

GLP-1 and GIP analogues in the treatment of obesity – Current State of Knowledge

ANALOGI GLP-1 I GIP W LECZENIU OTYŁOŚCI – aktualny stan wiedzy - Repetytorium

Marta Grycan^{ID}, Gabriela Grycan^{ID}, Michał Pstrągowski*^{ID}

Institute of Clinical Sciences,

Maria Skłodowska-Curie Medical University in Warsaw

*Correspondence: 

Abstract

Aim: A review of the latest data on the efficacy and safety of GLP-1 analogues and dual GLP-1/GIP agonists in the treatment of obesity and type 2 diabetes, including their impact on the cardiovascular system and global availability status.

Methods: Analysis of scientific literature (PubMed 2015-2025), including phase III randomized clinical trials, meta-analyses, and international guidelines.

Results: GLP-1 agonists and dual GLP-1/GIP agonists (tirzepatide) reduce body weight by 6–22.5%, improve glycemic control (HbA1c –1–2.5%), and in some cases demonstrate cardioprotective effects – reducing MACE (up to –26% for semaglutide). The SURMOUNT-5 study (2025) confirmed the superiority of tirzepatide over semaglutide. Main limitations include cost, the need for chronic use, and gastrointestinal side effects.

Conclusions: Incretin-based drugs represent a breakthrough in the treatment of obesity, but their full implementation requires consideration of accessibility, reimbursement, and long-term safety.

Keywords: obesity, GLP-1, GIP, tirzepatide, semaglutide, pharmacological treatment

Abstrakt

Cel: Przegląd najnowszych danych na temat skuteczności i bezpieczeństwa analogów GLP-1 oraz dualnych agonistów GLP-1/GIP w leczeniu otyłości i cukrzycy typu 2, z uwzględnieniem ich wpływu na układ sercowo-naczyniowy i status dostępności na świecie.

Metody: Analiza piśmiennictwa naukowego (PubMed 2015–2025), w tym randomizowanych badań klinicznych III fazy, metaanaliz i wytycznych międzynarodowych.

Wyniki: Agoniści GLP-1 i dualni agoniści GLP-1/GIP (tirzepatide) redukują masę ciała o 6–22,5%, poprawiają kontrolę glikemii (HbA1c -1 – $-2,5\%$) i w części przypadków wykazują działanie kardioprotekcyjne - redukują MACE (do -26% dla semaglutide). Badanie SURMOUNT-5 (2025) potwierdziło wyższość tirzepatide nad semaglutide. Główne ograniczenia to koszt i konieczność przewlekłego stosowania oraz efekty uboczne żołądkowo-jelitowe.

Wnioski: Leki inkretynowe stanowią przełom w leczeniu otyłości, ale ich pełne wdrożenie wymaga uwzględnienia kwestii dostępności, refundacji i długoterminowego bezpieczeństwa.

Słowa kluczowe: otyłość, GLP-1, GIP, tirzepatid, semaglutid, leczenie farmakologiczne

1. Mechanism of action of incretins

Incretins are gut hormones secreted in response to food intake. The main ones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Both substances play a key role in the regulation of carbohydrate and energy metabolism.

In individuals with obesity and type 2 diabetes, an impaired incretin response is observed, leading to disturbed secretion of insulin and glucagon, thereby promoting hyperglycemia and excessive appetite [1, 2].

1.1. GLP-1 – main actions

- Increases insulin secretion in a glucose-dependent manner.
- Inhibits glucagon secretion.

- Delays gastric emptying, enhancing satiety.
- Acts on the central nervous system, suppressing appetite.

GLP-1 agonists are designed to be resistant to degradation by the enzyme DPP-4, which ensures a longer half-life and clinical efficacy [3].

1.2. GIP – main actions

- Stimulates insulin secretion in a glucose-dependent manner.
- Influences lipid metabolism and adipogenesis.
- In insulin-resistant individuals, its effect is partially impaired.

Although GIP was once considered less relevant in therapy, current studies highlight its potential synergistic role with GLP-1 [4].

1.3. Dual GLP-1/GIP agonists – mechanism of synergy

Modern therapies, such as tirzepatide, combine GLP-1R and GIPR effects, leading to:

- Stronger appetite reduction.
- Increased glucose-dependent insulin secretion.
- Better glycemic control.
- Modulation of visceral fat metabolism.

Preclinical and clinical studies indicate that activation of both receptors produces an additive or synergistic effect on weight reduction and improvement of metabolic parameters [5, 6].

1.4. Impact on the central nervous system

- GLP-1 agonists and dual GLP-1/GIP agonists act on the arcuate nucleus of the hypothalamus.
- They inhibit NPY/AgRP (orexigenic) neurons.
- They activate POMC/CART (anorexigenic) neurons.
- The result is reduced appetite and decreased calorie intake.

Neuroimaging (fMRI) has confirmed decreased activity of brain regions associated with reward after treatment with GLP-1 agonists [7].

2. Review of GLP-1 and GIP-based therapies

Pharmacotherapy of obesity has undergone revolutionary changes in recent years. GLP-1 agonists and dual GLP-1/GIP agonists play a key role, offering efficacy comparable to bariatric surgery and proven metabolic benefits.

2.1. GLP-1 agonists

- **Liraglutide (Saxenda® 3 mg):**
 - administration: daily subcutaneous injection,
 - weight reduction: 6–8% [8],
 - SCALE study: effect stabilization after 56 weeks,
 - approved for obesity by FDA and EMA.
- **Semaglutide (Wegovy® 2.4 mg):**
 - administration: once weekly subcutaneous,
 - weight reduction: 14.9–17% [9],
 - STEP 1 study (NEJM 2021): –14.9% in 68 weeks,
 - approved for obesity in the USA and EU (2021–2022).
- **Dulaglutide (Trulicity®):**
 - administration: weekly,
 - weight reduction: 3–5% [10],
 - primarily for DM2, not approved for obesity.

2.2. Dual GLP-1/GIP agonists

- **Tirzepatide (Mounjaro®, Zepbound®):**
 - world's first dual GLP-1/GIP agonist,
 - administration: once weekly subcutaneous, doses 5–15 mg,
 - approvals:
 - FDA 2022–2023 – DM2,
 - FDA 2023 – Zepbound for obesity and OSA,
 - EMA – approved for DM2, obesity approval procedure ongoing (2025).
- **Retatrutide – a novel triple-action obesity therapy**

Retatrutide (LY-3437943) is an innovative peptide agonist of three incretin receptors: GLP-1, GIP, and glucagon receptor (GCGR). Its unique triple-action structure provides:

- substantial weight reduction (–22–25% within 24–48 weeks),
- improvement in glycemia (HbA1c reduction) and metabolic parameters [11],
- beneficial impact on liver fat reduction (MASLD/NAFLD) [12].

Regulatory status:

- FDA (USA): not approved, only available in phase III clinical trials (TRIUMPH, SURPASS-CVOT). As of now, FDA does not recognize retatrutide as an approved drug [13, 14].

- EMA (EU): not approved; still under global evaluation with no clinical indications approved.
- Phase III: central phase III studies planned for 2025–2026, completion will allow later registration submissions [14, 1].

Preclinical and Phase I/II results

- In a phase II study (48 weeks), doses of 8 and 12 mg of retatrutide demonstrated body weight reductions of –23.8% and –25.9%, respectively, with liver fat mass reduced by 81–82%.
- In phase I/II in patients with type 2 diabetes, improvements in body composition were observed (reduction of fat mass while preserving lean mass), as well as favorable changes in metabolic parameters – glucose, blood pressure, and lipids [15].

Table 1. Efficacy – summary of results

Dose (mg)	Body weight reduction (%)	Liver fat reduction (%)
8	–23.8%	–81.4%
12	–25.9%	–82.4%

Safety

The adverse event profile is consistent with GLP-1/GIP agonists – most commonly nausea, vomiting, and constipation, usually mild and transient. No serious adverse events were reported [15].

Clinical perspectives

Retatrutide represents a new generation of obesity therapies, combining incretin and glucagon activity. Several large phase III trials (e.g., TRIUMPH) are currently ongoing to assess its long-term safety and efficacy.

Preliminary results are very promising, but important considerations remain:

- Cost of therapy.
- Comparison with tirzepatide.
- Impact on comorbidities (e.g., NASH, diabetes).

2.3. Phase III clinical trial results (Table 2)

- **SCALE (liraglutide):**
 - weight reduction: ~8%,
 - sustained effect with continued therapy [8],

- **STEP 1 (semaglutide):**
 - −14.9% at 68 weeks,
 - HbA1c reduction of 1.5–2.0%,
 - cardioprotective effect (MACE reduction by 26% in SUSTAIN-6) [9, 16].
- **SURMOUNT-1 (tirzepatide):**
 - weight reduction: up to 22.5% at 72 weeks,
 - HbA1c reduction: 2.0–2.4% [17].
- **SURMOUNT-5 (2025):**
 - comparison: tirzepatide 10–15 mg vs semaglutide 2.4 mg,
 - tirzepatide: −20.2% vs semaglutide: −13.7% ($P < 0.001$) [18].

Table 2. Comparison of the effects of GLP-1 agonists and GIP/GLP-1 analogues in obesity treatment – data from clinical trials.

Drug	Dose	HbA1c Reduction (%)	Clinical Trials
Orlistat	120 mg 3×/day	no effect	XENDOS
Liraglutide (Saxenda®)	3 mg/day	1.0–1.5%	SCALE
Semaglutide (Wegovy®)	2.4 mg/week	1.5–2.0%	STEP 1
Dulaglutide	1.5–4.5 mg/week	1.0–1.5%	AWARD, REWIND
Tirzepatide (Zepbound®)	5–15 mg/week	2.0–2.4%	SURMOUNT-1, SURMOUNT-5 (2025)

Source: Author's own elaboration based on data from studies: Wilding JPH et al. *N Engl J Med.* 2021; 384:989–1002. PMID: 33567185; Jastreboff AM et al. *N Engl J Med.* 2022; 387:205–216. PMID: 35704300; Frias JP et al. *Nature Med.* 2023; 29:845–854. PMID: 37166354.

2.4. Meta-analyses and reviews (2025)

- Confirm the superiority of tirzepatide over semaglutide by ~4–5% body weight reduction [19].
- Analyses indicate lower incidence of gastrointestinal symptoms with gradual dose escalation [19, 20].

2.5. Mechanisms of synergistic action

- **GLP-1R:**
 - Glucose-dependent stimulation of insulin.
 - Glucagon inhibition.
 - Anorexigenic effect.
- **GIPR:**
 - Additional insulin stimulation.
 - Influence on adipocytes.
 - Synergistic appetite suppression.

Tirzepatide acts on both receptors, producing additive or synergistic effects [6, 18].

2.6. Impact on glycemic control

- HbA1c reduced by 1.0–2.5% in phase III trials.
- Particularly beneficial in type 2 diabetes.
- FDA and EMA recommend them in patients with DM2 and coexisting obesity [21].

3. Efficacy of body weight reduction (Figure 1)

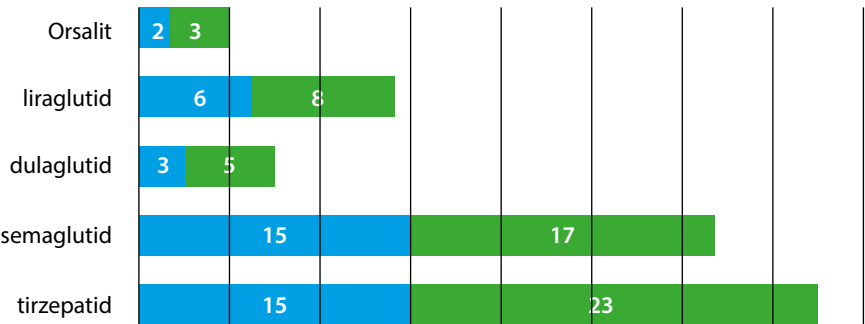
The efficacy of GLP-1 agonists and dual GLP-1/GIP agonists in reducing body weight has been confirmed in many phase III randomized clinical trials and meta-analyses up to 2025.

3.1. GLP-1 agonists

- **Liraglutide 3 mg (Saxenda®):**
 - average weight reduction: 6–8% [8],
 - SCALE study: –8% after 56 weeks,
 - stable effect with continued therapy.
- **Semaglutide 2.4 mg (Wegovy®):**
 - weight reduction: 14.9–17% at 68 weeks [9],
 - STEP 1: –14.9% mean vs –2.4% placebo,
 - effectiveness comparable to bariatric surgery in some post-hoc analyses.
- **Dulaglutide:**
 - weight reduction: 3–5%,
 - effect confirmed mainly in patients with DM2 [10].

Figure 1. Percentage weight loss in selected studies using GLP-1 agonists and GIP/GLP-1 analogues.

(Visual comparison shown: semaglutide ~15%, tirzepatide – up to 22%, retatrutide – up to 24% in phase III)



Source: Based on Wilding JPH et al. N Engl J Med. 2021; 384:989–1002. PMID: 33567185; Jastreboff AM et al. N Engl J Med. 2022; 387:205–216. PMID: 35704300; Frias JP et al. Nature Med. 2023; 29:845–854. PMID: 37166354.

3.2. Dual GLP-1/GIP agonist – tirzepatide

- **SURMOUNT-1:**
 - body weight reduction: up to –22.5% at 72 weeks,
 - placebo-adjusted reduction ~18% [17].
- **SURMOUNT-5 (2025):**
 - tirzepatide 10–15 mg: –20.2%,
 - semaglutide 1.7–2.4 mg: –13.7%,
 - tirzepatide superior to semaglutide by ~6.5% [18].

Meta-analysis 2025:

- tirzepatide 10–15 mg > semaglutide 2.4 mg by ~4–5% [19],
- stable effect with long-term use,

3.3. Mechanisms of body weight effects

- Appetite reduction (central anorexigenic action).
- Delayed gastric emptying.
- Improved insulin sensitivity.
- Reduction of visceral adipose tissue volume.
- Modulation of reward and satiety pathways in CNS [7].

3.4. Weight maintenance effect

- Observational studies (2023–2025) show that discontinuation of therapy leads to partial weight regain (~2/3 within 1–2 years) (21).
- Chronic treatment is necessary to maintain effect.

4. Safety, limitations of treatment, and adverse events

Pharmacotherapy of obesity using GLP-1 agonists and dual GLP-1/GIP agonists has significantly improved treatment options but is also associated with limitations and adverse effects that must be considered in clinical practice.

4.1. Most common adverse events

Gastrointestinal symptoms:

- nausea (20–40% of patients),
- vomiting,

- diarrhea or constipation,
- often transient and subside after several weeks.

Other:

- dyspepsia,
- feeling of fullness.

Studies from 2025 confirm that gradual dose escalation significantly reduces the frequency and severity of these adverse events [19, 20].

4.2. Rare but significant risks

- **Pancreatitis:**
 - rare cases reported in trials and safety reports,
 - no confirmed increased risk in large meta-analyses.
- **Medullary thyroid carcinoma (MTC):**
 - theoretical risk based on rodent studies,
 - no evidence of increased risk in humans (FDA, however, requires a warning label) [20].

4.3. Cardiovascular safety (Table 3)

Cardioprotective mechanisms include reduction in blood pressure (2–5 mmHg), improved lipid profile, and reduced low-grade inflammation.

Table 3. Comparison of cardiometabolic effects of GLP-1 agonists and GIP/GLP-1 analogues.

Drug	MACE reduction (%)	HR (vs placebo)	Clinical Trial
Liraglutide	–13%	0.87	LEADER
Semaglutide	–26%	0.74	SUSTAIN-6
Dulaglutide	–12%	0.88	REWIND
Tirzepatide	ongoing	n/a	SURPASS-CVOT

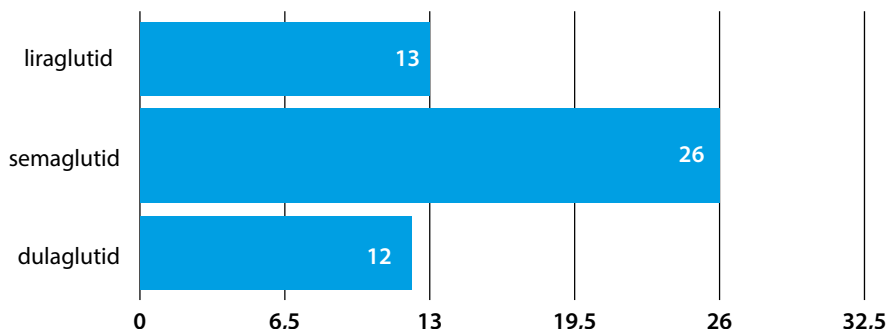
Source: Author's own elaboration based on: Marso SP et al. *N Engl J Med.* 2016; 375:311–322. PMID: 27295427; Gerstein HC et al. *Lancet.* 2019; 394:121–130. PMID: 31118100; Jastreboff AM et al. *N Engl J Med.* 2022; 387:205–216. PMID: 35704300; Frias JP et al. *Nature Med.* 2023; 29:845–854. PMID: 37166354

Large CVOT studies have demonstrated MACE reduction (Figure 2):

- **Liraglutide (LEADER):** –13% (HR 0.87) [16].
- **Semaglutide (SUSTAIN-6):** –26% (HR 0.74) [16].
- **Dulaglutide (REWIND):** –12% (HR 0.88) [15].
- **Tirzepatide:** SURPASS-CVOT results expected in 2025/26.

Figure 2. Effects of MACE reduction (%) in clinical trials using modern incretin mimetics

Orlistat was not studied in large randomized CVOTs, thus no data exist on its effect on MACE reduction. Tirzepatide is currently being evaluated in the SURPASS-CVOT study – results expected after 2025. Liraglutide, dulaglutide, and semaglutide have confirmed MACE reduction effects in dedicated clinical trials.



Source: Wilding JPH et al. *N Engl J Med.* 2021; 384:989–1002. PMID: 33567185; Jastreboff AM et al. *N Engl J Med.* 2022; 387:205–216. PMID: 35704300; Frias JP et al. *Nature Med.* 2023; 29:845–854. PMID: 37166354.

Additional effects:

- Blood pressure reduction (2–6 mmHg).
- Lipid profile improvement (↓TG, ↑HDL-C).
- Reduction of low-grade inflammation (CRP) [3, 6].

4.4. Treatment limitations

Cost of therapy:

- Tirzepatide and semaglutide are significantly more expensive than earlier drugs.
- Reimbursement in most countries is limited to DM2.

Need for chronic use:

- The weight loss effect disappears after discontinuation.
- Observational studies (2023–2025) show regain of ~2/3 of lost weight within 1–2 years without continued treatment [21].

Availability:

- Limited in low- and middle-income countries.
- Differences in registrations and reimbursement between FDA and EMA.

5. Availability and reimbursement of incretin therapies

The availability and reimbursement of GLP-1 and dual GLP-1/GIP agonist therapies remain key challenges in global obesity treatment. Although these drugs have revolution-

ized therapeutic approaches, their high cost and limited availability hinder widespread population-level use.

5.1. Registration status (2025)

- **Semaglutide (Wegovy®, Ozempic®, Rybelsus®):**
 - Wegovy® (2.4 mg s.c.) approved by FDA (2021) and EMA (2022) for obesity treatment (BMI ≥ 30 or ≥ 27 with comorbidities).
 - Ozempic® – registered for DM2, used off-label for weight reduction.
 - Rybelsus® – only oral GLP-1, registered for DM2.
- **Liraglutide (Saxenda® 3 mg):**
 - approved by FDA (2014) and EMA (2015) for obesity treatment,
 - daily s.c. injections.
- **Tirzepatide (Mounjaro®, Zepbound®):**
 - Mounjaro® – FDA and EMA approval for DM2.
 - Zepbound® (2023) – FDA approval for obesity and obstructive sleep apnea (OSA).
 - EMA – registration procedure for obesity ongoing in 2025.

5.2. Reimbursement in selected countries (Table 4)

- **USA:**
 - Wegovy® and Zepbound®: reimbursement depends on insurer; manufacturer discount programs available.
 - Ozempic®, Rybelsus®: reimbursed in DM2.
- **EU (including Poland):**
 - semaglutide and liraglutide reimbursed only in DM2,
 - no reimbursement for obesity indication (off-label use in clinical practice),
 - tirzepatide: reimbursed in DM2, no reimbursement for obesity in 2025.
- **UK:**
 - NICE in 2023 recommended limited funding of Wegovy® on NHS for selected groups (BMI ≥ 35 or ≥ 30 with complications),
 - reimbursement negotiations for tirzepatide ongoing in 2025.

Table 4. Availability of GLP-1 and GIP/GLP-1 drugs in the EU and USA (as of 2025).

Drug / Preparation	FDA	EMA	Poland – reimbursement DM2	Poland – reimbursement obesity	Administration
Wegovy® (semaglutide)	✓ (2021)	✓ (2022)	✓	✗	s.c. 2.4 mg/week
Ozempic® (semaglutide)	✓	✓	✓	off-label	s.c. 0.25–2 mg
Rybelsus® (semaglutide)	✓	✓	✓	✗	oral
Saxenda® (liraglutide)	✓ (2014)	✓ (2015)	✗	✗	s.c. 3 mg/day
Mounjaro® (tirzepatide)	✓ (2022, DM2)	✓ (DM2)	✓	✗	s.c. 5–15 mg/week
Zepbound® (tirzepatide)	✓ (2023, obesity)	in procedure (2025)	✓ (DM2)	✗	

Source: EMA, FDA, ClinicalTrials.gov, registration publications of manufacturers: Novo Nordisk, Eli Lilly (2021–2025).

5.3. Access limitations

- **High cost:**
 - Annual cost of Wegovy®, Zepbound® >10,000 USD in USA.
 - Limited availability in public systems.
- **Inequalities in access:**
 - Low- and middle-income countries practically without access to modern therapies.
 - Reimbursement barriers even within EU.
- **Systemic challenges:**
 - Need for medical staff education.
 - Therapy outcome monitoring
 - Implementation of public health strategies.

6. Summary and conclusions

Summary

Obesity is a chronic metabolic disease of global scope and growing epidemiological significance. In 2025, the number of obese individuals worldwide exceeded 1 billion, posing a serious public health, economic, and social challenge.

The pathophysiology of obesity is based on complex mechanisms: chronic low-grade inflammation, insulin resistance, impaired incretin secretion, and dysregulation of the central nervous system. Numerous comorbidities – type 2 diabetes, hypertension, dyslipidemia, NAFLD, OSA, and cardiovascular diseases – exacerbate the problem and increase mortality.

Incretin pharmacotherapy (GLP-1 agonists and dual GLP-1/GIP agonists) represents the greatest breakthrough in obesity treatment in decades. These drugs allow for body weight reduction of 6–22.5%, improve glycemic control (HbA1c –1–2.5%), decrease visceral adipose tissue volume, and in some cases reduce cardiovascular risk (MACE reduction up to 26% for semaglutide in SUSTAIN-6).

The dual GLP-1/GIP agonist tirzepatide achieves efficacy comparable to bariatric surgery, surpassing semaglutide by 4–6.5% in body weight reduction in phase III trials (including SURMOUNT-5 in 2025). Cardiovascular outcome trial results for tirzepatide (SURPASS-CVOT) are expected in 2025/26 and may confirm additional cardioprotective benefits.

Treatment limitations include high costs, lack of widespread reimbursement for obesity (outside of DM2), need for chronic use, and adverse effects – mainly gastrointestinal. The weight loss effect partially disappears after discontinuation, requiring long-term strategies and patient support.

In summary, incretin therapies represent the foundation of modern obesity treatment. However, their effective implementation requires systemic strategies, reimbursement, patient and medical staff education, as well as an integrated approach including behavioral, dietary, and – in selected patients – bariatric surgical interventions.

Conclusions

Obesity is one of the most serious health challenges of the 21st century, being a chronic disease with multifactorial etiology and numerous metabolic and cardiovascular consequences. The prevalence of obesity is increasing worldwide, including among children and adolescents.

The key pathophysiological mechanism of obesity is insulin resistance, which leads to the development of type 2 diabetes, atherogenic dyslipidemia, hypertension, and non-alcoholic fatty liver disease. Obesity is also associated with obstructive sleep apnea and increased cardiovascular risk.

In recent years, GLP-1 analogues and dual GLP-1/GIP agonists have gained enormous significance in pharmacological therapy. Their mechanism of action includes stimulation

of insulin secretion, inhibition of glucagon, delayed gastric emptying, and influence on central satiety mechanisms. Phase III trials have shown that GLP-1 agonists can reduce body weight by 6–17%, and the dual agonist tirzepatide by up to 22.5%, with effects comparable to bariatric surgery.

These drugs additionally demonstrate beneficial metabolic effects (HbA1c reduction by 1–2.5%) and, in some cases, cardioprotective benefits (MACE reduction up to 26% for semaglutide). However, their use requires chronic treatment, is associated with high cost, and carries a risk of adverse events such as nausea or diarrhea.

In conclusion, GLP-1 and GLP-1/GIP analogues represent a breakthrough in obesity treatment, but their implementation requires appropriate integration, patient education, and reimbursement/systemic strategies.

List of Abbreviations

- ADA – American Diabetes Association
- AgRP – Agouti-Related Peptide
- AWARD – Assessment of Weekly Administration of Dulaglutide
- BMI – Body Mass Index
- BP – Blood Pressure
- CART – Cocaine- and Amphetamine-Regulated Transcript
- CDC – Centers for Disease Control and Prevention
- CRP – C-reactive Protein
- CVOT – Cardiovascular Outcomes Trial
- DM2 – Type 2 Diabetes
- DPP-4 – Dipeptidyl Peptidase-4
- EMA – European Medicines Agency
- EASD – European Association for the Study of Diabetes
- FDA – Food and Drug Administration
- FFA – Free Fatty Acids
- GIP – Glucose-Dependent Insulinotropic Polypeptide
- GLP-1 – Glucagon-Like Peptide-1
- HbA1c – Glycated Hemoglobin
- HDL-C – High-Density Lipoprotein Cholesterol
- HR – Hazard Ratio
- IDF – International Diabetes Federation
- LEADER – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
- MACE – Major Adverse Cardiovascular Events
- MTC – Medullary Thyroid Carcinoma
- NAFLD – Non-Alcoholic Fatty Liver Disease
- NASH – Non-Alcoholic Steatohepatitis
- NICE – National Institute for Health and Care Excellence
- NPY – Neuropeptide Y
- NPY/AgRP – Neuropeptide Y / Agouti-Related Peptide (orexigenic neurons)

- OECD – Organisation for Economic Co-operation and Development
- OSA – Obstructive Sleep Apnea
- CNS – Central Nervous System
- POMC – Proopiomelanocortin
- RAA – Renin–Angiotensin–Aldosterone System
- REWIND – Researching Cardiovascular Events with a Weekly Incretin in Diabetes
- SBP – Systolic Blood Pressure
- SCALE – Satiety and Clinical Adiposity—Liraglutide Evidence
- STEP – Semaglutide Treatment Effect in People with Obesity
- SURMOUNT – Study of Tirzepatide in Obesity Management
- SURPASS – Study of Tirzepatide in Diabetes
- s.c. – Subcutaneously
- TG – Triglycerides
- UK – United Kingdom
- VLDL – Very-Low-Density Lipoprotein

References

1. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes Obes Metab.* 2018 Feb;20 Suppl 1:5-21. doi: 10.1111/dom.13129. PMID: 29364588.
2. Drucker DJ. GLP-1-based therapies for diabetes, obesity and beyond. *Nat Rev Drug Discov.* 2025 Aug;24(8):631-650. doi: 10.1038/s41573-025-01183-8. Epub 2025 Apr 25. Erratum in: *Nat Rev Drug Discov.* 2025 Jul;24(7):570. doi: 10.1038/s41573-025-01231-3. PMID: 40281304.
3. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab.* 2013 Jun 4;17(6):819-837. doi: 10.1016/j.cmet.2013.04.008. Epub 2013 May 16. PMID: 23684623.
4. Farr OM, Li CR, Mantzoros CS. Central nervous system regulation of eating: Insights from human brain imaging. *Metabolism.* 2016 May;65(5):699-713. doi: 10.1016/j.metabol.2016.02.002. Epub 2016 Feb 6. PMID: 27085777; PMCID: PMC4834455.
5. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med.* 2015 Jul 2;373(1):11-22. doi: 10.1056/NEJMoa1411892. PMID: 26132939.
6. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med.* 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.
7. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanus F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019 Jul 13;394(10193):121-130. doi: 10.1016/S0140-6736(19)31149-3. Epub 2019 Jun 9. PMID: 31189511.

8. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. PMID: 27295427; PMCID: PMC4985288.
9. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021 Aug 5;385(6):503-515. doi: 10.1056/NEJMoa2107519. Epub 2021 Jun 25. PMID: 34170647.
10. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A; SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022 Jul 21;387(3):205-216. doi: 10.1056/NEJMoa2206038. Epub 2022 Jun 4. PMID: 35658024.
11. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, Coskun T, Haupt A, Milicevic Z, Hartman ML; Retatrutide Phase 2 Obesity Trial Investigators. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. *N Engl J Med*. 2023 Aug 10;389(6):514-526. doi: 10.1056/NEJMoa2301972. Epub 2023 Jun 26. PMID: 37366315.
12. Drugs.com. Retatrutide FDA approval status. Accessed February 2024. Available from: <https://www.drugs.com/history/retatrutide.html>.
13. Amazing-Meds. Is Retatrutide FDA approved? Accessed June 2025. Available from: <https://www.amazing-meds.com/is-retatrutide-fda-approved>.
14. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, Cui X, Briere DA, Cabrera O, Roell WC, Kuchibhotla U, Moyers JS, Benson CT, Gimeno RE, D'Alessio DA, Haupt A. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. *Mol Metab*. 2018 Dec;18:3-14. doi: 10.1016/j.molmet.2018.09.009. Epub 2018 Oct 3. PMID: 30473097; PMCID: PMC6308032.
15. Frías JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, Urva S, Gimeno RE, Milicevic Z, Robins D, Haupt A. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018 Nov 17;392(10160):2180-2193. doi: 10.1016/S0140-6736(18)32260-8. Epub 2018 Oct 4. PMID: 30293770.
16. Yabe D, Kawamori D, Seino Y, Oura T, Takeuchi M. Change in pharmacodynamic variables following once-weekly tirzepatide treatment versus dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono substudy). *Diabetes Obes Metab*. 2023 Feb;25(2):398-406. doi: 10.1111/dom.14882. Epub 2022 Nov 2. PMID: 36184780; PMCID: PMC10092154.
17. Min T, Bain SC. The Role of Tirzepatide, Dual GIP and GLP-1 Receptor Agonist, in the Management of Type 2 Diabetes: The SURPASS Clinical Trials. *Diabetes Ther*. 2021 Jan;12(1):143-157. doi: 10.1007/s13300-020-00981-0. Epub 2020 Dec 15. PMID: 33325008; PMCID: PMC7843845.
18. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021 Aug 5;385(6):503-515. doi: 10.1056/NEJMoa2107519. Epub 2021 Jun 25. PMID: 34170647.

19. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021 Oct;9(10):653-662. doi: 10.1016/S2213-8587(21)00203-5. Epub 2021 Aug 20. PMID: 34425083.
20. Nauck MA, Wefers J, Meier JJ. Treatment of type 2 diabetes: challenges, hopes, and anticipated successes. *Lancet Diabetes Endocrinol.* 2021 Aug;9(8):525-544. doi: 10.1016/S2213-8587(21)00113-3. Epub 2021 Jun 25. PMID: 34181914.
21. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021 Oct;9(10):653-662. doi: 10.1016/S2213-8587(21)00203-5. Epub 2021 Aug 20. PMID: 34425083.

