International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

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ARTICLE TITLE	MULTIDIRECTIONAL CLINICAL BENEFITS OF GLP-1 AGONISTS: A REVIEW OF EFFICACY IN WEIGHT LOSS AND CARDIOVASCULAR PROTECTION
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6003
RECEIVED	29 May 2026
ACCEPTED	31 August 2026
PUBLISHED	04 September 2026
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MULTIDIRECTIONAL CLINICAL BENEFITS OF GLP-1 AGONISTS: A REVIEW OF EFFICACY IN WEIGHT LOSS AND CARDIOVASCULAR PROTECTION

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ABSTRACT

Objective: The aim of this article is to systematically review and synthesize current knowledge on the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in obesity therapy and their role in the prevention of cardiovascular and renal complications [1, 2]. The paper focuses on evaluating the clinical efficacy of novel molecules, such as semaglutide and tirzepatide, and analyzing molecular mechanisms extending beyond glycemic control [3, 4].

Methodology: An analysis of the literature from 2017–2026 was conducted, including 30 selected publications, comprising the results of key phase III trials (STEP, SURMOUNT, SELECT programs), meta-analyses, and real-world evidence studies [5, 6]. The analysis evaluated data on BMI reduction, the risk of major adverse cardiovascular events (MACE), and parameters of renal and cardiac function [7, 8].

Results: The analysis demonstrated that modern GLP-1RAs allow for a body mass reduction of 14.9–20.9%, which in certain populations constitutes an alternative to bariatric surgery [9, 10, 11]. It was shown that the use of semaglutide reduces the risk of MACE by 20% in patients with obesity without diabetes (SELECT trial) [12] and improves prognosis in patients with heart failure with preserved ejection fraction (HFpEF) [13]. Additionally, significant nephroprotective and anti-inflammatory effects were confirmed, manifested by a reduction in hsCRP levels and stabilization of atherosclerotic plaques [14, 15, 16].

Conclusions: GLP-1 receptor agonists constitute the foundation of a new therapeutic strategy, combining effective obesity treatment with multiorgan protection [17]. Despite proven efficacy, challenges such as high therapy costs, the risk of losing fat-free mass, and implementation Barries require further optimization of patient care [18, 19, 20]

KEYWORDS

GLP-1 Receptor Agonists, Obesity, Cardiovascular Prevention, Weight Loss, Semaglutide, Tirzepatide

CITATION

Strugała, N., Bulenda, M., Wiśniewska, M., Żurek, J., Bednarska, K., Sapała, E., Skrzeczyna, J., Wojtaszkiewicz, D., Noworolska, M., Kostrzewski, M., & Ciećkiewicz, N. (2026). Multidirectional clinical benefits of GLP-1 agonists: A review of efficacy in weight loss and cardiovascular protection. *International Journal of Innovative Technologies in Social Science*, 3(51). https://doi.org/10.31435/ijitss.3(51).2026.6003

1. Introduction

The global epidemic of obesity and its accompanying type 2 diabetes represents one of the most costly challenges for modern healthcare systems [1, 12]. Excess body weight is no longer perceived merely as an aesthetic defect, but as a chronic inflammatory disease with complex pathophysiology, leading to the premature development of atherosclerosis, heart failure, and chronic kidney disease [2, 21]. For years, pharmacological methods offered only moderate efficacy, leaving bariatric surgery as the only standard in the treatment of severe obesity [10, 22].

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1RAs) revolutionized the approach to the metabolic patient. These drugs, by mimicking the action of the endogenous incretin hormone, exhibit a multidirectional mechanism of action: from the central regulation of appetite in the hypothalamus, through the slowing of gastric emptying, to direct effects on receptors in the heart, blood vessels, and kidneys [3, 4, 23]. Currently, thanks to the results of breakthrough trials such as SELECT, the paradigm of using this class of drugs has expanded—from strictly antidiabetic agents to drugs that modify the overall cardiometabolic risk [12, 17].

Of particular importance are newer molecules, such as semaglutide (administered once a week) and tirzepatide (a dual GLP-1/GIP agonist), which demonstrate weight loss efficacy comparable to the effects of surgical interventions [11, 24]. At the same time, clinical data indicate their unique extrapancreatic properties, including the reduction of inflammation within atherosclerotic plaques and the improvement of myocardial perfusion [15, 25]. In the face of growing evidence of their effectiveness in preventing heart attacks, strokes, and heart failure, a deep understanding of the barriers limiting their widespread use, such as high cost, availability, and concerns about long-term safety, becomes necessary [18, 20, 26].

This paper aims to analyze the multidirectional benefits of GLP-1RA use based on the latest scientific reports. Subsequent chapters discuss the molecular mechanisms responsible for organ protection, compare the efficacy of individual preparations in BMI reduction, and present current evidence for the improvement of hard endpoints in cardiology and nephrology.

2. Methodology

Search Strategy and Selection Criteria: To fulfill the objectives of this review, a comprehensive literature search was conducted covering the period from 2017 to 2026. The primary databases utilized for this search included PubMed, Scopus, and Web of Science. The search strategy employed combinations of the following keywords and Medical Subject Headings (MeSH) terms: "GLP-1 receptor agonists", "obesity", "cardiovascular outcomes", "semaglutide", "tirzepatide", "nephroprotection", and "heart failure".

Inclusion and Exclusion Criteria: The inclusion criteria were strictly defined to ensure the high quality and clinical relevance of the analyzed data. The review included: (1) randomized controlled trials (RCTs), with a particular focus on pivotal phase III clinical programs such as STEP [13], SURMOUNT [11], and SELECT [12]; (2) systematic reviews and network meta-analyses [5, 16, 26]; and (3) large-scale real-world evidence (RWE) studies [6, 33]. Only articles published in peer-reviewed journals in the English language were considered. Studies involving solely animal models (preclinical data) were generally excluded, unless they were essential for explaining specific novel molecular pathways [3]. Case reports, editorials, and non-peer-reviewed preprints were also excluded to maintain the high validity of the synthesis.

Data Extraction and Analysis: A total of 34 key publications were selected for the final synthesis out of the initial search pool. The data extraction process focused on evaluating specific clinical endpoints, primarily: the percentage of body weight reduction [5, 11], the incidence and hazard ratios of major adverse cardiovascular events (MACE) [4, 12], and specific parameters of renal and cardiac function (e.g., eGFR decline, hospitalization rates for HFpEF) [7, 8, 28]. The extracted data were then qualitatively analyzed and categorized into thematic sections corresponding to weight management efficacy, cardiovascular and renal protection, and real-world implementation barriers [18, 23].

3. Results

3.1 Mechanisms of molecular and physiological action

The efficacy of GLP-1 receptor agonists (GLP-1RAs) in reducing body weight and improving metabolic parameters results from their multidirectional action, encompassing both central (neuroendocrine) and peripheral pathways.

The gut-brain axis and appetite regulation Endogenous glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted mainly by L cells of the ileum and colon in response to food intake. However, its natural half-life is extremely short (1–2 minutes) due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) [3]. Exogenous GLP-1 analogs, thanks to structural modifications (e.g., amino acid substitution and the addition of fatty acid chains in semaglutide), exhibit resistance to DPP-4, which significantly prolongs their action [9, 21]. The main mechanism of weight reduction is based on the stimulation of GLP-1 receptors in the central nervous system (CNS). These drugs cross the blood-brain barrier or act via circumventricular organs (e.g., area postrema), directly stimulating anorexigenic POMC/CART neurons in the hypothalamus while simultaneously inhibiting the activity of orexigenic AgRP/NPY neurons [3, 23]. This leads to an increased feeling of satiety, decreased hunger, and modulation of reward pathways, helping patients control their eating habits [15, 21].

Peripheral action and dual agonists Peripherally, GLP-1RAs slow down gastric motility, which delays the absorption of nutrients and reduces postprandial glycemic spikes [4]. Furthermore, in the pancreas, they stimulate insulin secretion in a glucose-dependent manner and inhibit glucagon release [3]. A new stage in pharmacotherapy is the development of dual agonists (so-called twincretins), such as tirzepatide, which activates both GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) receptors. GIP exhibits a synergistic effect with GLP-1 in satiety centers, and peripherally improves insulin sensitivity in white adipose tissue, optimizing lipid storage and preventing organ lipotoxicity [11, 23].

3.2 Clinical efficacy in weight reduction

The introduction of long-acting GLP-1RAs has revolutionized the conservative treatment of obesity, making it possible to achieve results comparable to some surgical interventions.

Comparison of preparation efficacy Data from clinical trials and network meta-analyses clearly indicate the varied effectiveness of individual molecules.

- Semaglutide (2.4 mg s.c. once weekly): Studies from the STEP program have proven that after 68 weeks of therapy, patients achieve an average weight reduction of approximately 14.9% to 16.9% compared

to placebo (approx. 2.4%). This drug is currently considered the gold standard in obesity pharmacotherapy [5, 21].

- Tirzepatide: As a dual GLP-1/GIP agonist, tirzepatide demonstrates superior efficacy over selective GLP-1RAs. Analysis of data from the SURMOUNT program showed that the highest dose (15 mg) allows for a weight reduction exceeding 20% (an average of approx. 22.5 kg) after 72 weeks of treatment, making it the most potent pharmaceutical currently available in this class [11, 23].
- Pediatric use: Studies confirm the high efficacy and acceptable safety profile of these drugs also in children and adolescents (from 12 years of age), allowing for a significant correction of the BMI index during a crucial developmental period [26].

GLP-1RAs vs. bariatric surgery Although metabolic and bariatric surgery (MBS) remains the most effective form of treatment for severe obesity (allowing for a loss of approx. 25–30% of total body weight), modern pharmacotherapy is becoming a strong alternative [10]. Retrospective studies and analyses using propensity score matching indicate that incretin drugs show a lower risk of acute perioperative complications, offering stable weight reduction in patients ineligible for surgery [22]. However, it is noted that the effects of pharmacotherapy persist only during the use of the drug, and its discontinuation is associated with a "rebound" effect (weight regain) [23].

Body composition and the role of exercise A significant clinical challenge is the risk of losing fat-free mass (sarcopenia) during rapid weight loss induced by GLP-1RAs, which is particularly dangerous, for example, for older women with obesity [20]. However, studies prove that incorporating regular physical exercise into GLP-1RA therapy (e.g., liraglutide) not only enhances the loss of fat mass (especially visceral fat) but also effectively protects against muscle tissue loss, further potentiating the reduction of systemic inflammation [27].

3.3 Cardiovascular and renal protection (CVOT trial results)

Initially, GLP-1 receptor agonists were perceived exclusively as hypoglycemic agents. However, the results of multicenter cardiovascular outcome trials (CVOTs) revised this paradigm, demonstrating their strong cardioprotective and nephroprotective properties, which go beyond glycemic control and weight reduction alone [4, 14, 21].

Reduction of the risk of cardiovascular events (MACE) Key evidence comes from trials such as LEADER (liraglutide) and SUSTAIN-6 (s.c. semaglutide), which showed a reduction in the risk of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE) in patients with type 2 diabetes [2, 4]. A breakthrough was the SELECT trial, which demonstrated that semaglutide at a dose of 2.4 mg reduces the risk of MACE by 20% in patients with overweight or obesity and established cardiovascular disease, but without coexisting diabetes [12, 17]. This suggests that the protective mechanisms of GLP-1RAs, such as improving endothelial function, direct anti-inflammatory effects in the vessel walls, and stabilization of atherosclerotic plaques, are universal and independent of HbA1c levels [15, 25]. Meta-analyses covering various populations confirm that these benefits are consistent across White, Black, and Asian patients [29].

Heart failure (HF) Traditionally, the treatment of heart failure in metabolic patients relied on SGLT2 inhibitors. Currently, data from the STEP-HFpEF program indicate that semaglutide significantly improves physical capacity (measured by the 6-minute walk test) and quality of life in patients with heart failure with preserved ejection fraction (HFpEF) and obesity [13, 28]. GLP-1RAs reduce heart failure symptoms by decreasing systemic inflammation and reducing the cardiac workload resulting from lower body weight and lower blood pressure [14, 17]. Moreover, in patients after an acute myocardial infarction, combination therapy with GLP-1RAs and SGLT2is demonstrates a synergistic effect in reducing recurrent coronary events [31].

Nephroprotection GLP-1RAs exhibit strong protective effects on the kidneys, which is particularly important in diabetic kidney disease (DKD). These mechanisms include the reduction of oxidative stress in the renal glomeruli, inhibition of renin-angiotensin-aldosterone (RAA) system activity, and anti-inflammatory effects [8, 14]. Studies have shown that the use of GLP-1RAs (e.g., semaglutide in the FLOW trial) leads to a significant slowing of the decline in the estimated glomerular filtration rate (eGFR) and a reduction in albuminuria [7, 8]. Renal benefits are visible even in patients with advanced chronic kidney disease (stages 4 and 5), in whom therapeutic options are usually limited [8].

Other vascular aspects New data point to the benefits of GLP-1RAs in less obvious areas of vascular surgery. The use of these drugs in patients with diabetes undergoing peripheral arterial bypass is associated with significantly better long-term survival and fewer metabolic complications in the postoperative period [30]. This is likely due to better tissue perfusion and the limitation of the progression of peripheral arterial disease [25].

4. Discussion

4.1 Implementation barriers and therapy limitations

Despite indisputable, multidirectional clinical benefits, the widespread implementation of GLP-1 receptor agonists in the treatment of obesity and cardiovascular prevention faces significant medical, economic, and psychological barriers [18, 23].

Tolerance and adverse effects: The most frequently reported limitation of GLP-1RA therapy is gastrointestinal adverse events, such as nausea, vomiting, diarrhea, and constipation. They occur in up to 40–70% of patients, usually during the initial phase of treatment and during dose titration [19, 32]. Although these symptoms are generally mild to moderate and self-limiting, they lead to treatment discontinuation in some patients. Attention is also drawn to the rarer, but more serious risk of complications, such as acute pancreatitis, delayed gastric emptying (gastroparesis), or cholelithiasis, resulting from rapid weight loss [19, 32].

Body composition changes and the risk of sarcopenia: Growing concerns within the medical community surround the impact of intensive pharmacotherapy on body composition. Studies indicate that the significant weight loss induced by GLP-1RAs (e.g., semaglutide or tirzepatide) is associated not only with fat mass reduction but also with the loss of fat-free mass (FFM), including muscle tissue [19, 20]. This phenomenon, leading to so-called sarcopenic obesity, is particularly dangerous for elderly patients (especially postmenopausal women), in whom it may exacerbate the risk of frailty syndrome and falls [20]. Preventing this phenomenon requires strictly combining pharmacotherapy with adequate protein intake and resistance training [20, 27].

Economic barriers and the "rebound" effect: The costs of incretin therapies currently represent one of the main systemic barriers. Comparative analyses with metabolic and bariatric surgery (MBS) have shown that although surgery involves high initial costs, long-term (multi-year) GLP-1RA pharmacotherapy generates significantly higher cumulative costs for healthcare systems and patients themselves [10]. Moreover, the treatment of obesity with this class of drugs is symptomatic and must be conducted chronically. Data from observational studies indicate that discontinuing the drug leads to a rapid return of body weight (the so-called rebound effect), and only a small percentage of patients maintain adherence after the first year [18, 33].

4.2 Future perspectives

Pharmacological and digital innovations: The future of metabolic disease treatment is heading towards increasing patient convenience and optimizing physiological pathways. A promising direction is the development of oral GLP-1RA formulations (e.g., oral semaglutide), which may eliminate the psychological barrier associated with injections [18]. In parallel, advanced research is underway on triple agonists (activating GLP-1, GIP, and glucagon receptors), which, thanks to the additional enhancement of thermogenesis and lipolysis in the liver by glucagon, may offer even more effective weight reduction and treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) [3, 23]. Complementing pharmacological innovations is the integration of therapy with digital medicine. The use of artificial intelligence (AI) algorithms and mobile applications to monitor eating habits, physical activity, and patient adherence can significantly improve the long-term maintenance of treatment effects [23, 34].

5. Conclusions

Based on a systematic review of current literature and the results of breakthrough clinical trials, the following conclusions can be drawn regarding the use of GLP-1 receptor agonists:

1. Breakthrough in obesity treatment: Modern incretin drugs, particularly semaglutide and tirzepatide, have revolutionized obesity pharmacotherapy. They allow for a weight reduction of 15–20% [11, 21], making them the first pharmacological alternative in history capable of competing with the results of bariatric surgery, especially in patients ineligible for surgical treatment [10, 22].
2. Independent organ protection: The action of GLP-1RAs extends far beyond glycemic control and weight reduction. The ability of these drugs to lower the risk of major adverse cardiovascular events (MACE) by 20% in patients with obesity without diabetes (as proven by the SELECT trial) [12], and their documented nephroprotective effects [7, 8], constitute a paradigm shift in preventive cardiology and nephrology [14, 17].
3. New perspectives in heart failure: GLP-1RA-based therapy significantly improves the quality of life and physical capacity in patients with obesity and heart failure with preserved ejection fraction (HFpEF), thereby filling a significant therapeutic gap in this patient group [13, 28].

4. Challenges and limitations: The main barriers preventing the widespread implementation of this therapy are the high, long-term costs of treatment, burdensome gastrointestinal adverse effects, and the "rebound" effect following treatment discontinuation [18, 32, 33].

5. Risk of sarcopenic obesity: A critical challenge identified in recent studies is the loss of fat-free mass (muscle tissue) accompanying rapid weight reduction. This necessitates the strict combination of pharmacotherapy with targeted lifestyle interventions, including adequate protein intake and resistance training, particularly in the geriatric population [20, 27].

In summary, GLP-1 receptor agonists are not merely another class of antidiabetic or weight-loss drugs, but represent a comprehensive tool in the treatment of multiorgan cardiometabolic syndrome. However, to maximize their potential and minimize systemic risks, it is necessary to transition from a "drug supplementation" model to the holistic management of obesity as a chronic inflammatory disease.

Conflicts of Interest: No conflicts of interest to declare.

Statement: This study did not receive any special funding.

Acknowledgments: The authors would like to acknowledge all the investigators and participants of the clinical trials reviewed in this manuscript.

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