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Cardiovascular Effects of Semaglutide in Patients with Obesity, With or Without Type 2 Diabetes (T2DM): An Umbrella Review

Amit Dang, **Dimple Dang**, Vallish Nagendra, Rachna Rana, Nagarani Vullengala, Satya Karthik Uddandi, Naga Shreshta Pesara, Syed Kashif Ali

MarksMan Healthcare Communications (Hyderabad, India)

Background

- Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), was initially developed for type 2 diabetes mellitus (T2DM) and later established as an effective treatment for obesity.
- By enhancing glucose-dependent insulin secretion, slowing gastric emptying, and reducing appetite, semaglutide improves both glycemic control and body weight.
- These metabolic effects have positioned semaglutide as a bridge between diabetes and obesity management: two conditions closely tied to cardiovascular risk.
- Emerging evidence from cardiovascular outcome trials and meta-analyses suggests that semaglutide may also exert direct cardiovascular benefits, including reductions in major adverse cardiovascular events (MACE) and improvements in surrogate markers such as blood pressure and lipids.
- However, findings across randomized controlled trials (RCTs) and systematic literature reviews (SLRs) remain heterogeneous in scope and population
- An umbrella review provides higher-level synthesis to integrate these results and evaluate the cardiovascular and cardiometabolic effects of semaglutide when used in the management of obesity in adults with or without T2DM.

Objective

- To synthesize evidence from SLRs and meta-analyses on cardiovascular and cardiometabolic outcomes associated with semaglutide use in adults with obesity, with or without T2DM.

Methodology

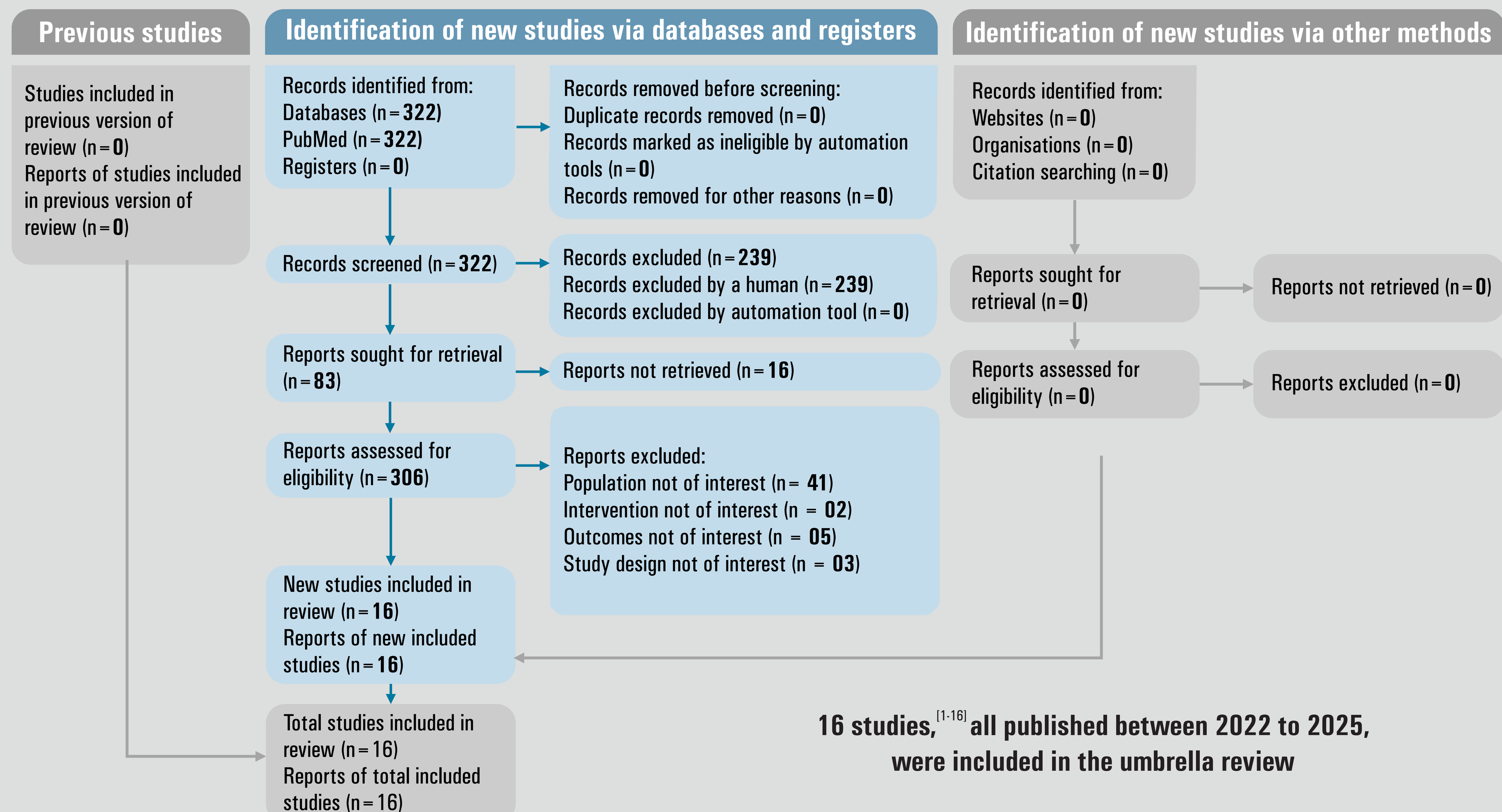
Eligibility Criteria

Facet	Inclusion	Exclusion
Population	• Adult patients of either gender suffering obesity with/without T2DM	• Patients not having obesity with/without T2DM • Pediatric population
Intervention	Semaglutide	No Semaglutide
Comparators	Any comparators (placebo and active comparators) or no comparators	None
Outcomes	**Primary Cardiovascular Outcomes** • Major adverse cardiovascular events (MACE) • Cardiovascular mortality • All-cause mortality • Myocardial infarction (fatal and non-fatal) • Stroke (fatal and non-fatal) • Heart failure (hospitalization or worsening) **Secondary Cardiovascular Outcomes** • Blood pressure changes (systolic/diastolic) • Atrial fibrillation/flutter • Sudden cardiac death • Coronary revascularization (PCI/CABG) • Peripheral arterial disease (including amputations) **Any other cardiac event**	Outcomes other than those listed
Study design	SLRs with or without meta-analyses, scoping reviews, targeted literature	All other study designs
Language	English language articles	Non-English

The SLR adhered to the PRISMA 2020 guidelines.

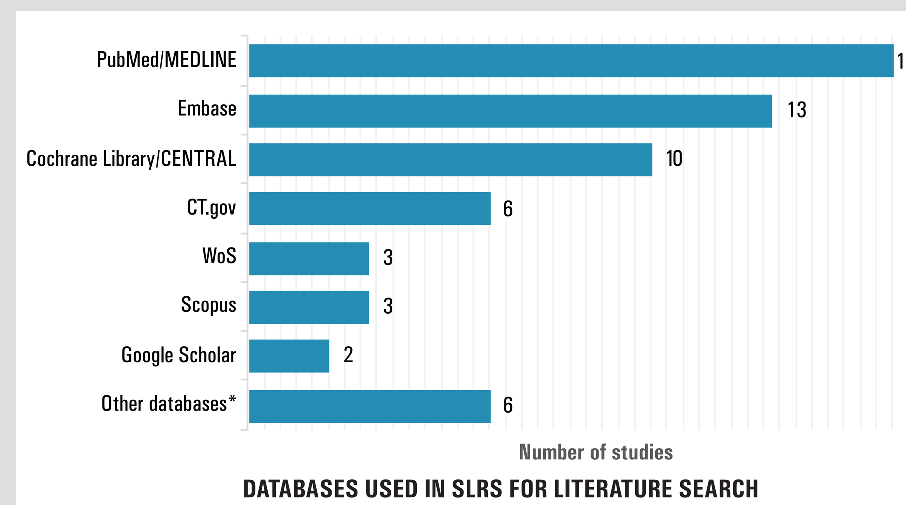
- **Literature sources:** PubMed; reference lists of identified SLRs for additional potential studies
- **Screening protocol:** Fully human, dual independent review with reconciliation; two levels (title-abstract, full-text)
- **Data extraction:** Based on a standardized data extraction template.
- **Risk of Bias:** Using the JBI Checklist for Systematic Reviews, the methodological quality of included SLRs was rated as High (≥80% score), Moderate (50–79%), or Low (<50%).
- Data were summarized qualitatively due to overlap of primary trials across SLRs; no quantitative pooling was performed at the umbrella-review level.

Results



Study Characteristics

- The 16 eligible SLRs included 429 primary RCTs (range 2-168 RCTs)
  - There were 43 RCTs relevant to the objectives of our review (range 1-15 RCTs)
  - Nine SLRs examined the role of semaglutide in improving metabolic health using pooled data from the STEP and PIONEER-4 trials.
- Eight SLRs focused on patients with obesity alone; eight on those with both obesity and T2DM.
- Semaglutide-treated patients ranged from 300 to 26,859 patients
- Most frequent comparator vs semaglutide: placebo
- Most frequent outcome: change in blood pressure
- Most SLRs searched between 2-6 databases
- All included SLRs were rated as moderate to high quality



Outcomes	Comparators (vs Semaglutide)				
	Placebo	Liraglutide	Dulaglutide	Canagliflozin	Dapagliflozin
All-cause mortality	4				
Cardiovascular mortality	3				
Myocardial infarction (fatal and non-fatal)	3				
Stroke (fatal and non-fatal)	3				
Systolic blood pressure changes	9	1	1	1	1
Diastolic blood pressure changes	8	1			1
Major adverse cardiovascular events (MACE)	3				
Atrial fibrillation/flutter	2				
Any other cardiac event	2				

Stoplight indicator for outcomes and comparators in the umbrella review

Green indicates an effective or beneficial intervention.

Amber indicates no difference compared with the comparator or unclear effect due to insufficient information.

Red indicates less effective intervention compared with the comparator.

Numbers written in the colored boxes are the number of SLRs reporting each outcome.

Cardiovascular Outcomes

Semaglutide demonstrated consistent cardiovascular benefits across multiple outcomes, including significant reductions in MACE (17–31%), nonfatal MI (25–30%), and atrial fibrillation (42–57%), along with modest reductions in blood pressure.

Outcome	No of SLRs	Summary of Key Findings	Quality of evidence
Systolic BP	9	Semaglutide consistently lowered systolic blood pressure, with mean reductions of **3.3-5.1 5.1 mmHg** across studies.	Moderate
Diastolic BP	9	Semaglutide reduced diastolic blood pressure by 0.8-2.5 mmHg in seven studies; two studies reported no clinically significant change.	Moderate
All-cause mortality	4	Semaglutide showed lower odds of all-cause mortality compared with orlistat, lorcaserin, and standard of care, but higher odds versus phentermine/topiramate, naltrexone/bupropion, and liraglutide, with no difference versus placebo.	Moderate
Cardiovascular mortality	3	No significant difference in cardiovascular mortality was observed between semaglutide and placebo.	Moderate
MACE	3	Semaglutide significantly reduced the risk of MACE by approximately 17-31% versus placebo [RR 0.69 (95% CI 0.55-0.86); RR 0.83 (95% CI 0.74-0.92)] across two systematic reviews.	High
MI	3	Semaglutide was associated with a 25-30% lower odds of nonfatal myocardial infarction versus placebo across two meta-analyses [OR 0.72 (95% CI 0.61-0.85); OR 0.75 (95% CI 0.51-1.10)], although statistical significance was reached in only one.	Moderate
Stroke	3	No significant difference was noted between semaglutide and placebo for non-fatal stroke.	Moderate
Atrial fibrillation/flutter	2	Semaglutide reduced the risk of incident atrial fibrillation by approximately 42% versus placebo (RR 0.58, 95% CI 0.40-0.85), with oral semaglutide showing a stronger 57% reduction (RR 0.43, 95% CI 0.21-0.87).	Moderate
Other CV outcomes	2	Semaglutide was associated with a 31-32% lower risk of cardiovascular events versus placebo, with oral semaglutide showing RR 0.68 (95% CI 0.51-0.92) and overall RR 0.69 (95% CI 0.55-0.86).	Low

Cardiometabolic Risk Factors and Surrogate Outcomes

In addition to improvements in CV outcomes, semaglutide consistently improved key cardiometabolic risk factors, including body weight, adiposity, glycemic control, lipid levels, and systemic inflammation, all of which contribute to cardiovascular risk reduction in individuals with obesity, with or without T2DM.

Outcome	No of SLRs	Summary of Key Findings	Quality of evidence
Body weight	10	Semaglutide consistently **reduced** body weight by **8-12kg** (10-12%), with greater reductions observed in individuals without diabetes.	High
Body mass index (BMI)	9	Semaglutide led to significant reductions in BMI (**−3 to 4 kg/m²**), reflecting improved adiposity-related cardiometabolic risk.	High
Waist circumference	7	Semaglutide reduced waist circumference by **6-15** cm, indicating a substantial decrease in visceral fat.	Moderate
Glycemic control (HbA1c, fasting plasma glucose)	9	HbA1c decreased by **0.3-1.5%** and fasting plasma glucose decreased by **0.4-1.0 mmol/L** , demonstrating improved glycemic and metabolic control even in non-diabetic populations.	High
Fasting insulin	5	Semaglutide lowered fasting insulin by approximately **20%**, suggesting improved insulin sensitivity.	Moderate
Lipid profile	8	**Improvements were observed in lipid profile,** including total cholesterol (−4.7%), LDL (−5.2%), VLDL (−15%), and triglycerides (−16%), with a modest HDL increase (+2%).	Moderate
C-reactive protein (CRP)	6	CRP levels were **44-55%** lower than control, indicating meaningful anti-inflammatory and cardioprotective effects.	Moderate
Quality of life / Physical functioning	3	Modest improvements were reported in quality of life, including SF-36 physical function scores, consistent with enhanced cardiometabolic well-being.	Moderate
Heart rate	2	A small mean **increase (∼3 bpm)** was noted; clinical significance remains uncertain.	Low
Adverse events / Safety	8	Adverse events occurred in around **89%** of participants **(mostly gastrointestinal)** and serious events in around **9%** , with no cardiovascular safety concerns identified.	Moderate

Discussion

- **From glycemic control to cardiometabolic transformation:** Once positioned purely as an antidiabetic agent, semaglutide now stands at the intersection of obesity, metabolic disease, and cardiovascular prevention. Its effects extend far beyond glycemic control, thereby influencing vascular biology, inflammation, and cardiac electrophysiology.
- **Integrated cardiometabolic benefit:** The synthesis of 16 SLRs confirms a coherent pattern.
  - Semaglutide improves multiple cardiovascular risk determinants simultaneously: body weight, blood pressure, lipid profile, and systemic inflammation
  - Together, this translates into fewer major adverse cardiovascular events
  - This multidimensional benefit differentiates it from traditional glucose-lowering drugs that target single pathways.
- **Evidence of direct cardiovascular protection:** Reductions in MACE and atrial fibrillation, observed consistently across high-quality meta-analyses, suggest that CV benefits seen with semaglutide are not simply a consequence of weight loss or glycemic improvement. Mechanistic data increasingly implicate anti-inflammatory, endothelial, and myocardial effects, highlighting semaglutide as a genuine cardioprotective agent rather than a metabolic bystander.
- **Reframing obesity as a cardiovascular condition:** These findings reinforce the concept that obesity is not merely a risk factor but a cardiovascular disease phenotype in itself. Addressing it pharmacologically can yield outcomes previously achievable only through lifestyle or surgical interventions. Semaglutide thus bridges metabolic and cardiovascular medicine, reshaping prevention paradigms.
- **Clinical implications:** The consistent reduction in MACE and favorable hemodynamic profile across diverse populations argue for including semaglutide in the therapeutic armamentarium for patients at cardiovascular risk, irrespective of diabetes status. In this context, semaglutide may represent the first pharmacologic class capable of targeting the metabolic–cardiovascular continuum holistically.
- **Evidence gaps:** The individual reviews incorporated in this umbrella analysis frequently reported heterogeneity in inclusion criteria, study populations, and outcome definitions (particularly for MACE and arrhythmias). Several relied on a limited number of RCTs, with small sample sizes and short follow-up durations, leading to wide confidence intervals and limited statistical power for certain endpoints. Some reviews also lacked consistent stratification by diabetes status or dosing regimen, thus obscuring population-specific effects.
- **Limitations of the present umbrella review:**
  - Synthesis was restricted to a single database (PubMed) and English language publications.
  - Publication bias is an inherent restriction.
  - Data overlap across SLRs limited the feasibility of quantitative re-analysis, necessitating a qualitative synthesis.

Conclusion

Semaglutide demonstrates clear cardiovascular and metabolic benefits in adults with obesity, with or without T2DM. It consistently reduces major adverse cardiovascular events and improves blood pressure, lipid, and inflammatory profiles, without evidence of cardiovascular harm. These multidimensional effects establish semaglutide as a cornerstone therapy for obesity and related cardiometabolic disease, where the benefits outweigh potential risks. Ongoing research will clarify the extent and durability of its cardiovascular protection.

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