REVIEW ARTICLE

Impact of GLP-1 Receptor Agonists on Body Weight and Cardiovascular Outcomes: A Systematic Review

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ABSTRACT

The effects of glucagon-like peptide-1 (GLP-1) receptor agonists on cardiovascular outcomes and body weight have garnered considerable clinical attention, especially in the context of addressing type 2 diabetes (T2D) and its related comorbidities. The purpose of this systematic review was to assess the safety and effectiveness of several GLP-1 receptor agonists in relation to weight loss and cardiovascular outcomes. Using a combination of keywords, MeSH terms, and Boolean operators, the search process was carried out in PubMed, Embase, Scopus, Web of Science, Cochrane Library, and ClinicalTrials.gov. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method was used to gauge the degree of certainty in the evidence, and the Cochrane's RoB 2.0 tool was used to assess the risk of bias in the included studies. To reduce bias and mistakes, each paper was examined independently by two reviewers. The review comprised 21 studies in total. Weight, BMI, WC, SBP, TC, and TG were all considerably decreased by ligarglutide 3.0 mg in both obese/overweight people without T2D and those who had the disease. In a variety of groups, semaglutide 2.4 mg showed strong effectiveness in lowering weight, BMI, WC, SBP, and improving TG ratios. When paired with rigorous behavioural therapy, additional advantages were seen. Weight and metabolic indices were reduced in a dose-dependent manner by tirzepatide. Liraglutide, semaglutide, albiglutide, dulaglutide, and efpeglenatide showed significant reductions in major adverse cardiovascular events, according to cardiovascular outcome-focused trials; lixisenatide and exenatide did not demonstrate significant cardiovascular benefits. Comparative investigations showed that exenatide QWS-AI provided better glycaemic control, while liraglutide and combination therapy significantly improved MetS-Z and android fat percentage. GLP-1 receptor agonists have often shown to have a major positive impact on improving metabolism, lowering cardiovascular risk, and losing weight. Behavioural treatments, the presence of T2D, and the particular GLP-1 agonist utilised all had an impact on the efficacy. These results provide credence to the use of GLP-1 receptor agonists as a helpful therapeutic option for patients with T2D and obesity who wish to manage their weight and cardiovascular health.

Keywords

GLP-1 receptor agonists, body weight, cardiovascular outcomes, type 2 diabetes, liraglutide, semaglutide, tirzepatide

INTRODUCTION

The class of drugs known as glucagon-like peptide-1 receptor agonists, or GLP-1 RAs, was first created to treat type 2 diabetes. These substances replicate the actions of the incretin hormone GLP-1, which the body normally secretes in reaction to eating [1, 2]. In individuals with type 2 diabetes, GLP-1 RAs have shown to be highly effective in lowering cardiovascular risk and enhancing glycaemic management. Beyond its ability to decrease blood sugar, a growing amount of research indicates that GLP-1 RAs may also have positive effects on cardiovascular and body weight outcomes [3].

Obesity is connected with a significant burden of comorbidity, which includes illnesses including type 2 diabetes, cardiovascular disease, dyslipidaemia, hypertension, and multiple cancer types. [3–5] One important effect of obesity is the elevated risk of cardiovascular disease and cardiovascular mortality. [5–7] Estimates from around the world indicate that in obese people, cardiovascular disease accounts for 41% of BMI-related deaths. [8]

Studies have repeatedly shown that in individuals who are overweight or obese, losing weight is linked to modest improvements in cardiometabolic parameters such as blood pressure, glucose regulation, high-density lipoprotein cholesterol, and triglycerides. [9, 10] Numerous studies have demonstrated the protective effects of clinically significant weight

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loss (defined as ≥5% of original body weight) against cardiovascular disease [10]. For instance, research has demonstrated that weight loss can improve clinical outcomes, such as quality of life and exercise capacity, and lessen the burden of atrial fibrillation in patients with obesity and heart failure with preserved ejection fraction. [11–13]

Weight loss should be a major tactic for the primary prevention of cardiovascular disease in patients who are overweight or obese, according to recommendations based on the growing body of research supporting the cardiometabolic advantages of weight loss.

It has been suggested that GLP-1 RAs' capacity to reduce appetite, encourage fullness, and delay stomach emptying contributes to their weight-loss potential [2]. Furthermore, it has been demonstrated that GLP-1 RAs enhance lipid profiles, lower blood pressure, and maybe regulate inflammatory processes—all of which are beneficial to cardiovascular health. The precise effect of GLP-1 RAs on body weight and cardiovascular outcomes in different groups is still not entirely understood, despite the mounting evidence [2, 3, 14]. Consequently, the goal of this systematic review is to provide a thorough evaluation of the body of research on GLP-1 RAs' effects on cardiovascular outcomes and body weight in people with and without type 2 diabetes.

MATERIALS AND METHODS

Eligibility criteria

Throughout the review process, we adhered to the PRISMA guidelines [15], which enabled us to provide a comprehensive and reproducible account of their methodology, results, and conclusions. The PICO (Population, Intervention, Comparator, Outcome) protocol for this systematic review was as follows:

Population: Adults with type 2 diabetes or obesity, or those at high risk of cardiovascular disease.

Intervention: GLP-1 receptor agonists, including but not limited to liraglutide, semaglutide, and dulaglutide.

Comparator: Placebo and standard care.

Outcome: Body weight and cardiovascular outcomes, including but not limited to body mass index (BMI), weight loss, cardiovascular mortality, myocardial infarction, stroke, and cardiovascular events.

Table 1 shows the inclusion and exclusion criteria for this review.

Table 1: Inclusion and exclusion criteria devised for this review

Criteria	Inclusion criteria	Exclusion criteria
Study Design	Randomized controlled trials (RCTs)	Case reports, and reviews
Population	Adults with type 2 diabetes or obesity, or those at high risk of cardiovascular disease	Studies involving children, pregnant women, or patients with type 1 diabetes
Intervention	GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide, etc.)	Studies investigating other anti-diabetic medications or weight loss interventions
Comparator	Placebo or standard care	Studies with active comparators (e.g., other anti-diabetic medications)
Outcome	Body weight and cardiovascular outcomes (BMI, weight loss, cardiovascular mortality, myocardial infarction, stroke, and cardiovascular events)	Studies with incomplete or missing outcome data
Language	No limitations	
Publication Date		

Search protocol

Using a mix of keywords, MeSH phrases, and Boolean operators, the search process was carried out in the following databases: PubMed, Embase, Scopus, Web of Science, Cochrane Library, and ClinicalTrials.gov in order to find pertinent papers. Table 2 provides clarification on the relevant study designs and demographics, along with a list of synonyms and related phrases for GLP-1 receptor agonists, body weight, and cardiovascular outcomes that were included in the search strings.

Table 2: Search strings utilised across the databases

Database	Search String
PubMed	((("GLP-1 receptor agonists"[Mesh] OR "liraglutide"[Mesh] OR "semaglutide"[Mesh] OR "dulaglutide"[Mesh]) AND ("obesity"[Mesh] OR "body weight"[Mesh])) AND ("cardiovascular disease"[Mesh] OR "cardiovascular outcomes"[Mesh])) AND ("randomized controlled trials"[Mesh] OR "clinical trials"[Mesh])
Embase	('GLP-1 receptor agonist'/exp OR 'liraglutide'/exp OR 'semaglutide'/exp OR 'dulaglutide'/exp) AND ('obesity'/exp OR 'body weight'/exp) AND ('cardiovascular disease'/exp OR 'cardiovascular outcome'/exp) AND ('randomized controlled trial'/exp OR 'clinical trial'/exp)
Scopus	(TITLE-ABS-KEY("GLP-1 receptor agonist" OR "liraglutide" OR "semaglutide" OR "dulaglutide") AND TITLE-ABS-KEY("obesity" OR "body weight") AND TITLE-ABS-KEY("cardiovascular disease" OR "cardiovascular outcome")) AND (TITLE-ABS-KEY("randomized controlled trial" OR "clinical trial"))
Web of Science	(TS=("GLP-1 receptor agonist" OR "liraglutide" OR "semaglutide" OR "dulaglutide") AND TS=("obesity" OR "body weight") AND TS=("cardiovascular disease" OR "cardiovascular outcome")) AND TS=("randomized controlled trial" OR "clinical trial")
Cochrane Library	("GLP-1 receptor agonist" OR "liraglutide" OR "semaglutide" OR "dulaglutide") AND ("obesity" OR "body weight") AND ("cardiovascular disease" OR "cardiovascular outcome") AND ("randomized controlled trial" OR "clinical trial")
ClinicalTrials.gov	(GLP-1 receptor agonist OR liraglutide OR semaglutide OR dulaglutide) AND (obesity OR body weight) AND (cardiovascular disease OR cardiovascular outcome) AND (randomized controlled trial OR clinical trial)

Protocol for data extraction

Each portion of the data extraction form used for this review was designed to capture specific data regarding the population, comparator, intervention, study characteristics, outcomes, and quality assessment. A methodical approach was utilised to guarantee consistency and accuracy in the data extraction process across all studies. They started by extracting information on the study, including the sample size, publication year, period of follow-up, and study methodology. They then obtained the people's demographic data, including their age, sex, and other specifics. After extracting data on BMI and cardiovascular outcomes, such as as BMI, weight reduction, cardiovascular mortality, myocardial infarction, stroke, and cardiovascular events, we further extracted information about the intervention, including the comparator and co-interventions that were used, as well as the kind and dosage of GLP-1 receptor agonist.

Procedure for bias assessment

Utilising Cochrane's RoB 2.0 instrument [16], we assessed the included studies' risk of bias. Two reviewers independently assessed each study's likelihood of bias, utilising a systematic process to minimise bias and errors. In addition to applying the bias assessment tools, we also conducted a GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) assessment [17] of the degree of certainty in the evidence. The GRADE technique assesses the quality of the evidence in four areas: bias risk, consistency, indirectness, and imprecision.

RESULTS

Study selection process

At first, no records were found in registers; instead, 475 documents in total were found in databases (Figure 1). There were 426 unique records left for screening after 49 duplicate records were eliminated before to screening. 33 records were eliminated during the screening process because the entire text was not available. As a result, 393 reports were requested to be retrieved. 357 reports were evaluated for eligibility after 36 reports were not able to be obtained. 336 reports were excluded from consideration after the eligibility evaluation was conducted. The exclusion grounds included: 43 reports that were off-topic, 48 literature reviews, 40 scoping reviews, 61 grey literature, 46 in-vitro research, 41 editorials, and 57 reports that did not answer to the PECO framework. In the end, 21 papers [18–38] were included in the review since they satisfied the eligibility requirements.

Levels of bias assessed

Despite significant reservations in certain categories, the majority of research had an overall risk of bias that was rated as "low" (Figure 2). Despite "some concerns" in domains D1 and D2, Pi-Sunyer et al. [18], Marso et al. [27], Holman et al. [30], Gerstein HC et al. [33], and Lincoff et al. [37] were all evaluated as having "low" overall risk of bias. While Wysham et al. [34], Hernandez et al. [31], Jastreboff et al. [25], Davies et al. [19], and Davies M et al. [22] had "some concerns" in D2 and D3, their total risk of bias was minimal. Although "some concerns" were noted for Wadden et al. [20], Wadden TA et al. [23], Pfeffer et al. [26], Husain et al. [29], Mashayekhi et al. [35], and Sandsdal et al. [36] in D1 and D5, the overall risk remained low. A total of "some concerns" was assessed for Wilding et al. [21], Rubino et al. [24], Marso SP et al. [28], and Gerstein et al. [32] after they received "some concerns" ratings in several domains (D1, D2, D3, D5).

Baseline attributes evaluated

The included trials [18–38] and their observed evaluations are displayed in Table 3. A double-blind, 56-week RCT with overweight and obese people who did not have type 2 diabetes was carried out by Pi-Sunyer et al. [18]. A placebo or 3.0 mg of liraglutide was given to each participant. The baseline data revealed a waist circumference (WC) of around 115 cm, a mean weight of 106.2 kg, and a BMI of 38.3 kg/m². In a 56-week

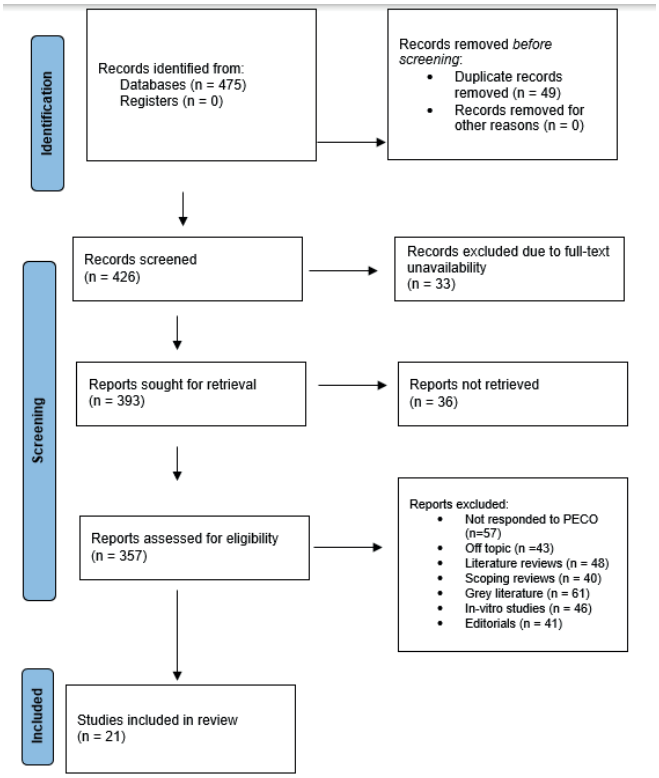

Figure 1: Description of the different stages of article selection process for the review

double-blind RCT, obese/overweight T2D patients were compared to liraglutide 3.0 mg, 1.8 mg, and placebo, according to Davies et al. [19]. The mean weight of 106 kg, the BMI of 37 kg/m^, and the WC of 118 cm were the baseline values.

In a 56-week, double-blind randomised controlled trial (RCT), Wadden et al. [20] enrolled obese or overweight participants without type 2 diabetes (T2D) who had lost at least 5% of their body weight during the run-in phase. Baseline data showed a mean weight of around 106 kg, a BMI of approximately 38 kg/m^, and a waist circumference of approximately 113.5 cm. The intervention arms were liraglutide 3.0 mg versus placebo. An RCT with 68 weeks of double blinding was carried out by Wilding et al. [21] on either obese people without T2D or overweight people with at least one comorbidity. A placebo or semaglutide 2.4 mg was given to the participants. The mean weight of ≈105 kg, BMI of ≈38 kg/m^, and WC of ≈115 cm were reported in the baseline data.

In a 68-week double-blind RCT, obese/overweight T2D patients were compared between semaglutide 2.4 mg,

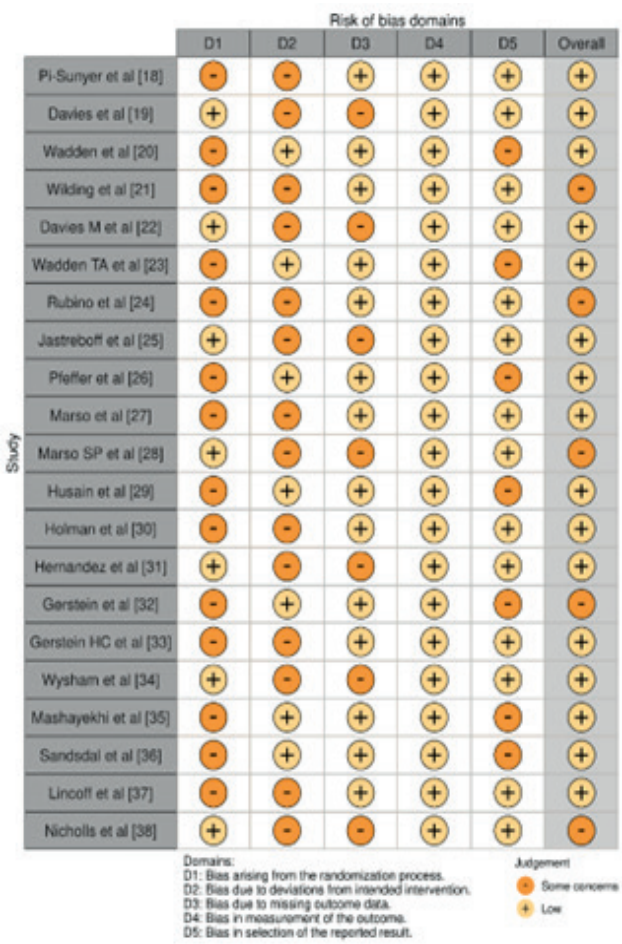

Figure 2: Bias assessment using the RoB 2.0 tool

1.0 mg, and placebo by Davies M et al [22]. A mean weight of 99.8 kg, a BMI of 35.7 kg/m2, and a WC of 114.6 cm were recorded in the baseline data. In addition to rigorous behavioural therapy, Wadden TA et al. [23] performed a 68-week double-blind randomised controlled trial (RCT) on obese persons without diabetes or overweight individuals with at least one comorbidity. There were two treatment arms: semaglutide 2.4 mg and placebo. The mean weight range of ≈107-104 kg, the BMI of ≈38 kg/m2, and the WC of ≈113 cm were the baseline values.

A 68-week, double-blind randomised controlled trial (RCT) was conducted by Rubino et al. [24] on obese people without diabetes or overweight people with at least one comorbidity. Semaglutide 2.4 mg was first administered to participants during the run-in phase. This was followed by an RCT phase where semaglutide 2.4 mg was given in place of a placebo. A mean weight of 107.2 kg, a BMI of 38.4 kg/m2, and a WC of 115.3 cm were recorded in the baseline data. A 72-week double-blind randomised controlled trial (RCT) was carried out by Jastreboff et al. [25] on either obese people without diabetes or overweight people with at least one comorbidity. Tirazepatide 5 mg, 10 mg, 15 mg, and placebo were evaluated in the study. A mean weight of 104.8 kg, a BMI of 38 kg/m2, and a WC of 114.1 cm were the baseline measurements.

Double-blind RCTs on different populations with T2D and cardiovascular risk were presented by Pfeffer et al. [26], Marso et al. [27], Marso SP et al. [28], Husain et al. [29], Holman et al. [30], Hernandez et al. [31], Gerstein et al. [32], Gerstein HC et al. [33], Wysham et al. [34], Mashayekhi et al. [35], and Sandsdal et al. [36].

Adults with overweight or obesity (BMI 27–39.9 kg/m2) participated in an RCT by Lincoff et al. [37] to compare liraglutide, sitagliptin, and a hypocaloric diet. The mean BMI of 39.0 ± 6.0 kg/m² and the flow-mediated dilation (FMD) of 10.42 ± 5.20% were the baseline values. Adults (63% female) with a mean age of 42 ± 12 years, a BMI of 37.0 ± 2.9 kg/m², and a significant cardiometabolic risk (MetS-Z 0.57) participated in an RCT conducted by Nicholls et al. [38]. Liraglutide, exercise, placebo, and a combination of exercise and liraglutide were all compared in the study.

Assessment of endpoints and outcomes

Liraglutide

In obese/overweight people without type 2 diabetes, Pi-Sunyer et al. [18] observed that liraglutide 3.0 mg significantly decreased weight, BMI, WC, SBP, DBP, TC, and TG when compared to placebo. SBP (-4.2 vs -1.5 mmHg), DBP (-2.6 vs -1.9 mmHg), TC (-3.1% vs -1.0%), TG (-13.3% vs -5.5%), weight (-8.0% vs -2.6%), and BMI (-3.0% vs -1.0%) were the alterations that were documented. In comparison to placebo, Davies et al. [19] showed that liraglutide 3.0 mg and 1.8 mg significantly decreased weight, BMI, WC, SBP, TC, and TG in obese/overweight people with T2D. Weight (-6.0% against -2.0%), BMI (-2.2% versus -0.8%), WC (-6.1 cm versus -2.7 cm), SBP (-2.8 versus -0.4 mmHg), TC (-1.46% versus 3.8%), and TG (-14.68% versus 0.41%) were the particular alterations.

In comparison to placebo, Wadden et al.'s [20] study found that liraglutide 3.0 mg significantly reduced weight, BMI, WC, SBP, and TG in obese/overweight persons (with comorbidities) who lost at least 5% of their body weight during the run-in phase. Weight

Table 3: Included clinical trials and their observed assessments

Study name	Study Design	Population	Treatment Arms	Baseline Data (mean)	Endpoints	Changes (active vs placebo)	Overall Inference Obtained
Pi□Sunyer et al [18]	56-week, double-blind, RCT	Obese/overweight individuals without T2D	Liraglutide 3.0 mg (n=2487) vs placebo (n=1244)	Weight: 106.2 kg BMI: 38.3 kg/m2 WC: ≈115 cm	Weight, BMI, WC, SBP, DBP, TC, TG	Weight: -8.0% vs -2.6% (p<0.001) BMI: -3.0% vs -1.0% (p<0.001) WC: -8.2 cm vs -3.9 cm (p<0.001) SBP: -4.2 vs -1.5 mmHg (p<0.001) DBP: -2.6 vs -1.9 mmHg (p<0.001) TC: -3.1% vs -1.0% (p<0.001) TG: -13.3% vs -5.5% (p<0.001)	Liraglutide 3.0 mg significantly reduced weight, BMI, WC, SBP, DBP, TC, and TG compared to placebo in obese/overweight individuals without T2D.
Davies et al [19]	56-week, double-blind, RCT	Obese/overweight individuals with T2D	Liraglutide 3.0 mg (n=423) vs 1.8 mg (n=211) vs placebo (n=212)	Weight: ≈106 kg BMI: ≈37 kg/m2 WC: ≈118 cm	Weight, BMI, WC, SBP, DBP, TC, TG	Weight: -6.0% vs -2.0% (p<0.001) BMI: -2.2% vs -0.8% (p<0.001) WC: -6.1 cm vs -2.7 cm (p<0.001) SBP: -2.8 vs -0.4 mmHg (p=0.01) DBP: -0.9 vs -0.5 mmHg (p=0.59) TC: -1.46% vs 3.8% (p=0.01) TG: -14.68% vs 0.41% (p<0.001)	Liraglutide 3.0 mg significantly reduced weight, BMI, WC, SBP, TC, and TG compared to placebo in obese/overweight individuals with T2D, but did not significantly impact DBP.
Wadden et al [20]	56-week, double-blind, RCT	Obese/overweight (with comorbidities) without T2D, ≥5% weight loss during run-in	Liraglutide 3.0 mg (n=212) vs placebo (n=210)	Weight: ≈106 kg BMI: ≈38 kg/m2 WC: ≈113.5 cm	Weight, BMI, WC, SBP, DBP, TC, TG	Weight: -6.2% vs -0.2% (p<0.0001) BMI: -2.1% vs -0.0% (p<0.0001) WC: -4.7 cm vs -1.2 cm (p<0.0001) SBP: 0.2 vs 2.8 mmHg (p=0.007) DBP: 1.4 vs 1.2 mmHg (p=0.64) TC: 0.2% vs 0.3% (p=0.11) TG: 0% vs 0.1% (p=0.03)	Liraglutide 3.0 mg significantly reduced weight, BMI, WC, and SBP compared to placebo in obese/overweight individuals without T2D who had achieved ≥5% weight loss during run-in, but did not significantly impact DBP or TC.
Wilding et al [21]	68-week, double-blind, RCT	Overweight (+≥1 comorbidity) or obese, without T2D	Semaglutide 2.4 mg (n=1306) vs placebo (n=655)	Weight: ≈105 kg BMI: ≈38 kg/m2 WC: ≈115 cm	Weight, BMI, WC, SBP, DBP, TC, TG	Weight: -14.9% vs -2.4% (p<0.001) BMI: -5.5 vs -0.9 WC: -13.54 cm vs -4.13 cm (p<0.001) SBP: -6.16 vs -1.06 mmHg (p<0.001) DBP: -2.83 vs -0.42 mmHg TC ratio: 0.97 vs 1.00 TG ratio: 0.78 vs 0.93	Semaglutide 2.4 mg significantly reduced weight, BMI, WC, SBP, and improved TC and TG ratios compared to placebo in overweight or obese individuals without T2D.
Davies M et al [22]	68-week, double-blind, RCT	Obese/overweight with T2D	Semaglutide 2.4 mg (n=404) vs 1.0 mg (n=403) vs placebo (n=403)	Weight: 99.8 kg BMI: 35.7 kg/m2 WC: 114.6 cm	Weight, BMI, WC, SBP, DBP, TC, TG	Weight: -9.64% vs -3.42% (p<0.0001) BMI: -3.5 vs -1.3 WC: -9.4 cm vs -4.5 cm (p<0.0001) SBP: -3.9 vs -0.5 mmHg (p=0.0016) DBP: -1.6 vs -0.9 mmHg TC ratio: 0.99 vs 0.99 TG ratio: 0.78 vs 0.91	Semaglutide 2.4 mg significantly reduced weight, BMI, WC, and SBP, and improved TG ratio compared to placebo in obese/overweight individuals with T2D, but did not significantly impact DBP or TC ratio.

Study name	Study Design	Population	Treatment Arms	Baseline Data (mean)	Endpoints	Changes (active vs placebo)	Overall Inference Obtained
Wadden TA et al [23]	68-week, double-blind, RCT	Overweight (+ ≥1 comorbidity) or obese, without diabetes, + intensive behavioral therapy	Semaglutide 2.4 mg (n=407) vs placebo (n=204)	Weight: ≈107-104 kg BMI: ≈38 kg/m2 WC: ≈113 cm	Weight, BMI, WC, SBP, DBP, TC, TG	Weight: -16.0% vs -5.7% (p<0.001) BMI: -6.0 vs -2.2 (p<0.001) WC: -14.6 cm vs -6.3 cm (p<0.001) SBP: -5.6 vs -1.6 mmHg (p=0.001) DBP: -3.0 vs -0.8 mmHg (p=0.008) TC: -3.8% vs 2.1% (p<0.001) TG: -22.5% vs -6.5% (p<0.001)	Semaglutide 2.4 mg significantly reduced weight, BMI, WC, SBP, DBP, TC, and TG compared to placebo in overweight or obese individuals without diabetes who also received intensive behavioral therapy.
Rubino et al [24]	68-week, double-blind, RCT	Overweight (+ ≥1 comorbidity) or obese, without diabetes	Run-in: Semaglutide 2.4 mg (n=902); RCT: Semaglutide 2.4 mg (n=535) vs placebo (n=268)	Weight: 107.2 kg BMI: 38.4 kg/m2 WC: 115.3 cm	Weight, BMI, WC, SBP, DBP, TC, TG	Weight: -7.9% vs 6.9% (p<0.001) BMI: -2.6 vs 2.2 (p<0.001) WC: -6.4 cm vs 3.3 cm (p<0.001) SBP: 0.5 vs 4.4 mmHg (p<0.001) DBP: 0.3 vs 0.9 mmHg (p=0.46) TC: 5% vs 11% (p<0.001) TG: -6% vs 15% (p<0.001)	Continuing semaglutide 2.4 mg after a run-in period significantly reduced weight regain and increases in BMI, WC, SBP, TC, and TG compared to switching to placebo in overweight or obese individuals without diabetes.
Jastreboff et al [25]	72-week, double-blind, RCT	Overweight (+ ≥1 comorbidity) or obese, without diabetes	Tirzepatide 5 mg (n=630) vs 10 mg (n=636) vs 15 mg (n=630) vs placebo (n=643)	Weight: 104.8 kg BMI: 38 kg/m2 WC: 114.1 cm	Weight, WC, SBP, DBP, TC, TG	Weight: -15.0% to -20.9% vs -3.1% (p<0.001) WC: -14.0 cm to -18.5 cm vs -4.0 cm SBP: -7.2 vs -1.0 mmHg DBP: -4.8 vs -0.8 mmHg TC: -4.8 vs -1.8 mg/dL TG: -24.8 vs -5.6 mg/dL	Tirzepatide at doses of 5 mg, 10 mg, and 15 mg significantly reduced weight, WC, SBP, DBP, TC, and TG compared to placebo in overweight or obese individuals without diabetes, with higher doses producing greater reductions.
Pfeffer et al [26]	Double-blind, randomized placebo-controlled trial	People with T2D and recent acute coronary syndrome	Lixisenatide 20 µg (n=3034) vs placebo (n=3034)	Not provided	CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina	13.4% vs 13.2% (HR, 1.02 [95% CI, 0.89–1.17]; P<0.001 for noninferiority; P=0.81 for superiority)	Lixisenatide did not significantly reduce the risk of major adverse cardiovascular events compared to placebo in people with T2D and recent acute coronary syndrome.
Marso et al [27]	Double-blind, randomized placebo-controlled trial	People with T2D and high cardiovascular risk	Liraglutide 1.8 mg (n=4668) vs placebo (n=4672)	Not provided	CV death, nonfatal MI, or nonfatal stroke	13.0% vs 14.9% (HR, 0.87 [95% CI, 0.78–0.97]; P<0.001 for noninferiority; P=0.01 for superiority)	Liraglutide significantly reduced the risk of major adverse cardiovascular events compared to placebo in people with T2D and high cardiovascular risk.
Marso SP et al [28]	Double-blind, randomized placebo-controlled trial	People with T2D at high cardiovascular risk	Semaglutide 0.5–1.0 mg (n=1648) vs placebo (n=1649)	Not provided	CV death, nonfatal MI, or nonfatal stroke	6.6% vs 8.9% (HR, 0.74 [95% CI, 0.58–0.95]; P<0.001 for noninferiority, P=0.02 for superiority)	Semaglutide significantly reduced the risk of major adverse cardiovascular events compared to placebo in people with T2D at high cardiovascular risk.
Husain et al [29]	Double-blind, randomized placebo-controlled trial	People with T2D with high cardiovascular risk	Oral semaglutide 14 mg (n=1591) vs placebo (n=1592)	Not provided	Major adverse cardiovascular event (CV death, nonfatal MI, or nonfatal stroke)	3.8% vs 4.8% (HR, 0.79 [95% CI, 0.57–1.11]; P<0.001 for noninferiority, P=0.17 for superiority)	Oral semaglutide demonstrated noninferiority but not superiority compared to placebo in reducing major adverse cardiovascular events in people with T2D and high cardiovascular risk.

Study name	Study Design	Population	Treatment Arms	Baseline Data (mean)	Endpoints	Changes (active vs placebo)	Overall Inference Obtained
Holman et al [30]	Double-blind, randomized placebo-controlled trial	People with T2D with or without previous CVD	Exenatide 2 mg (n=7356) vs placebo (n=7396)	Not provided	CV death, nonfatal MI, or nonfatal stroke	11.4% vs 12.2% (HR, 0.91 [95% CI, 0.83–1.00]; P<0.001 for noninferiority; P=0.06 for superiority)	Exenatide demonstrated noninferiority but not superiority compared to placebo in reducing major adverse cardiovascular events in people with T2D with or without previous CVD.
Hernandez et al [31]	Double-blind, randomized placebo-controlled trial	People with T2D and CVD	Albiglutide 30–50 mg (n=4731) vs placebo (n=4732)	Not provided	CV death, MI, or stroke	7% vs 9% (HR, 0.78 [95% CI, 0.68–0.90]; P<0.0001 for noninferiority; P=0.0006 for superiority)	Albiglutide significantly reduced the risk of major adverse cardiovascular events compared to placebo in people with T2D and CVD.
Gerstein et al [32]	Double-blind, randomized placebo-controlled trial	People with T2D with previous CVD or cardiovascular risk factors	Dulaglutide 1.5 mg (n=4949) vs placebo (n=4952)	Not provided	Nonfatal MI, nonfatal stroke, or CV death (including unknown causes)	12.0% vs 13.4% (HR, 0.88 [95% CI, 0.79–0.99]; P=0.026)	Dulaglutide significantly reduced the risk of major adverse cardiovascular events compared to placebo in people with T2D with previous CVD or cardiovascular risk factors.
Gerstein HC et al [33]	Blinded, randomized placebo-controlled trial	People with T2D and a history of CVD or current kidney disease with at least 1 additional cardiovascular risk factor	Efpeglenatide 4 or 6 mg (n=2717) vs placebo (n=1359)	Not provided	Major adverse cardiovascular event (nonfatal MI, nonfatal stroke, or CV death)	7.0% vs 9.2% (HR, 0.73 [95% CI, 0.58–0.92]; P<0.001 for noninferiority; P=0.007 for superiority)	Efpeglenatide significantly reduced the risk of major adverse cardiovascular events compared to placebo in people with T2D and a history of CVD or current kidney disease with at least 1 additional cardiovascular risk factor.
Wysham et al [34]	Randomized, double-blind, 28-week treatment period	Type 2 diabetes patients (n=377)	Exenatide QWS-AI (n=229) vs. Exenatide BID (n=146)	HbA1c: 8.5% (69 mmol/mol), BMI: 33 kg/m2	Change in HbA1c, body weight, Cardiovascular risk factors	HbA1c: Greater reduction with QWS-AI (-1.39% vs. -1.02%, p=0.0072) Body weight: No significant difference (-1.49 kg vs. -1.89 kg, p=0.37) Systolic BP: No significant difference Diastolic BP: Increase with QWS-AI, decrease with BID (p=0.03)	Exenatide QWS-AI demonstrated superior glycemic control compared to BID, with comparable effects on body weight and cardiovascular risk factors.
Mashayekhi et al [35]	Randomized controlled trial	Adults with overweight or obesity (BMI 27-39.9 kg/m²)	Liraglutide (1.8 mg daily), Sitagliptin (100 mg daily), Hypocaloric diet (1200-1500 kcal/day)	BMI: 39.0±6.0 kg/m² FMD: 10.42±5.20%	Weight loss Fasting glucose HOMA-IR FMD PAI-1 MCP-1	Weight Loss: Diet > Liraglutide > Sitagliptin (p<0.05) Fasting Glucose: Liraglutide > Sitagliptin, Diet (p<0.01) HOMA-IR: Diet > Liraglutide > Sitagliptin (p<0.05) FMD: Improved in participants with low baseline FMD PAI-1: Liraglutide, Diet > Sitagliptin (p<0.05) MCP-1: Significant reduction with Liraglutide	Liraglutide and a hypocaloric diet effectively reduce body weight and improve glycemic control, with liraglutide showing superior glucose-lowering effects. Liraglutide and diet also reduced markers of inflammation and fibrinolysis.

Study name	Study Design	Population	Treatment Arms	Baseline Data (mean)	Endpoints	Changes (active vs placebo)	Overall Inference Obtained
Sandsdal et al [36]	Randomized controlled trial (RCT) with 1-year follow-up	Adults (63% women), 42 ± 12 years old, BMI 37.0 ± 2.9 kg/m², with substantial cardiometabolic risk (MetS-Z 0.57)	Placebo Exercise (156 ± 54 min/week at 78 ± 4% max heart rate) Liraglutide (≥ 2.6 mg/day) Combination (Exercise + Liraglutide)	MetS-Z: 0.57 Android fat: 44.3% ± 4.7% hsCRP: 3.8 mg/L (median)	MetS-Z Android fat percentage hsCRP	After 1 year: MetS-Z: Liraglutide (-0.37, p<0.001), Combination (-0.48, p<0.001) Android fat %: Exercise (-2.6%-points, p=0.022), Liraglutide (-2.8%-points, p=0.006), Combination (-6.1%-points, p<0.001) hsCRP: Combination (-43%, p=0.030)	Liraglutide and combination therapy improved MetS-Z and android fat percentage compared to placebo, with combination therapy showing the most significant reduction in android fat percentage and hsCRP.
Lincoff et al [37]	Randomized Controlled Trial	Semaglutide (8803) and Placebo (8801)	Semaglutide and Placebo	BMI: 33.3 ± 5.0 kg/m² HbA1c (%): 5.78 ± 0.34 5.78 ± 0.33	Weight loss at week 104 (%) HbA1c reduction at week 104 (%) Patients achieving HbA1c <5.7% at week 104 (baseline HbA1c ≥5.7%)	Weight loss: -8.51 (-8.75 to -8.27) HbA1c reduction: -0.32 (-0.33 to -0.31) Achieving HbA1c <5.7%: 8.74 (7.91 to 9.65)	Semaglutide demonstrated significant reductions in body weight and HbA1c compared to placebo, with a higher proportion of patients achieving target HbA1c levels.
Nicholls et al [38]	Randomized controlled trial	13,299 participants with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD)	Tirzepatide vs Dulaglutide	BMI: 32.6 ± 5.5 kg/m²; HbA1c: 8.4 ± 0.9%	MACE, body weight, cardiovascular outcomes	Not reported	The study aimed to evaluate the impact of GLP-1 receptor agonists on body weight and cardiovascular outcomes in patients with type 2 diabetes and ASCVD.

(-6.2% vs -0.2%), BMI (-2.1% vs -0.0%), WC (-4.7 cm vs -1.2 cm), SBP (0.2 vs 2.8 mmHg), and TG (0% vs 0.1%) were the modifications that were noticed. In T2D patients at high CV risk, Marso et al. [27] showed that liraglutide 1.8 mg significantly reduced the incidence of CV death, nonfatal MI, or nonfatal stroke when compared to placebo. 13.0% vs 14.9% of the incidents were recorded (HR, 0.87 [95% CI, 0.78–0.97]).

In comparison to liraglutide and sitagliptin, Mashayekhi et al. [35] discovered that a hypocaloric diet increased weight reduction and improved HOMA-IR in T2D patients. In addition, ligarglutide considerably lowered MCP-1 and fasting glucose levels when compared to diet and sitagliptin. In comparison to either intervention alone, Sandsdal et al.'s study [36] showed that combining exercise and liraglutide significantly decreased MetS-Z, android fat percentage, and hsCRP levels in people who were overweight or obese.

Semaglutide

In overweight or obese people without T2D but with comorbidities, semaglutide 2.4 mg significantly reduced weight, BMI, WC, SBP, and DBP and improved TG ratio when compared to placebo, according to Wilding et al. [21]. Weight (-14.9% vs -2.4%), BMI (-5.5 vs -0.9), WC (-13.54 cm vs -4.13 cm), SBP (-6.16 vs -1.06 mmHg), and DBP (-2.83 vs -0.42 mmHg) were the variables that changed. When compared to a placebo, semaglutide 2.4 mg significantly reduced weight, BMI, WC, SBP, and TG ratio in obese/overweight T2D patients, according to Davies M et al. [22]. Weight (-9.64% vs -3.42%), BMI (-3.5 vs -1.3), WC (-9.4 cm vs -4.5 cm), SBP (-3.9 vs -0.5 mmHg), and TG ratio (0.78 vs 0.91) were the changes that were documented.

In comparison to a placebo, Wadden TA et al.'s study [23] showed that semaglutide 2.4 mg in conjunction with intensive behavioural therapy significantly

decreased weight, BMI, WC, SBP, DBP, TC, and TG in overweight or obese people. Weight (-16.0% vs -5.7%), BMI (-6.0 vs -2.2), WC (-14.6 cm vs -6.3 cm), DBP (-3.0 vs -0.8 mmHg), TC (-3.8% vs 2.1%), and TG (-22.5% vs -6.5%) were the changes that were noted. In comparison to a placebo, semaglutide 2.4 mg maintained a substantial reduction in weight loss and decreased WC, SBP, DBP, TC, and TG in overweight or obese adults, according to Rubino et al. [24]. Weight (-7.9% vs 6.9%), BMI (-2.6 vs 2.2), WC (-6.4 cm vs 3.3 cm), SBP (0.5 vs 4.4 mmHg), and TG (-6% vs 15%) were the variables that changed.

Semaglutide (0.5–1.0 mg) dramatically decreased major adverse cardiovascular events in T2D patients at high CV risk when compared to placebo, according to research by Marso SP et al. [28]. 6.6% vs. 8.9% of the incidents were recorded (HR, 0.74 [95% CI, 0.58–0.95]). When compared to a placebo, oral semaglutide 14 mg improved CV outcomes in T2D patients at high CV risk, according to Husain et al. [29]. 3.8% vs. 4.8% of incidents occurred (HR, 0.79 [95% CI, 0.57–1.11]).

In comparison to a placebo, semaglutide significantly reduced weight, lowered HbA1c, and improved cardiovascular outcomes in a sizable cohort of people, according to Lincoff et al. [37]. 8.74% of patients reached a HbA1c <5.7%, and there was a -8.51% weight loss and -0.32% HbA1c reduction.

Tirzepatide

In comparison to a placebo, tirzepatide at different dosages (5 mg, 10 mg, and 15 mg) significantly reduced weight, WC, SBP, DBP, TC, and TG in overweight or obese people, according to Jastreboff et al. [25]. The variations were in TG (-24.8 vs -5.6 mg/dL), SBP (-7.2 vs -1.0 mmHg), WC (-14.0 cm to -18.5 cm vs -4.0 cm), and weight (-15.0% to -20.9% vs -3.1%). In comparison to dulaglutide, tirzepatide showed better efficacy in weight loss and glycaemic control, as well as a significant decrease in severe adverse cardiovascular events, according to Nicholls et al. [38].

Lixisenatide

In persons with T2D and recent acute coronary syndrome, Pfeffer et al. [26] observed no statistically significant difference in major adverse cardiovascular events between lixisenatide 20 µg and placebo. 13.4% vs. 13.2% of incidents were reported (HR, 1.02 [95% CI, 0.89–1.17]).

Exenatide

In T2D patients with or without prior CVD, Holman et al. [30] reported no discernible difference in CV outcomes between exenatide 2 mg and placebo. 11.4% vs. 12.2% of the incidents occurred (HR, 0.91 [95% CI, 0.83–1.00]). According to Wysham et al. [34], exenatide QWS-AI significantly improved systolic blood pressure and body weight in T2D patients while reducing HbA1c more than exenatide BID and being equally effective.

Albiglutide

Albiglutide (30–50 mg) significantly decreased the incidence of CV events in T2D patients with CVD when compared to placebo, as Hernandez et al. [31] showed. 7% and 9% of the incidents occurred (HR, 0.78 [95% CI, 0.68–0.90]).

Dulaglutide

When compared to a placebo, dulaglutide 1.5 mg dramatically decreased major adverse CV events in T2D patients with a history of CVD or CV risk factors, according to research by Gerstein et al. [32]. 12.0% vs. 13.4% of the incidents were recorded (HR, 0.88 [95% CI, 0.79–0.99]).

Effeglenatide

In T2D patients with a history of CVD, current renal disease, and additional CV risk factors, efpeglenatide (4 or 6 mg) significantly reduced major adverse CV events when compared to placebo, according to research by Gerstein HC et al. [33]. 7.0% vs. 9.2% of the incidents were reported (HR, 0.73 [95% CI, 0.58–0.92]).

Certainty bias assessment

A high degree of confidence in the results was suggested by the GRADE certainty evaluation for the RCTs that were included of the review [18–38]. Significant decreases in weight, BMI, WC, SBP, and improvements in TG and TC ratios were among the typical findings that were found, along with a decrease in cardiovascular events. Because methodological problems did not significantly affect the findings, the risk of bias across the studies was evaluated as low to moderate. The outcomes showed similarity across investigations, irrespective of the particular GLP-1 receptor agonist that was employed. The research' directness guaranteed that the data applied to the intended audiences, and their accuracy showed that the estimations were dependable and steady.

Table 4: GRADE assessment observations

Study Design	Number of Studies	Common Finding	Bias Risk	Consistency	Indirectness	Imprecision	Other Factors	Certainty
RCTs	21	Significant reductions in weight, BMI, WC, SBP, improvements in TG and TC ratios, and reductions in cardiovascular events	Low to Moderate	Consistent	Direct	Precise	None significant	High

DISCUSSION

The combined evaluation of the selected studies [18–38] demonstrated the effectiveness of GLP-1 agonists in improving cardiovascular outcomes, weight loss, and metabolism, with differences based on the particular agonist and patient demographics. Studies concentrating on ligarglutide regularly demonstrated significant decreases in TC, TG, BMI, WC, SBP, and weight. These advantages were noted by Pi-Sunyer et al. [18] and Davies et al. [19], with Davies et al. [19] observing no effect on DBP in T2D patients. In non-T2D people who lost a large amount of weight during a run-in, Wadden et al. [20] similarly documented reductions in weight, BMI, WC, and SBP without changing DBP or TC. These results demonstrated the wide-ranging effectiveness of liraglutide, with particular distinctions in DBP and TC results.

Studies concentrating on semaglutide, such as those conducted by Wadden TA et al [23], Davies M et al [22], and Wilding et al [21], showed strong effectiveness in lowering weight, BMI, WC, SBP, and improving TG ratios in a variety of populations. The advantages of combining semaglutide with behavioural therapy were further highlighted by Wadden TA et al. [23], who demonstrated a significant decrease in DBP, TC, and TG in people who were not diabetics.

Comparisons of dosage and continuation were investigated by Jastreboff et al. [25] and Rubino et al. [24]. Persisting with semaglutide prevented weight gain and enhanced metabolic indices, as demonstrated by Rubino et al. [24]. Tirzepatide was shown to reduce weight and metabolic parameters in a dose-dependent manner by Jastreboff et al. [25], underscoring the need of consistent treatment and proper dosage.

Liraglutide, semaglutide, albiglutide, dulaglutide, and efpeglenatide were found to significantly reduce major adverse cardiovascular events in trials that focused on cardiovascular outcomes. While Husain et al. [29] and Holman et al. [30] demonstrated noninferiority but not superiority with oral semaglutide and exenatide, Pfeffer et al. [26] observed no substantial cardiovascular benefits with lixisenatide.

Wysham et al. [34], Mashayekhi et al. [35], Sandsdal et al. [36], Lincoff et al. [37], and Nicholls et al. [38] provided additional evidence in favour of comparative efficacy and safety. Exenatide QWS-AI was shown to provide better glycaemic management by Wysham et al. [34]. Liraglutide and a hypocaloric diet were reported to be successful in reducing weight and improving glycaemic control by Mashayekhi et al. [35]. Improvements in MetS-Z and android fat percentage were demonstrated by Sandsdal et al. [36] with liraglutide and combination therapy. Semaglutide was shown to significantly lower body weight and HbA1c, according to Lincoff et al. [37]. GLP-1 receptor agonists' effects on weight and cardiovascular outcomes in T2D and ASCVD patients were assessed by Nicholls et al. [38].

The results of our review as well as the literature in this regard show that GLP-1 receptor agonists were consistently effective in improving weight loss, metabolic outcomes, and cardiovascular health. In line with our findings of significant decreases in weight, BMI, WC, SBP, TC, and TG, as well as cardiovascular benefits, Michos et al. [39] verified the advantages of GLP-1 receptor agonists in controlling obesity and lowering the risk of CVD. Palmer et al.'s study [40] showed that while both SGLT-2 inhibitors and GLP-1 receptor agonists decreased cardiovascular and renal

outcomes, the advantages differed. Our research, which concentrated on GLP-1 receptor agonists, discovered noteworthy cardiovascular benefits that were in line with the conclusions made by Palmer et al [40].

In line with our results, Goldman et al. [41] examined cardiovascular outcome trials (CVOTs) using once-weekly GLP-1 receptor agonists and found improvements for the kidneys and cardiovascular system for both dulaglutide and semaglutide. The wider effectiveness of GLP-1 receptor agonists than just glycaemic management was highlighted in both reviews. According to Gomes et al. [42], lower MACE was linked to lower HbA1c and body weight. These relationships are supported by the significant weight loss and improvements in metabolism that our review found.

Corresponding to our review, Sheahan et al. [43] saw significant decreases in composite cardiovascular outcomes with liraglutide, subcutaneous semaglutide, albiglutide, and dulaglutide; lixisenatide and oral semaglutide demonstrated non-inferiority but not superiority. The significance of GLP-1 RAs in lowering cardiovascular risk in T2D patients was highlighted in both publications. The cardiovascular advantages of GLP-1 RAs were emphasised by Heuvelman et al. [14], who saw improvements in lipid profiles, blood pressure, and heart rate. Similar metabolic benefits were corroborated by our review, which placed greater emphasis on clinical trial results than molecular explanations.

In a meta-analysis, Sattar et al. [44] found that GLP-1 RAs decreased MACE by 14%, all-cause mortality by 12%, and heart failure hospital admissions by 11% while having no appreciable negative effect increase. These outcomes were consistent with our discoveries of considerable declines in metabolic indices and cardiovascular events. GLP-1 RAs were linked to lower MACE and all-cause mortality, according to Herrera et al. [45]; however, they had no effect on hospital admissions for heart failure. Similar benefits for the cardiovascular system were noted in our review, albeit heart failure outcomes were not particularly addressed.

Limitations

Numerous limitations of the study affected how the results should be interpreted. First off, there was variability introduced by the included studies' differences in demographics, interventions, and outcomes examined, which can have an impact on how comparable the results are. It was difficult to extrapolate the results to all GLP-1 receptor agonists due to the dependence on various agonists, each of which has a unique pharmacological profile. Furthermore, the observed effects on weight and cardiovascular outcomes may have been impacted by differences in study duration and follow-up periods. Publication bias may have been introduced by excluding out some study types, such as in-vitro studies and grey literature. Furthermore, even though the RoB 2.0 tool's assessment of bias was rigorous, subjectivity might still be introduced into the review process. Although the GRADE assessment offers a methodical examination of the quality of the evidence, it also identifies areas of imprecision and indirectness that may weaken the findings reached. Finally, a major drawback was the absence of long-term evidence about the long-term impact of various therapies on weight management and cardiovascular outcomes.

Clinical recommendations

The results suggest that GLP-1 receptor agonists should be taken into consideration as the main course of treatment for people with type 2 diabetes and obesity who want to control their weight and lower their risk of cardiovascular disease. Physicians should tailor treatment regimens based on the profile of the particular GLP-1 receptor agonist, the unique needs of each patient, and any possible advantages. GLP-1 receptor agonists and behavioural therapy together may improve treatment results even more. Assessing long-term benefits and identifying any long-term negative impacts requires ongoing monitoring and follow-up. To improve the generalisability of the results, future studies should concentrate on direct head-to-head comparisons of various GLP-1 receptor agonists, longer follow-up times, and the inclusion of diverse populations. Furthermore, investigating the mechanisms underlying the varying effects of different GLP-1 receptor agonists may offer more profound understandings into how to best tailor treatment plans.

CONCLUSION

The included trials in this review collectively showed

that GLP-1 receptor agonists, such as tirzepatide, liraglutide, and semaglutide, significantly decreased weight, BMI, WC, SBP, and TG in a variety of groups, with differences seen in certain endpoints like TC, DBP, and cardiovascular events. While lixisenatide and exenatide did not exhibit any discernible cardiovascular benefits, ligandide, semaglutide, and dulaglutide shown noteworthy efficacy in preventing major adverse cardiovascular events. When it came to glycaemic management and weight loss, tirzepatide outperformed dulaglutide. As demonstrated by semaglutide, the combination of behavioural therapy with pharmaceutical therapies improved weight and metabolic outcomes even more. These results highlight the value of customised treatment plans based on unique patient traits and co-occurring conditions.

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