the following outcomes were extracted:

- **Primary:** mean change in body weight (kg), change in BMI (kg/m^2), the proportion of participants who achieved greater than 5%, 10%, and 15% changes in body weight.
- **Secondary:** changes in the systolic and diastolic BPs (mm Hg) and lipid profiles (mg/dL), including high-density lipoprotein (HDL), LDL, very low-density lipoprotein (VLDL), triacylglycerol (TAG), and total cholesterol (TC), of individuals without diabetes administered different subtypes of GLP-1 RAs. The safety profiles assessing gastrointestinal (GI) disorders, nausea, diarrhea, constipation, and vomiting were also reported.

Quality Assessment

Quality assessment of the included studies was conducted using the Joanna Briggs Institute critical appraisal checklists.[22]

Statistical Analysis

All statistical analyses were performed on Review Manager (version 5.4.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The outcomes were pooled using a random-effects model comparing the means with their standard deviations. Higgins I^2 was used to assess the statistical heterogeneity between trials; an I^2 statistic of >50% was considered to have significant heterogeneity, and a value of <50% was considered acceptable. In all cases, a P value of $\leq$.05 was considered significant.[23] Subgroup analyses were performed according to the different drug classes. Publication bias was assessed by visual inspection of the Begg funnel plot.[24]

Results

Literature Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart summarizes our literature review (Fig. 1). The search strategy provided a total of 7835 potential articles. After the removal of duplicates and screening, we evaluated 56 articles for inclusion. A total of 14 RCTs were included in our study. Four different single incretin GLP-1 RAs (semaglutide, liraglutide, exenatide, and orforglipron) and 1 dual incretin, tirzepatide, were included in our analysis: (1) 6 trials of semaglutide,[25-30] (2) 6 trials of liraglutide,[25,28,31-34] (3) 1 trial of tirzepatide,[35] (4) 2 trials of exenatide,[36,37] and (5) 1 trial of orforglipron.[38] Lastly, 2 trials used semaglutide and liraglutide concomitantly.[25,28]

Participant Characteristics

A total number of 10 638 obese individuals (BMI, >30 kg/m^2) without diabetes were included in this review, of whom 2581, 3147, 630, 114, 53, and 4113 received semaglutide, liraglutide, tirzepatide, exenatide, orforglipron, and placebo, respectively. The median follow-up duration was 54 ± 19.9 months. The mean age of participants was 48.3 ± 3.67 years. The baseline characteristics of the included studies are summarized in the Table.

Intervention and Follow-up

To standardize the impact of varying dosages, we collected data for semaglutide at a fixed dosage of 2.4 mg across all studies, except the study by O'Neil et al,[25] which reported a maximum dosage of 0.4 mg. All studies used injectable formulations of semaglutide. For studies involving liraglutide, we extracted data for the universally reported dosage of 3.0 mg. It is important to note that both of these dosages (semaglutide and liraglutide) are the approved dosages according to current guidelines and, hence, the most commonly followed regimen for RCTs.[9] Data for tirzepatide accounted for the maximum dosage of 15 mg, whereas orforglipron was analyzed at a dosage of 24 mg. For exenatide, 2 studies provided data for different dosages, specifically 10 and 20 μg.

Additionally, the mode of drug administration was predominantly subcutaneous for semaglutide, liraglutide, and tirzepatide. In contrast, orforglipron was administered orally, and exenatide was administered through both oral and subcutaneous routes, as detailed in the included studies.

Result of Meta-Analysis

Mean Change in Body Weight

Fourteen studies were evaluated to assess the association of weight loss in GLP-1 RA consumers. Overall, the results showed twice as much weight loss in GLP-1 RA consumers compared with that in placebo consumers (mean difference [MD], −8.77 kg; 95% confidence interval [CI], −10.98 to −6.56; P <.01; I^2 = 100%) (Fig. 2).

In our subgroup analysis by drug type, we found distinct variations in weight loss outcomes. Tirzepatide exhibited the most substantial weight reduction at 17% (95% CI, −19.33 to −6.27; P <.01). Semaglutide followed closely with a 12% weight loss (95% CI, −13.56 to −1.60; P <.01; I^2 = 82%), whereas orforglipron achieved a 10% weight loss (95% CI, −12.99 to −41; P <.01). Liraglutide led to a weight loss of 5% (95% CI, −6.36 to −.85; P <.01; I^2 = 99%) among obese individuals without diabetes. Exenatide showed the smallest reduction in weight at 3.3% (95% CI, −4.4 to −.17; P <.01; I^2 = 0%).

Change in BMI

Ten studies that reported the effect of GLP-1 RAs on BMI were evaluated, which showed a significant decrease in BMI with GLP-1 RAs compared with placebo (MD, −3.12 kg/m^2; 95% CI, −3.94 to −.31; P <.01; I^2 = 100%). Subgroup analysis showed that semaglutide had the greatest effect in reducing BMI compared with the rest of the GP-1 RAs (MD, −4.41 kg/m^2; 95% CI, −4.73 to −4.09; P <.01; I^2 = 80%) (Fig. 3).

Change in BP

Twelve studies assessed the relation of GLP-1 RAs on the systolic BP. A significant reduction was noted in the systolic BP (MD, −4.13 mm Hg; 95% CI, −4.87 to −.39; P <.01; I^2 = 60%) (Fig. 4).

Twelve studies assessed the diastolic BP. GLP-1 RAs were found to also significantly decrease the diastolic BP (MD, −1.39 mm Hg; 95% CI, −2.32 to −.46; P <.01; I^2 = 95%) (Fig. 5).

5% Reduction in Body Weight

The evaluation of 12 studies that assessed 5% weight loss with GLP-1 RAs showed that a significantly greater percentage of participants achieved >5% weight loss than those on placebo (odds ratio [OR], 8.19; 95% CI, 5.81-11.54; P <.01; I^2 = 90%). Subgroup analysis revealed that all subtypes of GLP-1 RAs resulted in a

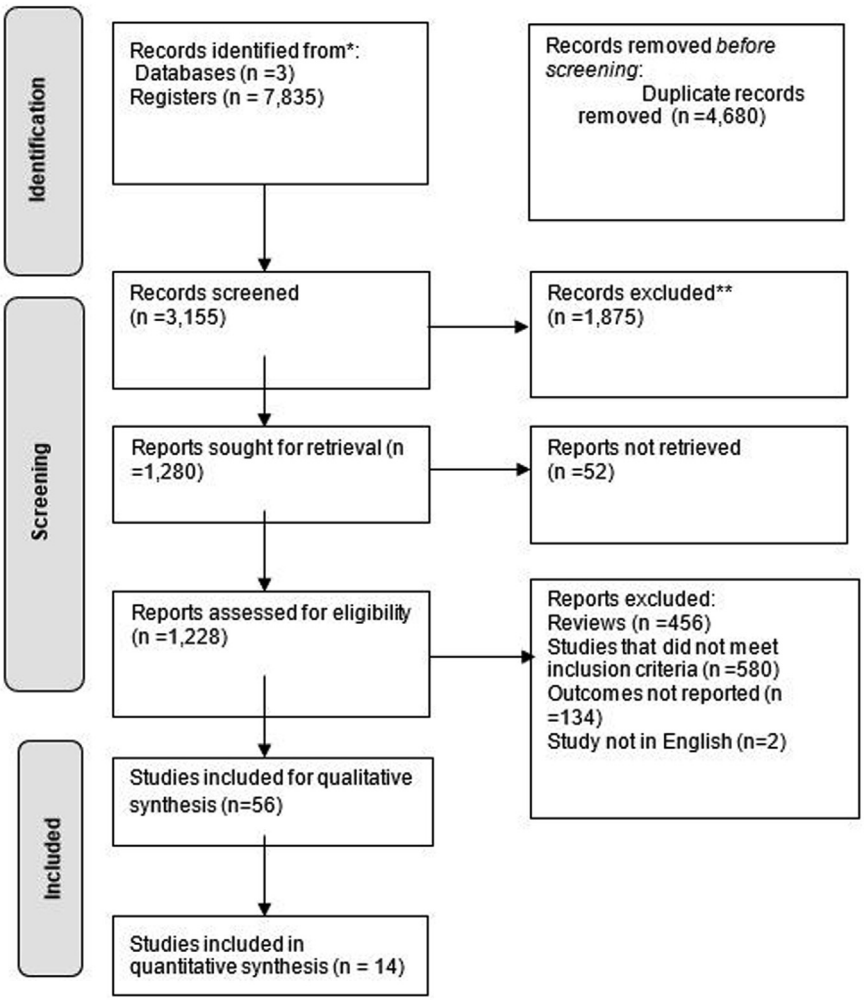

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart summarizing the results of the literature search.

significantly greater number of participants achieving >5% weight loss (Supplementary Fig. 1).

10% Reduction in Body Weight

Twelve studies that reported the association of GLP-1 RAs with 10% weight loss were evaluated. A greater percentage of participants achieved 10% weight reduction than the placebo group (OR, 10.41; 95% CI, 6.75-16.07; P <.01; I^2 = 91%). Subgroup analysis indicated that a greater proportion of individuals who received tirzepatide experienced a 10% reduction in weight, as shown in Supplementary Fig. 2.

15% Reduction in Body Weight

Nine studies that assessed the 15% reduction in body weight were evaluated, which showed significant odds of achieving a 15% reduction in body weight in GLP-1 RAs compared with that in placebo (OR, 12.20; 95% CI, 7.36-20.25; P <.01; I^2 = 88%). Subgroup analysis showed that greater odds of achieving a 15% weight reduction were associated with participants who received tirzepatide (Supplementary Fig. 3).

Lipid Profile

We assessed changes in the LDL, TC, TAG, HDL, and VLDL levels with GLP-1 RAs.

Change in the HDL Levels. Nine studies that reported data on changes in the HDL levels were evaluated. The results from these studies, when pooled, showed a significant change in the HDL levels with GLP-1 RAs compared with that with placebo (standardized mean difference [SMD], 0.11 mg/dL; 95% CI, 0.04-0.18; P <.01; I^2 = 89%).

Subgroup analysis showed that semaglutide (SMD, 0.0; 95% CI, −0.0 to 0.0; P =.99) and liraglutide (SMD, 0.05; 95% CI, −0.03 to 0.14; P =.22; I^2 = 69%) did not significantly increase the HDL levels, whereas tirzepatide (SMD, 0.36; 95% CI, 0.25-0.47; P <.01) and orforglipron (SMD, 1.31; 95% CI, 0.89-1.74; P <.01) showed a modest but significant increase in the HDL levels (Supplementary Fig. 4).

Change in the LDL Levels. Nine studies that reported data on changes in the LDL cholesterol levels were evaluated. The LDL cholesterol levels significantly decreased with GLP-1 RAs compared with those with placebo (SMD, −0.27 mg/dL; 95% CI, −0.43 to −.11; P <.01; I^2 = 88%) (Supplementary Fig. 5).

Subgroup analysis showed that semaglutide (SMD, −0.30 mg/dL; 95% CI, −0.40 to −.20; P <.01, I), tirzepatide (SMD, −0.30 mg/dL; 95% CI, −0.08 to 0.79), liraglutide (SMD, −0.10 mg/dL; 95% CI, −0.16 to −.04; P <.01), and orforglipron (SMD, −2.04 mg/dL; 95% CI, −2.52 to −.56) all showed a significant reduction in the LDL cholesterol levels. Orforglipron was associated with the greatest reduction in the LDL cholesterol levels, whereas exenatide failed to show any

Table
Baseline Characteristics of the Included Studies

Demographics	O'Neil et al,[25] 2018		Rubino et al,[26] 2021	Wadden et al,[27] 2021	Rubino et al,[28] 2022	
Name of trial	…	…	STEP 4	STEP 3	STEP 8	
Intervention	Semaglutide	Liraglutide	Semaglutide	Semaglutide	Semaglutide	Liraglutide
Sample size	957		803	611	338	
Intervention group participants	718	103	535	407	126	127
Dosage	0.4	3.0	2.4	2.4	2.4	3.0
Duration of study (wks)	52	52	48	68	68	68
No. of men (n, %)	254 (35)	36 (36)	169 (21)	116 (18)	24 (19)	30 (23.6)
No. of women (n, %)	464 (65)	67 (64)	634 (78)	495 (82)	102 (81)	97 (76.4)
Mean age (SD)	48 (13)	49 (11)	47 (12)	46 (13)	48 (14)	49 (13)
Body weight (kg) (SD)	113.2 (26.4)	108.7 (21.9)	96.5 (22.5)	106.9 (22.8)	102.5 (25.3)	103.7 (22.5)
Mean BMI (kg/m^2)	39.9 (8.8)	38.6 (6.6)	34.5 (6.9)	38.1 (6.7)	37 (7.4)	37.2 (6.4)
HbA1c% (SD)	5.5 (0.4)	5.5 (0.4)			5.5 (0.3)	5.5 (0.3)
Blood pressure						
Systolic (mm Hg) (SD)	…	…	121 (13)	124 (15)	125 (14)	126 (16)
Diastolic (mm Hg) (SD)	…	…	78 (9)	80 (10)	81 (9)	81 (10)
Total cholesterol (mg/dL)	189.5	197.2	177.2 (289)	185.4 (19.8)	184.9 (21)	188.6 (20.8)
Low-density lipoprotein (mg/dL)	112.1	119.8	110.4 (234)	107.7 (30.3)	106.4 (32.5)	108.1 (30.4)
Triacylglycerol (mg/dL)	124	132.8	95.2 (304)	107.9 (50.3)	110.1 (49.1)	113.1 (49.4)
High-density lipoprotein (mg/dL)	46.4	46.4	44.4 (82)	51.6 (24)	51.9 (24.1)	53.7 (25.3)
Very low-density lipoprotein (mg/dL)	24.8	26.5	18.5 (61)	21 (49.7)	21.4 (47.2)	22 (48.1)

Demographics	Jastreboff et al,[35] 2022	Kadowaki et al,[29] 2022	Astrup et al,[31] 2009	Pi-Sunyer et al,[32] 2015	Wadden et al,[33] 2013	Blackman et al,[34] 2016
Name of trial	SURMOUNT 1	STEP 6		SCALE Obesity	SCALE Maintenance	SCALE Sleep Apnea
Intervention	Tirzepatide	Semaglutide	Liraglutide	Liraglutide	Liraglutide	Liraglutide
Sample size	2539	401	564	3731	422	359
Intervention group participants	630	199	93	2437	207	180
Dosage	15 mg	2.4 mg	3.0 mg	3.0 mg	3.0 mg	3.0 mg
Duration of study (wks)	72	68	20	56	56	32
No. of men (n, %)	1261 (49.6)	253 (63)	135 (24)	803 (21)	78 (18)	258 (71)
No. of women (n, %)	1278 (50.4)	148 (37)	429 (76)	2928 (78)	344 (81)	101 (29)
Mean age (SD)	44.9 (12.3)	51 (11)	45.9 (10.7)	45.1 (12.0)	45.9 (11.9)	48.6 (9.9)
Body weight (kg) (SD)	105.6 (22.9)	87.5 (15.2)	97.6 (13.7)	106.2 (21.5)	100.4 (20.8)	117.6
Mean BMI (kg/m^2)	38.1 (6.6)	31.9 (4.3)	34.8 (2.8)	38.3 (6.4)	36 (5.9)	38.9 (6.4)
HbA1c% (SD)	5.6 (0.36)	6.4 (1.2)	…	…	5.6 (0.4)	…
Blood pressure						
Systolic (mm Hg) (SD)	123 (12.9)	134 (14)	124 (11.3)	12 3 (12.9)	…	…
Diastolic (mm Hg) (SD)	79.3 (8.2)	84 (11)	77.8 (8.3)	78.8 (8.6)	…	…
Total cholesterol (mg/dL)	187.4 (19.9)	201.1	188.3	193.7 (19.1)	…	190.4 (20.9)
Low-density lipoprotein (mg/dL)	109.5 (30)	119.8	131.4	111.4 (27.7)	…	111.6 (28.9)
Triacylglycerol (mg/dL)	127.9 (47.5)	132.8	124	127.5 (58.2)	…	140.3 (55.9)
High-density lipoprotein (mg/dL)	47.5 (25.5)	50.27	49.5	51.4 (26.2)	…	45.7 (22.8)
Very low-density lipoprotein (mg/dL)	…	26.5	24.8	25.1 (49.6)	…	28 (53.3)

Demographics	Wilding et al,[30] 2021	Dushay et al,[36] 2012	Rosenstock et al,[37] 2010	Wharton et al,[38] 2023
Name of trial	STEP 1	…	…	…
Intervention	Semaglutide	Exenatide	Exenatide	Orforglipron
Sample size	1961	41	152	272
Intervention group participants	1212	41	73	53
Dosage	2.4 mg	20 μg	10 μg	24 mg
Duration of study (wks)	68	16	24	36
No. of men (n,%)	508 (26)	0	28 (18)	111 (41)
No. of women (n,%)	1453 (74)	41	124 (82)	161 (59)
Mean age (SD)	46 (13)	48 (11)	46 (12)	57 (9.1)
Body weight (kg) (SD)	105.4 (22.1)	89 (14)	109.5 (2.7)	112.1 (30.2)
Mean BMI (kg/m^2)	37.8 (6.7)	33 (4)	39.6 (7.0)	38.1 (7.7)
HbA1c% (SD)	5.7 (0.3)	…	…	5.7 (0.3)
Blood pressure				
Systolic (mm Hg) (SD)	126 (14)	128 (14)	…	129.7 (10.8)
Diastolic (mm Hg) (SD)	80 (10)	75 (8)	…	82.1 (7.4)
Total cholesterol (mg/dL)	189.6 (20.5)	198 (32)	…	198.9 (5.9)
Low-density lipoprotein (mg/dL)	110.3 (31.6)	114 (28)	…	118.1 (5.3)
Triacylglycerol (mg/dL)	126.2 (47.4)	111 (64)	…	119.1 (7.5)
High-density lipoprotein (mg/dL)	49.4 (25.6)	62 (19)	…	51.3 (1.9)
Very low-density lipoprotein (mg/dL)	24.5 (45.8)	…	…	23.8 (1.5)

Abbreviations: BMI = body mass index; HbA1c% = hemoglobin A1c%; SD = standard deviation.

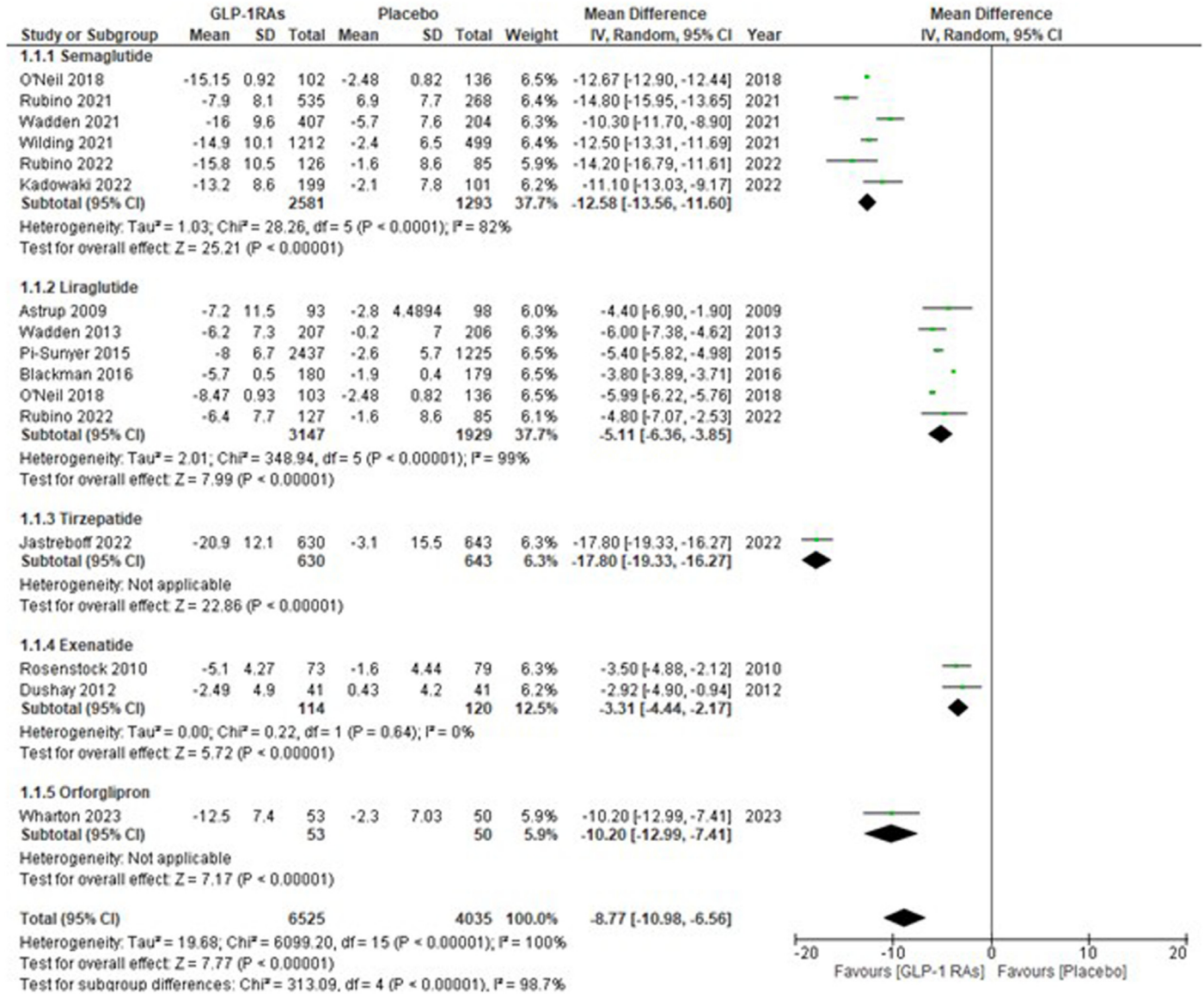

Fig. 2. Efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on weight loss in kilogram. Random-effects model. Mean difference, standard deviation (SD), 95% confidence interval (CI), and I^2 statistics.

significant reduction in these levels (SMD, 0.36 mg/dL; 95% CI, −0.08 to 0.79).

Change in the TC Levels. Nine studies evaluated the effect of GLP-1 RAs on the TC levels. The TC levels significantly decreased with GLP-1 RAs compared with those with placebo (SMD, −0.73 mg/dL; 95% CI, −1.06 to −.39; P <.01; I^2 = 97%) (Supplementary Fig. 6).

Subgroup analysis showed that a significant reduction in the TC levels was associated with semaglutide (SMD, −1.32 mg/dL; 95% CI, −2.29 to −.35; P <.01), liraglutide (SMD, −0.15 mg/dL; 95% CI, −0.21 to −.08; P <.01), and tirzepatide (SMD, −0.39 mg/dL; 95% CI, −0.50 to −.28; P <.01) and the greatest reduction was observed with orforglipron (SMD, −2.72 mg/dL; 95% CI, −3.26 to −.18; P <.01). Exenatide did not show any significant change in the TC levels (SMD, 0.32 mg/dL; 95% CI, −0.12 to 0.75; P =.15).

Change in the TAG Levels. Nine studies that reported data on changes in the TAG levels were evaluated. The TAG levels significantly decreased with GLP-1 RAs compared with those with placebo (SMD, −0.99 mg/dL; 95% CI, −1.35 to −.63; P <.01; I^2 = 98%) (Supplementary Fig. 7).

Our subgroup analysis highlighted that a significant reduction in the TAG levels was associated with semaglutide (SMD, −1.74 mg/dL; 95% CI, −2.85 to −.63; P <.01), liraglutide (SMD, −0.28 mg/dL; 95% CI, −0.38 to −.19; P <.01), and tirzepatide (SMD, −0.54 mg/dL; 95% CI, −0.65 to −.43; P <.01) and the greatest reduction was observed with orforglipron (SMD, −3.15 mg/dL; 95% CI, −3.73 to −.56; P <.01). However, exenatide failed to show any reduction in the TAG levels (SMD, 0.17 mg/dL; 95% CI, −0.26 to 0.61; P =.43).

Change in the VLDL Levels. Eight studies evaluated the effects of GLP-1 RAs on the VLDL cholesterol levels. The VLDL cholesterol levels significantly decreased with GLP-1 RAs compared with those with placebo (SMD, −1.11 mg/dL; 95% CI, −1.47 to −.74; P <.01; I^2 = 98%) (Supplementary Fig. 8).

Subgroup analysis showed that a significant reduction in the VLDL cholesterol levels was associated with semaglutide (SMD, −1.43 mg/dL; 95% CI, −2.37 to −.48; P <.01), liraglutide

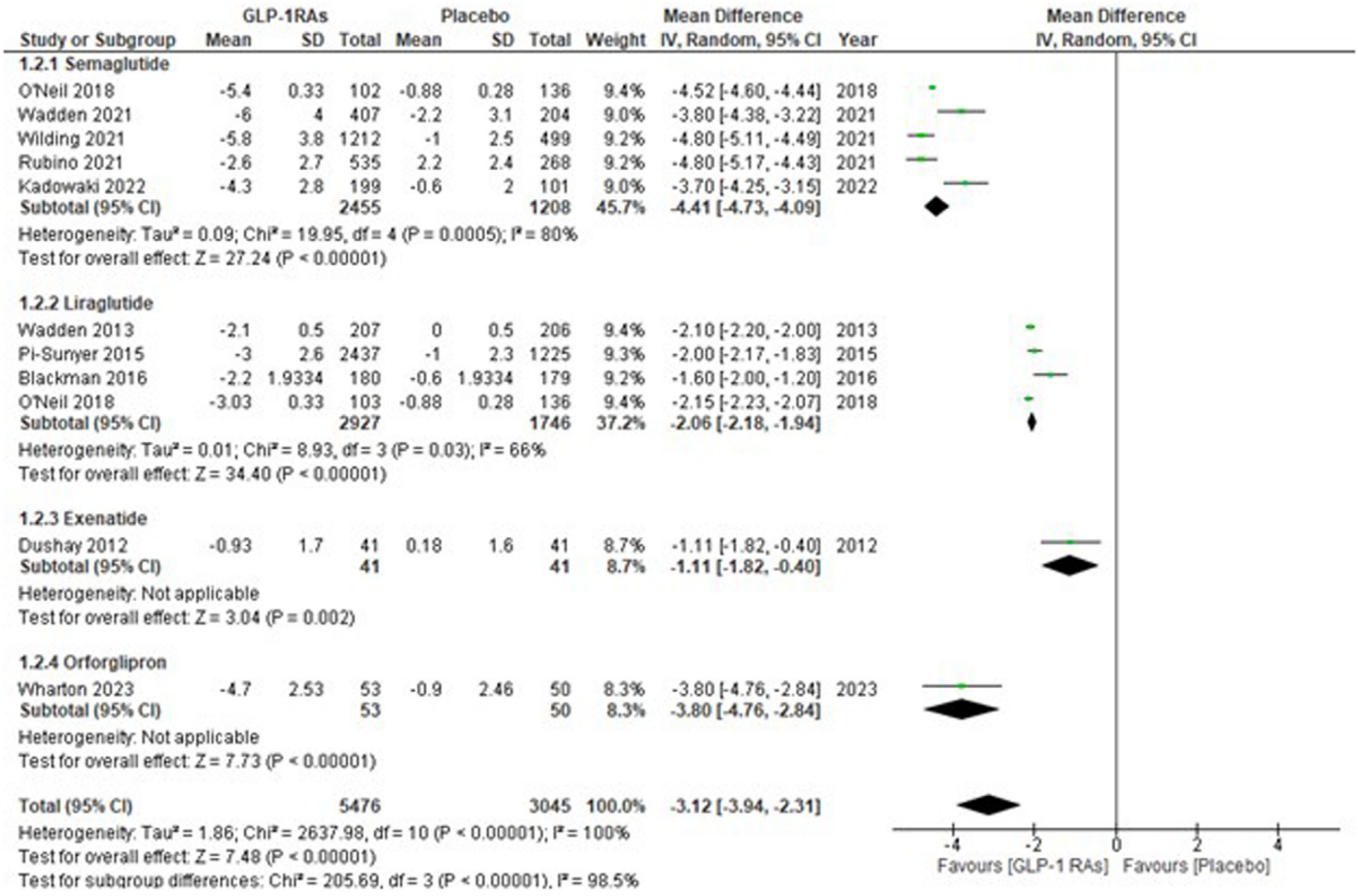

Fig. 3. Effect of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on body mass index in kilogram per square meter. Random-effects model. Mean difference, standard deviation (SD), 95% confidence interval (CI), and I^2 statistics.

(SMD, −0.47 mg/dL; 95% CI, −0.77 to −.17; *P* <.01), and tirzepatide (SMD, −0.79 mg/dL; 95% CI, −0.90 to −.68; *P* <.01). Orforglipron was associated with the greatest reduction in the VLDL cholesterol levels (SMD, −3.16 mg/dL; 95% CI, −3.74 to −.57; *P* <.01).

Safety Profile

GI Disorders. Eight studies reported the risk of GI disorders. These studies highlighted a significantly increased risk with the administration of GLP-1 RAs compared with that with a placebo in a population of individuals without diabetes (relative risk [RR], 1.67; 95% CI, 1.50-1.85; *P* <.01; $I^2 = 69\%$) (Supplementary Fig. 9).

Nausea. Fourteen studies reported the risk of experiencing nausea symptoms with the administration of GLP-1 RAs compared with placebo in individuals without diabetes. A significantly increased risk was associated with the group administered GLP-1 RAs compared with the placebo group (RR, 3.02; 95% CI, 1.76-5.17; *P* <.01; $I^2 = 98\%$) (Supplementary Fig. 10).

Diarrhea. Nine studies reported the risk of developing diarrhea with different GLP-1 RAs. A significantly increased risk of developing diarrhea was observed with administration of GLP-1 RAs overall compared with placebo (RR, 1.98; 95% CI, 1.52-2.59; *P* <.01; $I^2 = 75\%$) (Supplementary Fig. 11).

Constipation. Twelve studies reported the risk of developing constipation. These studies highlighted a significantly increased risk with the administration of GLP-1 RAs compared with placebo in a population of individuals without diabetes (RR, 2.21; 95% CI, 1.80-2.71; *P* <.01; $I^2 = 63\%$) (Supplementary Fig. 12).

Vomiting. Twelve studies evaluated the incidence of vomiting among patients without diabetes treated with GLP-1 RAs versus placebo. GLP-1 RAs were associated with thrice the risk of developing vomiting compared with a placebo (RR, 3.82; 95% CI, 3.27-4.46; *P* <.01; $I^2 = 0\%$) (Supplementary Fig. 13).

Hypoglycemia. Nine studies evaluated the risk of developing hypoglycemia with GLP-1 RAs. No significantly increased risk of hypoglycemia was observed with GLP-1 RAs (RR, 1.18; 95% CI, 0.61-2.30; *P* =.62; $I^2 = 44\%$) (Supplementary Fig 14).

Subgroup analysis showed that only tirzepatide was associated with a significantly increased risk of hypoglycemia (RR, 10.21; 95% CI, 1.31-79.5; *P* =.03).

Publication Bias

Visual inspection of the funnel plot showed mild asymmetry, suggesting low-risk publication bias (Supplementary Fig. 15).

Quality Assessment and Sensitivity Analysis

The Joanna Briggs Institute critical appraisal checklist for RCTs was used to assess the quality of the included studies. Four studies did not report the methods employed for the randomization process.[28,35-37] Eight studies failed to provide the reasons and impact

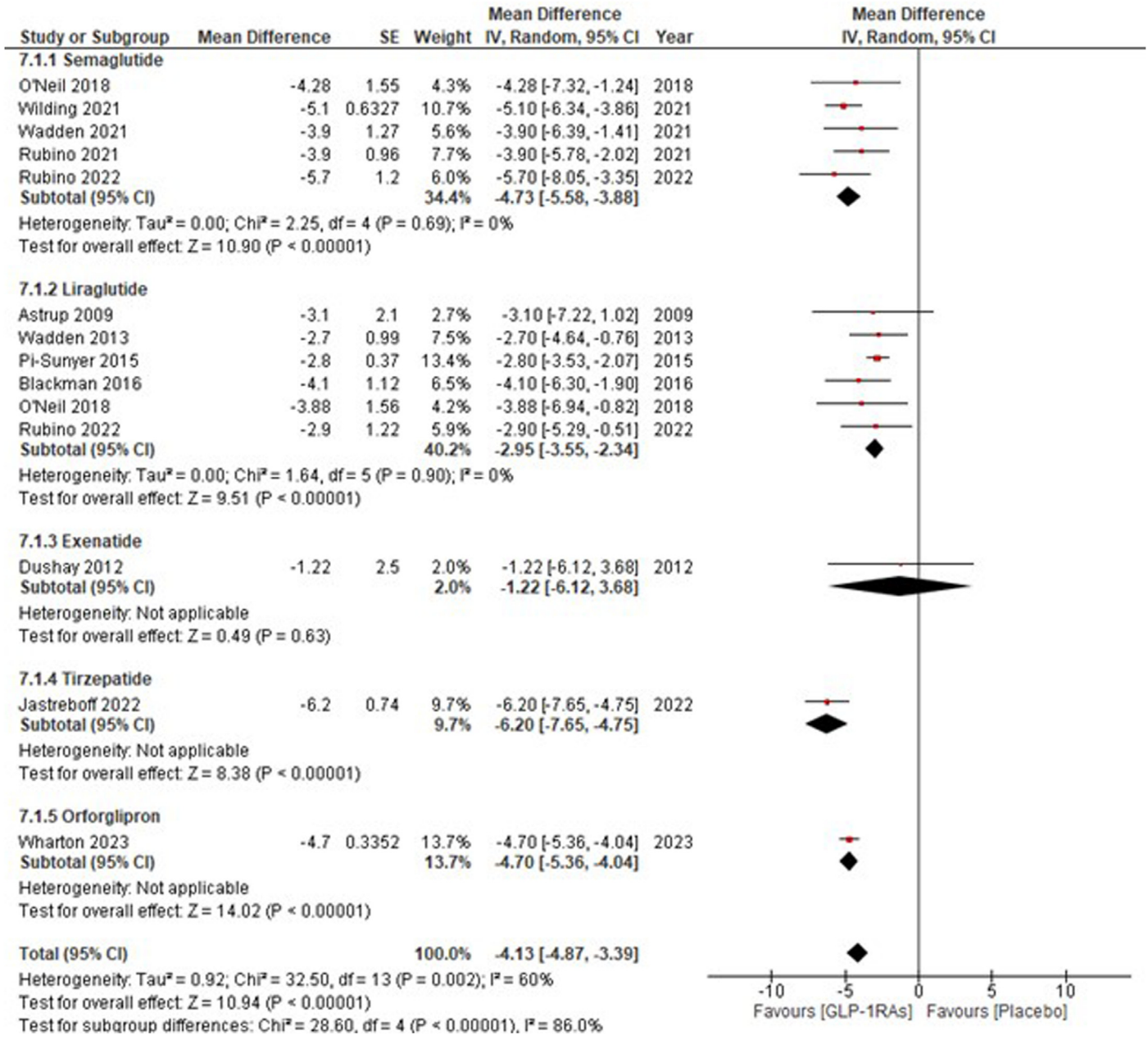

Fig. 4. Effect of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on the systolic blood pressure in millimeter of mercury. Random-effects model. Mean difference, standard deviation (SD), 95% confidence interval (CI), and I^2 statistics.

of incomplete follow-up.[26-28,30,32,33,36,38] All of the studies included participants in the arms with similar baseline characteristics (Supplementary Table 1). Sensitivity analysis was performed to identify studies contributing the most to heterogeneity across all outcomes. The results are summarized in Supplementary Table 2.

Discussion

In the present meta-analysis, we assessed the efficacy of 4 different GLP-1 RAs (semaglutide, liraglutide, exenatide, and orforglipron) and a dual incretin (tirzepatide) from 14 RCTs in a patient population with obesity without diabetes. We observed significant reductions in weight and BMI and a greater number of participants achieving 5%, 10%, and 15% reductions in body weight when using GLP-1 RAs as compared with placebo. In addition, a significant improvement in the BP and lipid profile values was observed in the population with GLP-1 RAs. However, a higher risk of developing adverse events, such as nausea, diarrhea, constipation, and vomiting was associated with the use of GLP-1 RAs compared with placebo.

Several previous studies have shown the efficacy of GLP-1 RAs for weight loss. Xie et al[19] compared the efficacy of semaglutide and liraglutide across different dosages and observed that higher doses resulted in greater weight loss. Yeh et al[20] demonstrated that improved glycemic control with GLP-1 RAs led to a significant reduction in weight across different patient populations, such as patients with diabetes and obesity, patients with polycystic ovary syndrome, and those with chronic kidney disease. However, both studies included patients with T2DM. In addition, only semaglutide and liraglutide were primarily assessed in the previous literature.

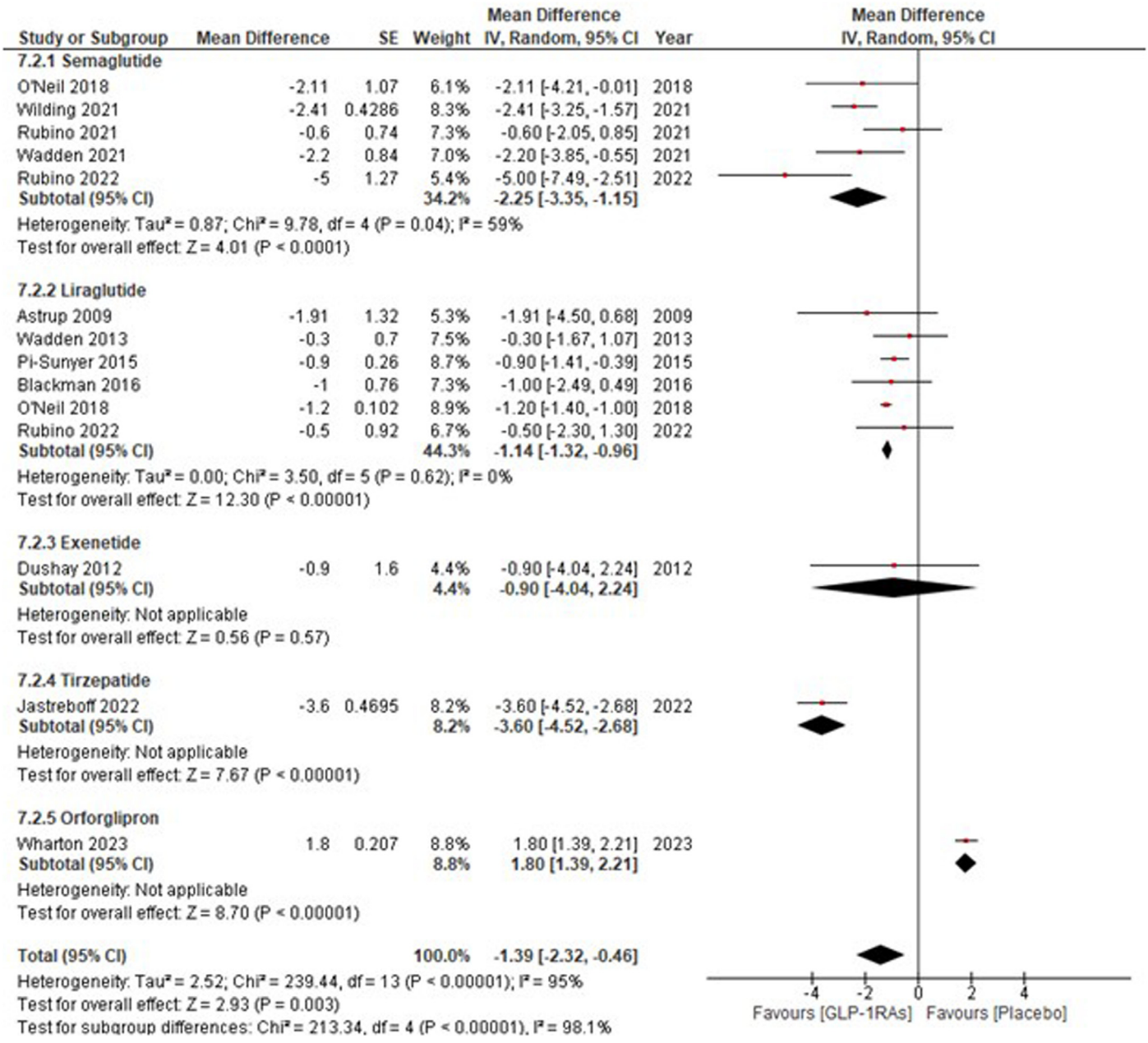

Fig. 5. Effect of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on the diastolic blood pressure in millimeter of mercury. Random-effects model. Mean difference, standard deviation (SD), 95% confidence interval (CI), and I^2 statistics.

We demonstrate that other GLP-1 RAs, including exenatide, orforglipron, and dual incretins, such as tirzepatide, also demonstrate a significant reduction in body weight.

When assessing weight reduction across different subtypes, we observed tirzepatide to produce the greatest magnitude of effect compared with other types of GLP-1 RAs relative to placebo. The SURPASS 2 trial compared tirzepatide with semaglutide and observed a 7% to 11% decrease in weight with tirzepatide compared with 5% with semaglutide.[39] In addition, the study by Azuri et al[40] analyzed data from the STEP 1 and SURMOUNT-1 trials and observed a weight loss of 17.8% with tirzepatide compared with 12.4% with semaglutide. Furthermore, the cost of 72 weeks of tirzepatide was lower overall than that of the 68-week course of semaglutide (17 527$ vs 22 878$).[40] Following tirzepatide, semaglutide was observed to be the second most effective agent for weight loss. Similar outcomes were noted in the SUSTAIN trials, where the efficacy of semaglutide was compared with those of other GLP-1 RAs. Specifically, the SUSTAIN 3, 7, and 10 trials compared semaglutide with exenatide, dulaglutide, and liraglutide, respectively.[41-43] In each of these trials, semaglutide consistently resulted in a substantial weight reduction. However, because of a lack of direct comparative trial data, we were unable to conduct a head-to-head comparison of different types of GLP-1 RAs; thus, we encourage future trials that compare GLP-1 RAs with each other to offer more thorough insight. The proportion of individuals achieving greater than or equal to 5%, 10%, or 15% weight loss was greater in the GLP-1 RA groups than in the placebo group. In both 5% and 10% weight losses, orforglipron was observed to produce the

maximal effect, followed by semaglutide. The achievement of these thresholds of weight loss is a long process, and the mechanism of action of orforglipron may somehow contribute to the results as it produces cAMP signaling similar to other GLP-1 RAs but also results in relatively low β-arrestin pathway activation, which, in turn, leads to less internalization of the GLP receptor, thus prolonging the effects.[44] However, the smaller sample size in the orforglipron group undermines the robustness of the results.

An increased BP level is a well-known comorbidity of obesity.[45] The metabolic, cardiovascular, and renal changes associated with obesity all lead to the development of increased BP levels.[45] In this study, we hypothesized that weight reduction would lead to a significant reduction in the BP levels. We demonstrate that the use of GLP-1 RAs leads to a significant improvement in the BP levels compared with a placebo. Initially, the efficacy of GLP-1 RAs in controlling BP was controversial. Patoulias et al[46] failed to demonstrate a significant improvement in the BP levels, and the study by Zhao et al[47] showed a modest reduction in BP; however, the effect was not sustained for longer periods. Nonetheless, in recent years, extensive studies were conducted and showed that GLP-1 RAs were associated with significantly improved BP control. The studies by Usman et al,[48] Lundgren et al,[49] and Wang et al[50] reported a substantial reduction in BP with GLP-1 RA usage. The mechanism underlying this effect of GLP-1 RAs has been hypothesized to be due to their vasodilatory effects on blood vessels, diuretic effects on the kidneys, and/or interaction with the central nervous system.[49] Subgroup analysis showed that the greatest magnitude of effect resulted from the use of tirzepatide, whereas no significant effect was observed with and orforglipron failed to decrease the diastolic BP to a significant degree. GLP-1 RAs have also demonstrated potential to be used in other cardiovascular disease states. The recent STEP-HFpEF reported the efficacy of semaglutide in significantly improving heart failure symptoms and increasing exercise capacity.[16] Because greater improvements in BP control were observed with tirzepatide, we hypothesize that tirzepatide can prove to be more efficacious than other GLP-1 RAs.

We assessed the efficacy of GLP-1 RAs on lipid profiles—mainly LDL, HDL, VLDL, TAG, and TC. Overall, GLP-1 RAs were observed to significantly decrease the LDL, VLDL, TAG, and TC levels and increase the HDL levels. We observed variable effects across the drug types. Semaglutide significantly decreased the LDL, VLDL, TAG, and TC levels but was not found to increase the HDL levels. The effect on TAG was found marginal at best. Similarly, liraglutide was observed to decrease the LDL, VLDL, TC, and TAG levels; however, its effects on the HDL levels were nonsignificant. Exenatide demonstrated no efficacy in improving lipid profile. Orforglipron and tirzepatide were the only GLP-1 RAs that proved to significantly improve the lipid profile across all parameters in obese individuals without diabetes. Although the impact of GLP-1 RAs on lipid profiles is statistically significant across trials, the magnitude of these effects has been relatively modest. For instance, in the DURATION 6 trial, exenatide was compared with liraglutide in patients with T2DM.[51] Liraglutide was associated with decreases of only 0.15, 0.09, and 0.18 mmol/L in the TC, LDL cholesterol, and non-HDL cholesterol levels, respectively.[51] Furthermore, the use of exenatide led to changes of 0.05, 0.02, 0.05, and 0.08 mmol/L in the TC, HDL, LDL cholesterol, and non-HDL levels, respectively.[51] Similarly, the efficacy of semaglutide was assessed in the SUSTAIN 1 and 4 trials, where semaglutide demonstrated minimal changes in the lipid levels.[52,53] This is expected, given that the primary mode of action of GLP-1 RAs involves increasing feelings of fullness and reducing food intake, rather than directly targeting lipid metabolism.[11] However, it is worth noting that tirzepatide induced more substantial changes in the lipid profiles than other GLP-1 RAs. This distinction can be attributed to the dual incretin activity of tirzepatide, particularly its simultaneous impact on the GIP receptors.[35] Research has shown that this dual incretin activity significantly improves dyslipidemia. In the SURPASS 2 trial, tirzepatide was observed to decrease the lipid values by 15% to 20% more than semaglutide. Coupled with its greater effectiveness in inducing weight loss, this suggests that dual incretin therapy is more advantageous for individuals with obesity than the treatment with GLP-1 RAs alone.[39]

In our study, GLP-1 RAs were found to significantly increase the risk of adverse events such as nausea, diarrhea, constipation, and vomiting; however, no increased risk of hypoglycemia was noted. Orforglipron was observed to incur the higher risk of developing nausea and constipation, whereas tirzepatide was observed to pose the highest risk of developing diarrhea and vomiting. The reported adverse events were of mild to moderate severity and often self-limiting. Although vomiting, nausea, and diarrhea are undesired side effects, it is hypothesized that these adverse effects may contribute to the weight loss function of this class of drugs.[11] Indeed, nausea as a side effect of liraglutide caused an additional kilogram weight loss of 2.9% compared with that of individuals without nausea.[11,12] Similarly, in the SUSTAIN trials, slightly higher weight loss was observed in the treatment arm.[54] However, this was not a significant change, and the STEP trials reported that the adverse events were responsible for the increased discontinuation of treatment in the semaglutide group compared with that in the placebo group.[55] This loss of compliance will ultimately lead these patients to regain weight, predisposing them once again to multiple comorbidities.

The results of our meta-analysis should be interpreted in light of certain limitations. The meta-analysis was conducted under the assumption that the baseline characteristics of the participants in the included studies were substantially similar. In addition, only English-language articles that had been published were included, which may introduce language bias in our study. Only 1 study that assessed the effects of tirzepatide and orforglipron was included; hence, their greater effects on outcomes could be overestimated. Substantial heterogeneity was observed throughout the study. This can be attributed to several factors, such as pooling of different GLP-1 RA subtypes with varying baseline characteristics. The inclusion of tirzepatide, a dual incretin targeting both GLP-1 and GIP receptors, may have introduced variability in the intervention. In addition, the different dosages used in the trials of both intra- and intersubtypes could be a possible cause of heterogeneity. Individuals who received background or adjunctive therapies were not reported in several studies, which could introduce heterogeneity in the results. Several trials had a small sample size population, which could have introduced a small-study bias.[29,36-38] Furthermore, in a subset of included RCTs, the randomization process was not adequately defined. This lack of clarity in reporting could potentially introduce bias into our observations.

Conclusions

Our comprehensive meta-analysis of published studies demonstrates the beneficial effects of GLP-1 RAs on weight loss in an obese population without diabetes. In addition, we observed that GLP-1 RAs effectively decreased the BP, protecting patients from deleterious cardiovascular outcomes. It is noteworthy that GLP-1 RAs have also been shown to significantly improve patients' lipid profiles, although certain aspects of the literature suggest that there is some controversy regarding this outcome. Therefore, we recommend future trials to investigate the underlying mechanisms

associated with the reduction in lipid profiles and their translation into providing clinical benefit.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

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Author Contributions

S.U.Q. conceptualized and designed the study; N.N. and A.S.A. acquired the data; H.U.H.A. and S.U.Q. analyzed and interpreted the data; H.I., A.H.S., and Z.A. drafted the manuscript; and F.S., S.Q., and S.G. critically revised the manuscript. All authors reviewed and approved the final manuscript.

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