Journal of Clinical Question. 2025; 2(6): e93
https://doi.org/10.69854/jcq.2025.0033
Advance access publication date 22 November 2025

Journal of Clinical Question
Gleam Publishing

Original Research

Comparative Efficacy and Safety of Semaglutide, Cagrilintide, and CagriSema in Adults with Overweight or Obesity: A Bayesian Network Meta-Analysis

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Submitted: September 30, 2025 **Accepted:** November 21, 2025

Clinical Question Box

In adults with overweight or obesity, does the combination of Semaglutide and Cagrilintide provide the most effective weight loss while maintaining an acceptable safety profile?

Evidence suggests that the combination therapy, known as CagriSema, produces the largest reductions in both body weight and waist circumference. Semaglutide alone results in substantial weight loss with additional glycemic benefits, whereas Cagrilintide is better tolerated but less effective. Liraglutide appears to be both less effective and less tolerable. None of these agents are associated with an increased risk of serious adverse events, although gastrointestinal side effects are more frequent with glucagon-like peptide-1–based therapies.

Abstract

Introduction: Incretin-based therapies, including glucagon-like peptide-1 receptor agonists and amylin analogues, have emerged as promising treatments for obesity. However, the relative efficacy and safety of Semaglutide, Cagrilintide, Liraglutide, and the novel combination therapy CagriSema remain uncertain. **Methods:** A systematic review and network meta-analysis of randomized controlled trials was conducted in adults with overweight or obesity (body mass index 25–40 kg/m^2), with or without comorbidities. Outcomes included reductions in body weight and waist circumference, glycated hemoglobin, serious adverse events (SAEs), overall treatment discontinuation, and discontinuation due to gastrointestinal symptoms. Mean differences (MDs) and log odds ratios (LORs) with 95% confidence intervals (CIs) were calculated. **Results:** Twelve trials involving 25,401 patients were included,

with follow-up periods ranging from 20 to 104 weeks. CagriSema achieved the greatest reduction in body weight (MD: 17.7%, 95% CI: 14.2–21.3), followed by Semaglutide (MD: 11.1%, 95% CI: 9.5–12.7) and Cagrilintide (MD: 5.9%, 95% CI: 1.5–10.0). CagriSema also showed the largest reduction in waist circumference (MD: −13.4 cm, 95% CI: −17.1 to −9.7), followed by Semaglutide (MD: −8.4 cm, 95% CI: −10.0 to −7.0) and Cagrilintide (MD: −3.6 cm, 95% CI: −7.0 to 0.0). None of the treatments increased the risk of SAEs compared with placebo. However, Semaglutide was associated with higher rates of treatment discontinuation (LOR: 0.6, 95% CI: 0.1–1.2). Gastrointestinal-related discontinuation was highest with Liraglutide (LOR: 3.6, 95% CI: 1.5–5.6), followed by CagriSema (LOR: 2.5, 95% CI: 1.3–3.7) and Semaglutide (LOR: 1.7, 95% CI: 1.0–2.3), while no significant effect was observed with Cagrilintide. **Conclusions:** CagriSema provides the greatest reductions in body weight and waist circumference. Semaglutide combines substantial weight loss with glycemic benefits, whereas Cagrilintide is better tolerated but less effective. Meanwhile, Liraglutide is both less effective and less tolerable.

Keywords: Semaglutide, Cagrilintide, CagriSema, obesity, overweight, network meta-analysis

Introduction

Obesity has become a defining health challenge of the modern era. According to the World Health Organization (WHO), more than 2.5 billion adults worldwide are overweight, and nearly 900 million meet the criteria for obesity.[1] These conditions substantially increase the risk of cardiometabolic disease, nonalcoholic fatty liver disease, sleep-disordered breathing, and certain malignancies, and are associated with diminished life expectancy.[2] Beyond their clinical consequences, obesity and overweight impose a substantial societal burden, with far-reaching psychological, social, and economic costs.[3] Despite the central role of lifestyle modification, long-term adherence to dietary and behavioral interventions is difficult, and durable, clinically meaningful weight loss is uncommon.[4] As a result, pharmacologic therapy has become a critical component of comprehensive obesity management.[5]

Among the available agents, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have redefined therapeutic expectations.[6] Semaglutide, a long-acting GLP-1 RA, has consistently produced weight loss of unprecedented magnitude in randomized controlled trials (RCTs).[7] In the STEP program, once-weekly subcutaneous Semaglutide (2.4 mg) resulted in weight reductions approaching those typically seen after bariatric surgery, alongside broad improvements in cardiometabolic risk factors.[8] The drug's safety profile is generally acceptable, though gastrointestinal adverse events, particularly nausea, vomiting, and diarrhea, are frequent.[9] The striking efficacy of Semaglutide has intensified efforts to develop novel peptide-based therapies that target complementary pathways involved in appetite and energy balance. Liraglutide, an earlier GLP-1 RA, demonstrated proof of concept that incretin-based therapy can facilitate weight reduction, though with more modest effects compared with Semaglutide.

One such complementary pathway involves amylin, a pancreatic hormone co-secreted with insulin that slows gastric emptying and promotes satiety.[10] Cagrilintide, a next-generation, long-acting amylin analogue, has demonstrated reductions in food intake and clinically meaningful weight loss in both preclinical and early-phase clinical trials.[11] Notably, Cagrilintide has also shown additive benefits when combined with GLP-1 RA, offering a strong rationale for dual-hormone approaches.[12,13] The fixed-dose combination of Cagrilintide and Semaglutide, known as CagriSema, represents a novel therapeutic approach designed to exploit this synergy.[14] Early trials suggest that CagriSema may achieve greater weight loss than either agent alone, with parallel improvements in metabolic outcomes and an acceptable safety profile.[15] These encouraging findings have fueled considerable interest in dual-target therapies to address the limitations of monotherapy and meet the unmet needs of patients with obesity. However, direct head-to-head comparisons of Semaglutide, Cagrilintide, and CagriSema remain limited.

Bayesian network meta-analysis (NMA) provides a robust framework for evaluating such interventions. By synthesizing direct and indirect evidence, NMA allows simultaneous comparison of multiple agents and generates probabilistic treatment rankings to inform clinical decision-making. Given the rapidly evolving pharmacologic landscape, a comprehensive analysis of Semaglutide, Cagrilintide, and

CagriSema is timely. The present study was designed to assess the relative efficacy and safety of these agents and to establish their comparative ranking in the treatment of overweight and obesity.

Methods

Protocol and Registration

This systematic review and NMA were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 and the PRISMA extension for NMAs (PRISMA-NMA). The protocol was prospectively registered in the Open Science Framework to ensure methodological transparency and reduce duplication (Registration ID: osf.io/m3f6w).

Eligibility Criteria

Eligible studies were RCTs enrolling adults (≥18 years) with overweight (body mass index [BMI] ≥25 kg/m^2) or obesity (BMI ≥30 kg/m^2). Interventions of interest included GLP-1 RAs (Liraglutide or Semaglutide), Cagrilintide, or their combination, compared with placebo or active comparators. All interventions were administered subcutaneously with a minimum follow-up of 20 weeks. Studies including participants with prediabetes were eligible, whereas trials primarily focused on type 2 diabetes were excluded. Open-label, crossover, or observational studies, as well as those combining pharmacologic therapy with additional nonpharmacologic interventions, were excluded.

Search Strategy

A systematic search of PubMed, Embase, the Cochrane Library, and Web of Science was performed from database inception through August 15, 2025. The search strategy combined Medical Subject Headings and relevant keywords. Terms describing the study population included "overweight" and "obesity." Intervention terms included "semaglutide," "cagrilintide," "CagriSema," "GLP-1 receptor agonist," and "amylin analogue." Comparator terms included "placebo" and "controlled." No language restrictions were applied. Reference lists of eligible studies and relevant systematic reviews were also screened. The detailed search strategy is provided in Table S1.

Study Selection

Titles and abstracts were independently screened by two reviewers, followed by full-text evaluations of potentially eligible reports. Disagreements were resolved through consensus or, when necessary, consultation with a third reviewer. The selection process was summarized in a PRISMA flow diagram.

Data Extraction

Data were extracted independently by two reviewers using a standardized electronic form. Extracted information included study characteristics (author, year, country, design, sample size, follow-up duration), participant characteristics (age, sex, baseline BMI), intervention details (drug, dose, route, schedule), and outcomes. When numerical data were unavailable, corresponding authors were contacted or data were estimated from published figures using validated extraction methods.

Risk of Bias Assessment

The quality of the included studies was assessed using the Cochrane Risk of Bias 2.0 tool, which evaluates randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Each trial was rated as "low risk," "some concerns," or "high risk." Assessments were performed independently by two reviewers, with discrepancies resolved through discussion.

Statistical Analysis

A Bayesian NMA was performed to compare the efficacy and safety of Semaglutide, Cagrilintide, and CagriSema. Random-effects models were used to account for heterogeneity. Analyses were conducted

using Markov Chain Monte Carlo simulations in R with the gemtc and BUGSnet packages. Four chains of 50,000 iterations were run, following a burn-in of 20,000 iterations and a thinning interval of 10. Convergence was assessed by inspecting trace plots and the Gelman–Rubin statistic. Results were expressed as mean differences (MDs) or odds ratios (ORs) with 95% credible intervals (CIs).

Outcomes

The primary outcome was the percentage change in body weight from baseline. Secondary outcomes included changes in waist circumference, glycated hemoglobin (HbA1c), and safety outcomes such as serious adverse events (SAEs), discontinuations due to adverse events, and discontinuations due to gastrointestinal symptoms. Comparative effectiveness was further evaluated using the surface under the cumulative ranking curve (SUCRA), which estimates the probability of each treatment being the most effective.

Assessment of Inconsistency and Heterogeneity

Global inconsistency was evaluated using the design-by-treatment interaction model, while local inconsistency was examined using node-splitting analyses. Statistical heterogeneity was quantified using the posterior distribution of τ^2, representing between-study variance. Publication bias was identified by Egger's test.

Certainty of Evidence

The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework adapted for NMAs. Considerations included risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence for each major outcome was rated as high, moderate, low, or very low.

Results

Study Selection and Characteristics

A total of 4,648 records were identified from four databases. After removing 216 duplicates, 4,432 records were screened. Of these, 4,311 records were excluded, leaving 121 reports that were assessed for eligibility. A further 109 reports were excluded (reviews, non-RCTs, duplicates, oral admissions, or different backgrounds). Ultimately, 12 studies met the eligibility criteria (Fig. S1). The included trials recruited adults with overweight or obesity (BMI 25–40), often with comorbidities such as osteoarthritis, prediabetes, or cardiovascular disease (Table 1).[16–27] Most studies compared Semaglutide against placebo, while several also tested CagriSema, Cagrilintide, or Liraglutide. Sample sizes ranged from fewer than 40 participants in early-phase work to more than 17,000 in the largest cardiovascular outcomes trial. Follow-up durations spanned from 20 to 104 weeks. Participants were typically in their 40s and 50s, although the cardiovascular trial enrolled an older cohort with a mean age of 62 years. Women comprised two-thirds to four-fifths of most study populations. Average BMI values generally ranged from 32 to 40 kg/m^2. Mean baseline HbA1c values were mostly close to the non-diabetic range (5.3–6.4%). All data included in the analysis were derived from studies using the approved doses of Cagrilintide or Semaglutide 2.4 mg.

Table 1. Characteristics and background of enrolled studies

Author	Inclusion criteria	Treatment arms	Cases	Age (years)	Female (%)	BW (kg)	BMI (kg/m^2)	WC (cm)	HbA1c (%)	Follow-up
Bliddal et al., 2024	BMI > 30 with osteoarthritis	Semaglutide vs. Placebo	407	56 (10)	332 (82)	109 (24)	40.3 (7.2)	119 (16)	—	68 w
Enebo et al., 2021	BMI 27.0–39.9 kg/m^2	CagriSema vs. Semaglutide	36	42 (9)	15 (42)	97 (15)	32.2 (2.8)	—	5.3 (0.4)	20 w
Garvey et al., 2022	BMI ≥ 27 with complication or BMI ≥ 30	Semaglutide vs. Placebo	304	47 (11)	236 (78)	106 (22)	38.6 (6.9)	116 (15)	5.7 (0.4)	104 w
Garvey et al., 2025	BMI ≥ 27 with complication or BMI ≥ 30	CagriSema vs. Semaglutide vs. Cagrilintide vs. Placebo	3,417	47 (12)	2309 (68)	107 (23)	37.9 (6.8)	115 (16)	5.5 (0.4)	68 w
Kadowaki et al., 2022[a]	BMI ≥ 27 with complication or BMI ≥ 35	Semaglutide vs. Placebo	300	51 (11)	111 (37)	88 (16)	32 (4.5)	104 (11)	6.4 (1.2)	68 w
Lau et al., 2021	BMI ≥ 27 with complication or BMI ≥ 30	Cagrilintide vs. Placebo vs. Liraglutide	302	52 (10)	199 (66)	107 (23)	37.9 (6.9)	114 (14)	5.6 (0.4)	26 w
Lim et al., 2025	BMI ≥ 25	Semaglutide vs. Placebo	150	39 (11)	111 (74)	84 (18)	31.3 (5.2)	98 (12)	5.6 (0.3)	44 w
Lincoff et al., 2023	BMI ≥ 27 with preexisting cardiovascular disease	Semaglutide vs. Placebo	17,604	62 (9)	4892 (28)	97 (18)	33.3 (5.0)	111 (13)	5.8 (0.3)	48 w
McGowan et al., 2024	BMI > 30 with prediabetes	Semaglutide vs. Placebo	207	53 (11)	147 (71)	112 (22)	40.1 (6.9)	120 (15)	5.9 (0.3)	52 w
Mu et al., 2024[b]	BMI ≥ 27 with complication or BMI ≥ 30	Semaglutide vs. Placebo	375	40 (11)	170 (45)	96 (18)	34 (4.8)	108 (11)	6.3 (1.1)	44 w
Rubino et al., 2022	BMI ≥ 27 with complication or BMI ≥ 31	Semaglutide vs. Liraglutide vs. Placebo	338	49 (13)	265 (78)	105 (24)	37.5 (6.8)	113 (16)	5.5 (0.3)	68 w
Wilding et al., 2021	BMI ≥ 27 with complication or BMI ≥ 30	Semaglutide vs. Placebo	1,961	46 (13)	1453 (74)	105 (22)	37.9 (6.6)	115 (15)	5.7 (0.3)	68 w

Note: a. Ninety-nine (25%) patients were diagnosed with type 2 diabetes mellitus; b. ninety-six (25.6%) patients were diagnosed with type 2 diabetes mellitus. BW: body weight; BMI: body mass index; WC: waist circumference; w: weeks; vs.: versus.

Body Weight Reduction

The network of included studies assessing body weight is shown in Fig. 1A. Eight trials evaluated Semaglutide vs. placebo, with additional comparisons of Liraglutide vs. placebo, Cagrilintide vs. placebo, and CagriSema vs. placebo. The estimated effects relative to placebo are presented in Fig. 2A. CagriSema produced the greatest reduction in body weight (MD: 17.7%, 95% CI: 14.2–21.3), followed by Semaglutide (MD: 11.9%, 95% CI: 9.5–12.7), Cagrilintide (MD: 5.9%, 95% CI: 1.5–10.0), and Liraglutide (MD: 4.3%, 95% CI: 0.7–7.6). The NMAs are summarized in Table 2. CagriSema was superior to all active comparators, compared with Semaglutide (MD: 6.6%, 95% CI: 3.0–10.3), Cagrilintide (MD: 11.8%, 95% CI: 6.5–17.5), and Liraglutide (MD: 13.4%, 95% CI: 8.8–18.5). Semaglutide was also superior to Cagrilintide (MD: 5.2%, 95% CI: 1.0–9.7) and Liraglutide (MD: 6.8%, 95% CI: 3.5–10.4). In contrast, Cagrilintide and Liraglutide did not differ significantly from each other (MD: 1.6%, 95% CI: −2.6 to 5.8).

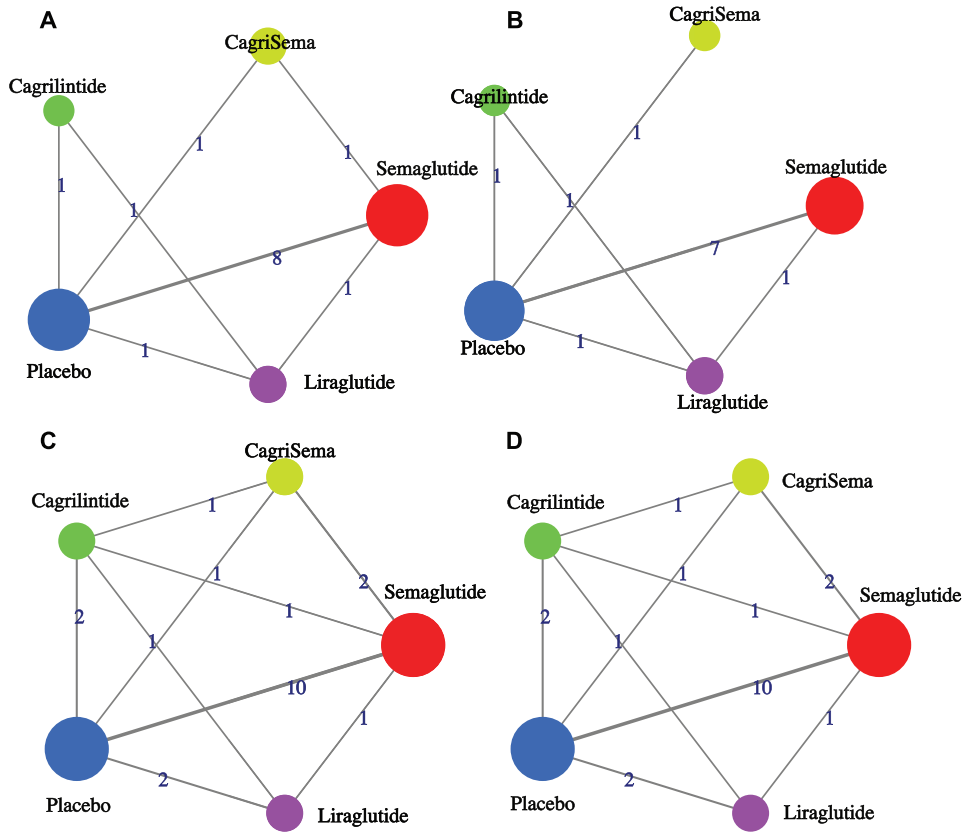

Figure 1. Network graph of enrolled studies. (A) Body weight; (B) waist circumference; (C) serious adverse events and treatment discontinuation; (D) treatment discontinuation due to gastrointestinal symptoms.

SUCRA rankings (Fig. S2) were as follows: CagriSema (0.999), Semaglutide (0.747), Cagrilintide (0.450), Liraglutide (0.298), and placebo (0.005). Egger's test indicated no evidence of small-study effects ($p = 0.34$). The consistency assessment (Fig. S3) showed no statistically significant differences ($p \geq 0.05$) between direct, indirect, and network estimates, indicating no notable inconsistency.

Waist Circumference Reduction

The network of included studies assessing waist circumference is shown in Fig. 1B. Seven trials evaluated Semaglutide vs. placebo, with additional comparisons of Liraglutide vs. placebo, Cagrilintide vs.

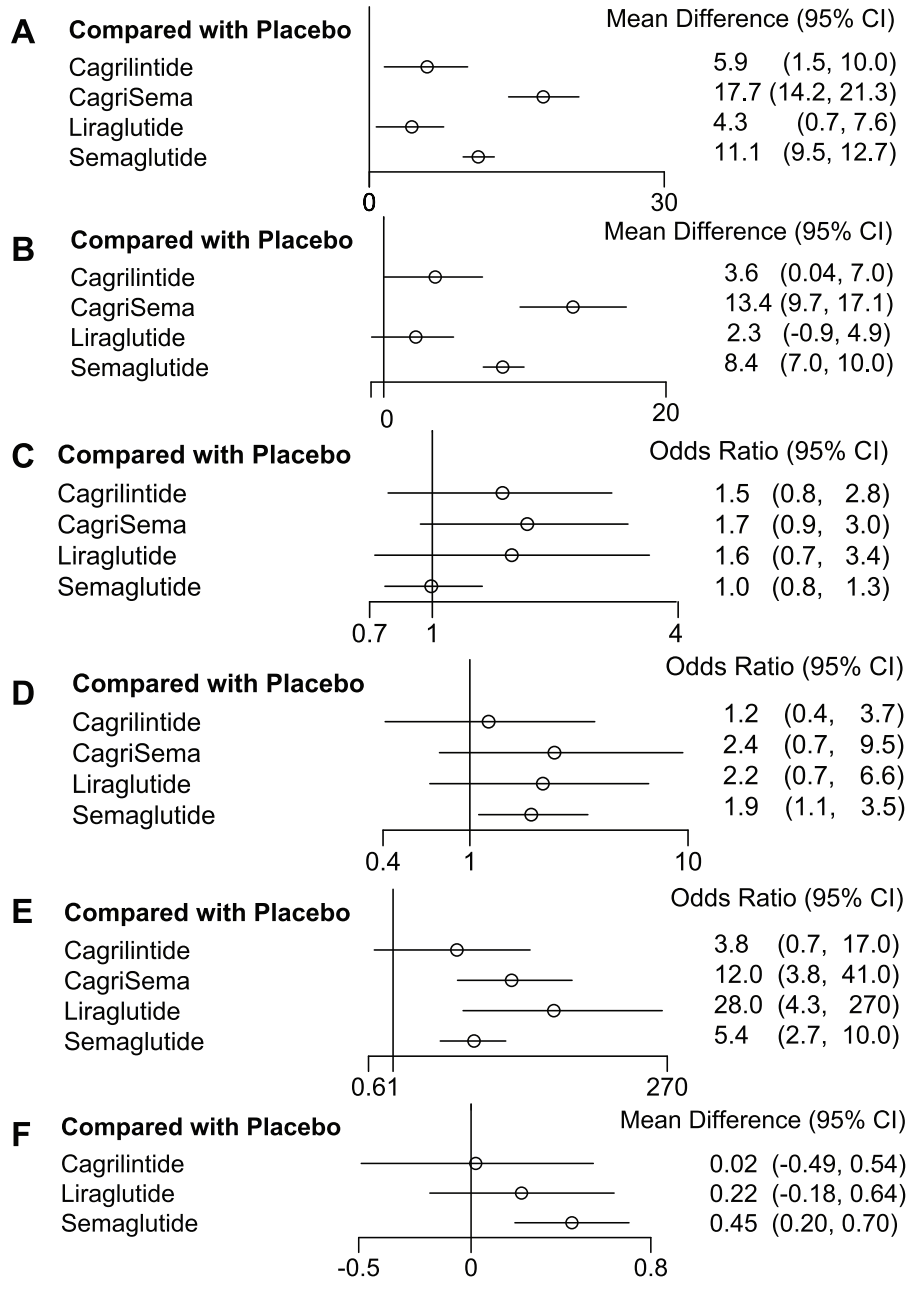

Figure 2. Effects of each agent compared with placebo across different outcomes. (A) Body weight; (B) waist circumference; (C) serious adverse events; (D) treatment discontinuation; (E) discontinuation due to gastrointestinal symptoms; (F) HbA1c reduction.

placebo, and CagriSema vs. placebo. The estimated effects relative to placebo are presented in Fig. 2B. CagriSema produced the greatest reduction in waist circumference (MD: 13.4 cm, 95% CI: 9.7–17.1), followed by Semaglutide (MD: 8.4 cm, 95% CI: 7.0–10.0), Cagrilintide (MD: 3.6 cm, 95% CI: 0.7–7.0), and Liraglutide (MD: 2.3 cm, 95% CI: −0.9 to 4.9). The NMA results are summarized in

Table 2. Network meta-analysis of body weight and waist circumference changes

Body weight[#]				
CagriSema				
6.6 (3.0, 10.3)	**Semaglutide**			
11.8 (6.5, 17.5)	5.2 (1.0, 9.7)	**Cagrilintide**		
13.4 (8.8, 18.5)	6.8 (3.5, 10.4)	1.6 (−2.6, 5.8)	**Liraglutide**	
17.7 (14.2, 21.3)	11.1 (9.5, 12.7)	5.9 (1.5, 10.0)	4.3 (0.7, 7.6)	**Placebo**
Waist circumference				
CagriSema				
4.9 (0.9, 8.9)	**Semaglutide**			
9.7 (4.8, 15.0)	4.8 (1.4, 8.7)	**Cagrilintide**		
11.1 (6.7, 16.0)	6.2 (3.5, 9.4)	1.4 (−1.9, 5.0)	**Liraglutide**	
13.4 (9.7, 17.1)	8.4 (7.0, 10.0)	3.6 (0.0, 7.0)	2.3 (−0.9, 4.9)	**Placebo**
Serious adverse events[#]				
Semaglutide				
−0.4 (−1.0, 0.3)	**Cagrilintide**			
−0.5 (−1.2, 0.3)	−0.1 (−1.0, 0.9)	**Liraglutide**		
−0.5 (−1.1, 0.1)	−0.1 (−0.8, 0.6)	−0.1 (−1.0, 0.9)	**CagriSema**	
−0.0 (−0.3, 0.3)	0.4 (−0.3, 1.0)	0.5 (−0.3, 1.2)	0.5 (−0.1, 1.1)	**Placebo**
Treatment discontinuation				
CagriSema				
0.1 (−1.4, 1.9)	**Liraglutide**			
0.2 (−1.0, 1.6)	0.1 (−1.1, 1.3)	**Semaglutide**		
0.7 (−0.7, 2.1)	0.6 (−0.9, 1.9)	0.4 (−0.7, 1.6)	**Cagrilintide**	
0.9 (−0.3, 2.2)	0.8 (−0.4, 1.9)	0.6 (0.1, 1.2)	0.2 (−0.9, 1.3)	**Placebo**
Treatment discontinuation due to gastrointestinal symptoms				
Liraglutide				
0.9 (−1.3, 3.3)	**CagriSema**			
1.7 (−0.2, 3.9)	0.8 (−0.2, 2.0)	**Semaglutide**		
2.1 (−0.3, 4.8)	1.1 (−0.2, 2.8)	0.3 (−1.1, 2.0)	**Cagrilintide**	
3.3 (1.5, 5.6)	2.5 (1.3, 3.7)	1.7 (1.0, 2.3)	1.3 (−0.4, 2.9)	**Placebo**

Note: #: Cells highlighted in yellow indicate statistically significant differences.

Table 2. CagriSema was superior to all active comparators: Semaglutide (MD: 4.9 cm, 95% CI: 0.9–8.9), Cagrilintide (MD: 9.7 cm, 95% CI: 4.8–15.0), and Liraglutide (MD: 11.1 cm, 95% CI: 6.7–16.0). Semaglutide was also superior to Cagrilintide (MD: 4.8 cm, 95% CI: 1.4–8.7) and Liraglutide (MD: 6.2 cm, 95% CI: 3.5–9.4). In contrast, Cagrilintide and Liraglutide did not differ significantly from each other (MD: 1.4 cm, 95% CI: −1.9 to 5.0).

SUCRA rankings (Fig. S4) were as follows: CagriSema (0.996) ranked highest, followed by Semaglutide (0.751), Cagrilintide (0.453), Liraglutide (0.278), and placebo (0.022). Egger's test indicated no evidence of small-study effects ($p = 0.52$). The consistency assessment (Fig. S5) showed no

statistically significant differences ($p \geq 0.05$) between direct, indirect, and network estimates, indicating no notable inconsistency.

SAEs

The network of included studies assessing SAEs is shown in Fig. 1C. Ten trials evaluated Semaglutide vs. placebo, two trials compared Liraglutide or Cagrilintide with placebo, and two trials compared CagriSema with Semaglutide. The estimated effects relative to placebo are presented in Fig. 2C: Semaglutide (odds ratio [OR]: 1.0, 95% CI: 0.8–1.3), Cagrilintide (OR: 1.5, 95% CI: 0.8–2.8), Liraglutide (OR: 1.6, 95% CI: 0.7–3.4), and CagriSema (OR: 1.7, 95% CI: 0.9–3.0). None of these agents demonstrated a statistically significant increase in the risk of SAEs compared with placebo.

The NMA results of LORs are summarized in Table 2, showing that no treatment was superior or inferior to the others. SUCRA rankings (Fig. S6) indicated that Semaglutide (0.812) and placebo (0.804) had the highest probabilities of being safest, followed by Cagrilintide (0.358), Liraglutide (0.318), and CagriSema (0.208). Egger's test showed no evidence of small-study effects ($p = 0.55$). The consistency assessment (Fig. S7) revealed no statistically significant differences ($p \geq 0.05$) between direct, indirect, and network estimates, indicating no notable inconsistency.

Treatment Discontinuation

The network of included studies assessing treatment discontinuation was the same as for SAEs (Fig. 1C). The estimated effects relative to placebo are presented in Fig. 2D. Semaglutide (OR: 1.9, 95% CI: 1.1–3.5) was associated with a significantly higher risk of treatment discontinuation compared with placebo. In contrast, Cagrilintide (OR: 1.2, 95% CI: 0.4–3.7), Liraglutide (OR: 2.2, 95% CI: 0.7–6.6), and CagriSema (OR: 2.4, 95% CI: 0.7–9.5) did not show statistically significant differences.

The NMA results of LORs are summarized in Table 2. No treatment was superior or inferior to the others, except for Semaglutide, which showed a higher risk of discontinuation than placebo. SUCRA rankings (Fig. S8) placed placebo highest (0.873), followed by Cagrilintide (0.709), Semaglutide (0.373), Liraglutide (0.314), and CagriSema (0.232). Egger's test showed no evidence of small-study effects ($p = 0.21$). The consistency assessment (Fig. S9) revealed some inconsistency in studies comparing Semaglutide or Cagrilintide with Liraglutide.

Gastrointestinal Symptoms

The network of included studies assessing treatment discontinuation due to gastrointestinal symptoms is shown in Fig. 1D. Seven trials evaluated Semaglutide vs. placebo, and two trials compared CagriSema with Semaglutide. The estimated effects relative to placebo are presented in Fig. 2E. Cagrilintide showed the lowest risk of treatment discontinuation (OR: 3.8, 95% CI: 0.68–17.0) without significant statistical differences. Other agents showed a higher risk of treatment discontinuation with Semaglutide (OR: 5.4, 95% CI: 2.7–10.0), CagriSema (OR: 12.0, 95% CI: 3.8–41.0), and Liraglutide (OR: 28.0, 95% CI: 4.3–270).

The NMA results of LORs are summarized in Table 2. No treatment was superior or inferior to the others, except for Semaglutide, which showed a higher risk of discontinuation than placebo. SUCRA rankings (Fig. S10) placed placebo at the highest for the lowest risk of discontinuation due to GS (0.985), followed by Cagrilintide (0.664), Semaglutide (0.556), CagriSema (0.225), and Liraglutide (0.070). Egger's test showed no evidence of small-study effects ($p = 0.21$). The consistency assessment (Fig. S11) revealed no statistically significant differences ($p \geq 0.05$) between direct, indirect, and network estimates, indicating no notable inconsistency.

HbA1c

The network of included studies assessing waist circumference is shown in Fig. S12. Four trials evaluated Semaglutide vs. placebo, with additional comparisons of Liraglutide and Cagrilintide versus placebo. The estimated effects relative to placebo are presented in Fig. 2F. Semaglutide produced the greatest reduction in waist circumference (MD: 0.45%, 95% CI: 0.20–0.70), followed by Liraglutide (MD: 0.22%, 95% CI: −0.18 to 0.64), and Cagrilintide (MD: 0.02%, 95% CI: −0.49 to 54). The NMA

results are summarized in Table S2. Semaglutide was superior to the placebo (log odds ratio [LOR]: 0.4, 95% CI: 0.2–0.7), while no other agents were superior or inferior to the others.

SUCRA rankings (Fig. S13) were as follows: Semaglutide (0.949) ranked highest, followed by Liraglutide (0.611), Cagrilintide (0.253), and placebo (0.187). Egger's test indicated no evidence of small-study effects ($p = 0.52$). The consistency assessment (Fig. S14) showed no statistically significant differences ($p \geq 0.05$) between direct, indirect, and network estimates, indicating no notable inconsistency.

Certainty of Evidence

The risk of bias is presented in Fig. S15. Two studies showed some concerns regarding the overall risk of bias, while the remaining 10 studies were assessed as having a low risk of bias. The certainty of evidence is summarized in Table 3: high for reductions in body weight and waist circumference, consistently showing that CagriSema was the most effective, followed by Semaglutide. Evidence for HbA1c reduction was also rated high for Semaglutide, but low to moderate for Liraglutide and Cagrilintide, both of which showed no significant effect. For safety outcomes, the certainty of evidence was moderate: no agent increased the risk of SAEs, although Semaglutide and Liraglutide were associated with higher rates of treatment discontinuation, particularly due to GS. Overall, the evidence supports a high level of confidence in efficacy outcomes and a moderate level of confidence in safety and tolerability outcomes.

Table 3. Summary of certainty of evidence

Outcomes	Impact (relative to Placebo)	No. of participants (studies)	Certainty of the evidence (GRADE)
Body weight reduction	CagriSema (MD: −17.7%), Semaglutide (MD: −11.9%), Cagrilintide (MD: −5.9%), Liraglutide (MD: −4.3%)	25,401 (12 studies)	⊕⊕⊕⊕ High
Waist circumference reduction	CagriSema (MD: −13.4 cm), Semaglutide (MD: −8.4 cm), Cagrilintide (MD: −3.6 cm), Liraglutide (MD: −2.3 cm)	24,958 (10 studies)	⊕⊕⊕⊕ High
HbA1c reduction	Semaglutide (MD: −0.45%)	18,923 (5 studies)	⊕⊕⊕⊕ High
Serious adverse events	No significant increase observed (OR range: 1.0–1.7)	25,401 (12 studies)	⊕⊕⊕⊖ Moderate
Treatment discontinuation	Semaglutide was associated with an increased risk (OR: 1.9), while other agents showed no statistically significant differences	25,401 (12 studies)	⊕⊕⊕⊖ Moderate
Treatment discontinuation due to gastrointestinal symptoms	Cagrilintide showed no statistically significant difference	24,742 (9 studies)	⊕⊕⊕⊖ Moderate

Note: No.: number; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; MD: mean Difference; OR: odds ratio.

Discussion

This NMA consolidates evidence from randomized trials comparing CagriSema, Semaglutide, Cagrilintide, Liraglutide, and placebo in adults with overweight or obesity. The principal finding is that dual-agonist therapy with CagriSema provides the greatest reductions in body weight and waist circumference. Semaglutide also yields substantial benefits, achieving weight loss exceeding 10%, alongside meaningful improvements in glycemic control. Liraglutide and Cagrilintide, while superior to placebo, produce comparatively more modest effects, generally achieving weight loss of more than 5%.[28] This NMA represents the ranking of all available agents across multiple outcomes in a single comparative framework, confirming the superiority of CagriSema and clarifying the trade-off between efficacy and tolerability. These results align with recent data from the REDEFINE program, which showed CagriSema achieving greater weight reductions than Semaglutide alone. This is consistent with earlier findings from the STEP program, confirming the superiority of Semaglutide over Liraglutide in weight management.[29,30]

Different agents demonstrated distinct profiles when considering weight, glycemic outcomes, and safety. CagriSema consistently ranked highest for weight and waist circumference reduction, confirming its additive benefit over single-agent therapies and mirroring results from REDEFINE-1, where weight loss in adherent participants exceeded 20%.[19] Semaglutide maintains a central role due to its dual impact on weight and glycemic control, supported by both trial and real-world data demonstrating significant HbA1c improvements and durable weight loss.[31,32] Oral Semaglutide also demonstrated more flexible usage in weight control; however, it is not included in the NMA.[33] Liraglutide, though widely studied, is less potent than Semaglutide and is associated with higher rates of gastrointestinal adverse events, as shown in STEP-8 and corroborated in observational cohorts.[26,34] Cagrilintide, in contrast, is generally better tolerated but achieves smaller reductions in weight and metabolic outcomes, suggesting a niche role for patients prioritizing tolerability over maximum efficacy.[35]

Safety outcomes across trials show broadly comparable rates of SAEs between active agents and placebo, consistent with prior GLP-1 receptor agonist meta-analyses.[36] However, gastrointestinal adverse events, particularly nausea, vomiting, and diarrhea, remain the primary tolerability issue and a major driver of discontinuation.[37] Higher discontinuation rates with semaglutide and liraglutide reflect the well-established dose-dependent relationship between incretin therapies and gastrointestinal side effects.[38] These symptoms often peak during dose escalation, especially at higher maintenance doses or in combination regimens.[39] Although structured titration schedules in trials help mitigate intolerance, real-world adherence to these protocols may be variable, contributing to greater symptom burden and higher discontinuation rates. Individuals such as older adults or those with multimorbidity may be especially vulnerable.

The findings of this analysis have important implications for clinical practice. Notably, most included trials enrolled relatively younger and healthier adults. The generalizability of these results to older adults, individuals with multimorbidity, and other clinically complex subgroups remains uncertain. These populations may exhibit different patterns of treatment response, tolerability, and adherence, highlighting the need for dedicated studies to better characterize the effectiveness and safety of these therapies in higher-risk groups. It is also important to situate these findings within the broader landscape of obesity pharmacotherapy. Several other agents, such as tirzepatide, phentermine/topiramate, naltrexone/bupropion, orlistat, and emerging incretin-based combinations, are widely used in clinical practice.[40,41] Although comparisons with these therapies were outside the scope of this NMA, clinicians should interpret the present results in the context of the full range of available treatment options. Treatment selection should be individualized, incorporating considerations of efficacy, tolerability, comorbidities, accessibility, and patient preference. Because long-term adherence is a key determinant of real-world effectiveness, proactive strategies to support persistence with therapy are essential for achieving and sustaining meaningful clinical outcomes.

Longer-term studies are needed to clarify the durability of weight loss, relapse rates, and maintenance strategies beyond 2 years. Cardiovascular and renal outcomes, which have been established for some GLP-1 RAs, must be evaluated specifically for dual agonists like CagriSema. Direct comparative studies with emerging agents, including tirzepatide and other multi-agonists, are also warranted to

determine the optimal balance of efficacy and tolerability. Future research should incorporate real-world data to capture the effects of adherence, discontinuation, and cost, all of which may substantially affect effectiveness outside controlled trial conditions. Additionally, outcomes beyond weight and glycemia, such as quality of life, functional capacity, and patient-reported outcomes, should be more systematically integrated into trials to inform patient-centered care.

This analysis has several limitations. First, substantial heterogeneity across the included trials, encompassing differences in population characteristics, baseline comorbidities, and follow-up durations, may have influenced the validity of the indirect comparisons. Two studies with relatively short follow-up periods were also included; however, because they evaluated different agents, a robust sensitivity analysis could not be performed. Second, although no major inconsistency was identified, reporting of safety and treatment discontinuation outcomes varied considerably among studies, limiting the precision of the pooled estimates. Third, many of the included trials were industry-sponsored, which may introduce reporting bias or selective emphasis on favorable outcomes. Finally, because this NMA is composed of indirect rather than direct comparisons, further head-to-head trials are required to strengthen the evidence base.

Conclusion

This NMA confirms that CagriSema provides the greatest efficacy for body weight and waist circumference reduction, with Semaglutide offering a strong balance of efficacy and glycemic benefit. Cagrilintide demonstrates better tolerability with modest effects, while Liraglutide is both less effective and less well tolerated. These findings underscore the central role of incretin-based therapies in obesity management and highlight the need for individualized treatment strategies. Future trials with extended follow-up and direct comparisons against emerging therapies are necessary to further define optimal treatment approaches.

Acknowledgment

None.

Funding

None.

Author Contributions

Y.M. and T.J. designed the study, conducted the literature search, performed the quality assessment, extracted data, carried out the analyses, and drafted the manuscript. L.R., M.L.T., and Y.W. contributed to data interpretation and critically revised the manuscript. All authors have read and approved the final version of the manuscript and agree with its content and data.

Data Availability Statement

The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

Ethical Statement

Institutional Review Board approval was waived, as this study is a meta-analysis of previously published data.

Conflict of Interest

The authors declare no conflicts of interest.

Supplemental Information

Supplemental information for this article can be found online at https://sup.jclinque.com/api/articles/93/download-suppl.

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