Real-world Evidence on the Broader Benefits of GLP-1 RA-based Therapies: A Global Targeted Literature Review

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Background

- The glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide (Wegovy®) and dual GLP-1 RA/glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide (Mounjaro®) have transformed the treatment of overweight/obesity.[1,2]
- However, health technology assessment (HTA) bodies have criticised the evidence for longer-term impacts on weight-related comorbidities as insufficient.[3,4]
- As weight-related comorbidities are a major driver of the economic burden of overweight/obesity,[5-8] understanding the broader impact of GLP-1 RA-based therapies may better capture their value to healthcare systems and society.

Objectives

- **The goal of the study was to review published real-world benefits of GLP-1 RA-based therapies beyond their established effects on weight loss and glycaemic control.**

Methods

- A targeted literature review was conducted in Embase and Medline using a predefined search strategy for real-world evidence (RWE) on semaglutide or tirzepatide published through 4 June 2025.
- No restrictions were applied to the patient population.
- Records reporting clinical outcomes beyond body weight/composition and glycaemic control were included.
- For each study, data from the longest observation period per endpoint were analysed qualitatively.
- Results are presented as the number of studies showing improvement among those reporting a given endpoint and comparison (n/N).
- Detailed results per included study can be obtained by scanning the quick response (QR) code below.

Results

- Of 580 records screened, 186 advanced to full-text screening and 133 were included. The number of unique studies identified for each outcome and the number of reported endpoints are summarised in **Figure 1**.

Cardiovascular Outcomes

- GLP-1 RAs improved systolic, diastolic and pulmonary artery pressure (each 1/1) vs. baseline, and arrhythmia (2/2), heart failure (HF), HF exacerbation, atrial fibrillation, ischaemic heart disease, peripheral vascular disease, cardiovascular (CV) disease, myocardial infarction, major adverse cardiovascular events (MACE) and congestive heart disease (each 1/1) vs. no GLP-1 RA, but showed no effect on ischaemic stroke (0/1).
- Semaglutide improved N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (2/2), New York Heart Association (NYHA) class (2/2), 6 Minute Walk Test (6MWT), atherogenic index of plasma, carotid intima-media thickness, HF-related emergency department (ED) visits, HF-related hospitalisation, Kansas City Cardiomyopathy Questionnaire (KCCQ), lipid triad index, risk of atherosclerotic CV disease, uric acid/high-density lipoprotein (HDL) ratio (each 1/1), systolic blood pressure (SBP) (22/35) and diastolic blood pressure (DBP) (18/35) vs. baseline, and improved SBP (2/2) and reduced the risk of ischemic stroke (3/4) vs. no GLP-1 RA.
- Tirzepatide improved 6MWT, KCCQ, left ventricular ejection fraction, NT-proBNP, NYHA class, heart rate (each 1/1), SBP (5/5) and DBP (3/4) vs. baseline, and improved HF exacerbation (1/1), MACE (2/2) and a composite endpoint of HF exacerbation and all-cause mortality (ACM) (1/1), stabilised SBP (1/1) and DBP (1/1) and reduced the risk of ischaemic stroke (1/1) vs. no GLP-1 RA-based therapy.
- Tirzepatide reduced the incidence of cerebral infarction vs. semaglutide (1/1) but there was no difference in ischemic stroke, acute coronary syndrome, HF or ischemic heart disease (each 0/1).

Renal Outcomes

- GLP-1 RAs improved blood urea nitrogen (1/1) and renal resistive index (1/1) vs. baseline. No improvements were reported for albuminuria (0/1), creatinine (0/4), urine albumin-creatinine ratio (UACR) (0/1) or urea (0/1). Improvements were observed in acute kidney injury (1/1) and renal resistive index (1/1), with mixed results for estimated glomerular filtration rate (eGFR) (1/4), vs. no GLP-1 RAs.
- Semaglutide improved UACR (13/19) and uric acid (5/10) vs. baseline. Few studies reported improvements in chronic kidney disease (CKD) status (1/1), creatinine (3/18), albuminuria (0/1), blood urea nitrogen (0/2), microalbuminuria (0/1) or eGFR (1/27). Improvements were reported in the risk of acute kidney injury (2/3), with mixed results for eGFR (1/2), vs. no GLP-1 RAs.
- Tirzepatide improved eGFR (3/4) but not creatinine (0/1) vs. baseline. Improvements were noted in eGFR (1/1) and major adverse kidney events (1/1) vs. no GLP-1 RA-based therapy.
- Tirzepatide showed improvements vs. GLP-1 RAs in the risk of acute kidney injury (2/2), kidney events (1/1), major adverse kidney events (1/1) and UACR (1/1).

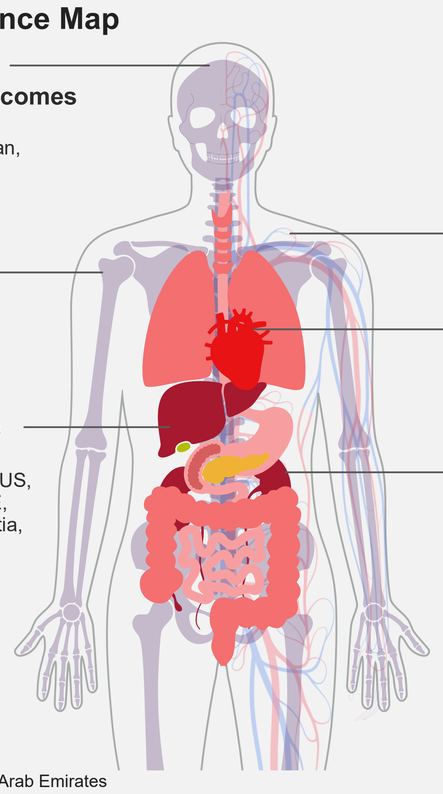
Hepatic Outcomes

- GLP-1 RAs had mixed effects on alkaline phosphatase (ALP) (1/2), alanine transaminase (ALT) (2/6) and ultrasound attenuation parameter (1/1) vs. baseline, and no impact on aspartate aminotransferase (AST) (0/5), enhanced liver fibrosis score (0/1), gamma-glutamyl transferase (GGT) (0/1), liver stiffness (0/1) or total bilirubin count (0/2).
- Semaglutide improved ALT (15/19), AST (10/17), GGT (8/13), fibrosis-4 index (7/8), hepatic steatosis index (5/5), AST to platelet ratio (3/4), controlled attenuation parameter (4/4), fatty liver index (3/3) and triglyceride-glucose index (3/3) vs. baseline, but had mixed effects on liver stiffness measurement (2/5), total bilirubin (1/3) and type IV collagen (1/3).
- Tirzepatide improved AST vs. baseline and ALT, AST and GGT vs. GLP-1 RA (dulaglutide) (each 1/1).
- No studies comparing semaglutide and tirzepatide were identified.

Lipid Profile

- GLP-1 RA-based therapies had mixed effects on high-density lipoprotein cholesterol (HDL-C) (2/9), low-density lipoprotein cholesterol (LDL-C) (6/10), total cholesterol (TC) (4/10) and triglycerides (TG) (4/9) vs. baseline.
- Semaglutide improved LDL-C (35/45), non-HDL-C (4/5), TC (30/34) and TG (32/47) vs. baseline. Most studies reported no effect on HDL-C (9/45). Improvements were reported in LDL-C (2/2), with mixed results for HDL-C (1/2) and TG (1/2), vs. no GLP-1 RA.
- Tirzepatide improved HDL-C (2/5), LDL-C (5/7), TC (6/6) and TG (6/7) vs. baseline and TG (1/1) vs. no GLP-1 RA.
- No studies comparing semaglutide and tirzepatide were identified.

Figure 1. Evidence Map



Abbreviation: UAE = United Arab Emirates

Bone Health

- GLP-1 RAs improved bone turnover markers (carboxyterminal telopeptide [1/1], bone isoenzyme of alkaline phosphatase [1/1]), adiponectin (1/1) and myostatin (1/1) vs. baseline, but not bone mineral density (0/1). GLP-1 RAs reduced the risk of pseudoarthritis (2/2) and osteoarthritis (1/1) and improved hypercalcaemia, hypocalcaemia, calcium and vitamin D (each 1/1) vs. no GLP-1 RA.
- Semaglutide reduced the risk of osteoarthritis (1/1) and hypercalcaemia (1/1) vs. no GLP-1 RA.
- Tirzepatide improved hypocalcaemia vs. no GLP-1 RA-based therapy (1/1).
- Tirzepatide reduced the risk of osteoarthritis vs. semaglutide (1/1).

Neurological and Psychological Outcomes

- GLP-1 RA-based therapies reduced alcohol consumption (1/1) and the risk of Alzheimer's disease (2/2), Lewy body dementia, vascular dementia and seizures (each 1/1) vs. no GLP-1 RA-based therapy. No effect on Parkinson's disease (0/1) was reported, and results for depression were mixed (1/2).
- Semaglutide improved cravings (2/2), emotional eating behaviours (2/2), binge episodes (1/1) and food addiction (1/1) vs. baseline. Semaglutide improved stimulant misuse, nicotine misuse, alcohol misuse, cannabis misuse and smoking cessation (each 3/3) vs. no GLP-1 RA. Semaglutide reduced the risk of depression, psychosis and suicidality vs. no GLP-1 RA, but had no impact on bipolar disorder, anxiety disorder, OCD or negative control outcomes (each 1/1). Semaglutide reduced the risk of Alzheimer's disease (2/2), encephalitis (1/1), cognitive deficit (1/1), dementia (1/1), epilepsy/seizures (1/1), insomnia (1/1), Lewy body dementia (1/1) and vascular dementia (1/1) vs. no GLP-1 RA.
- No studies were identified for tirzepatide.

Cancer Risk

- GLP-1 RAs (semaglutide, liraglutide, dulaglutide) reduced the risk of pancreatic, gastrointestinal, skin, breast, female genital, male genital, prostate, urinary tract, eye, brain, central nervous system, thyroid, respiratory, mesothelial and lymphoid/hematopoietic cancers (each 1/1) vs. no GLP-1 RA.
- No studies were identified for tirzepatide.

All-cause Mortality

- Both semaglutide (4/5) and tirzepatide (3/3) improved ACM vs. no GLP-1 RA-based therapy.
- Tirzepatide was associated with a lower risk of death vs. GLP-1 RAs (2/2) and semaglutide specifically (1/1).

Conclusions

RWE suggests that GLP-1 RA-based therapies have a broad range of benefits beyond weight loss and glycaemic control, which could be relevant to HTA bodies and healthcare systems when evaluating the health and economic value of these treatments. Of note, evidence suggests that GLP-1 RAs may have a significant positive impact on ACM when compared with no GLP-1 RA, and that semaglutide and tirzepatide improve a range of CV outcomes (including blood pressure), lipid profile and neurological/psychological outcomes compared with baseline. Further research is needed to understand the comparative effects of semaglutide and tirzepatide across all outcomes included in this review.

References

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Disclosures

All authors are employees of PPD™ Evidera™ Health Economics and Market Access, Thermo Fisher Scientific. This poster was funded by Thermo Fisher Scientific. Editorial and graphic design support were provided by Amara Tiebout and Kawthar Nakayima of Thermo Fisher Scientific.

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Presented at ISPOR —The Professional Society for Health Economics and Outcomes Research—Europe | 9–12 November 2025 | Glasgow, Scotland, UK

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