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Invited Review Article

GLP1-RAs: long-term use versus discontinuation events of an emerging therapy for obesity and cardiovascular diseases

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ABSTRACT

Obesity is a highly prevalent chronic disease strongly associated with cardiometabolic complications, including type 2 diabetes, hypertension, heart failure and other cardiovascular diseases. The growing understanding of these interrelationships has fundamentally changed clinical approaches to their management. In this context, a new class of agents, the glucagon-like peptide-1 receptor agonists (GLP-1 RAs), has gained increasing importance in patient care, supported by relevant scientific evidence that made them a first-line therapeutic option in various clinical settings. Nevertheless, in clinical practice, there is still concern about their long-term use and the potential risk of adverse effects. As a consequence, GLP1-RAs are often prescribed only for limited periods and discontinued once weight reduction has been achieved. The aim of this review is to examine the clinical effects and main indications of GLP-1 RAs and to compare the risk of long-term adverse outcomes associated with their use versus the risks related to their discontinuation.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP1-RAs) represent a relatively new class of agents that have progressively assumed an important role in therapeutic management of cardiovascular diseases. Initially developed as antidiabetic drugs, due to their hypoglycemic effect on significantly reducing hemoglobin A1c (HbA1c), their clinical indications have recently expanded to include weight reduction and cardioprotection, also in patients not affected by diabetes mellitus. In particular, some GLP1-RAs such as albiglutide, liraglutide, dulaglutide, semaglutide and tirzepatide have demonstrated beneficial effects in reducing atherosclerotic disease.

In this narrative review we aim to examine the clinical effects and main indications of GLP-1 RAs and to compare the risk of long-term adverse outcomes associated with their use versus the risks related to their discontinuation. We performed a literature search in PubMed, Cochrane Library, and MEDLINE for studies published up to June 2025 using the keywords ‘GLP1 receptor agonists’, ‘semaglutide’, ‘liraglutide’, ‘obesity’, ‘heart failure’, ‘adverse events’, ‘long-term use’. We included randomized controlled trials, meta-analyses, and large observational studies evaluating long-term efficacy, safety, and discontinuation outcomes in adults. Only English-language papers were included. We selected the studies based on clinical relevance, population size, adequate follow-up duration (>12 months), and availability of cardiovascular or renal endpoints

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Glucagon-like peptide-1 receptor agonists

Molecular pharmacology of GLP1-RAs

GLP-1 receptor agonists (GLP-1 RAs) are peptide-based molecules that bind to the GLP-1 receptor, mimicking the action of the endogenous incretin hormone produced by post-translational processing of the protein encoded by the proglucagon gene in L-type enteroendocrine cells [1].

More specifically, these molecules contain structural modifications that enhance their resistance to degradation by DDP-4 enzyme. While they share broadly similar pharmacological profiles, they differ in their duration of action. In particular, analogues with amino acid substitutions in the human GLP-1 sequence are classified as long acting, whereas those derived from exendin-4 -such as exenatide and lixisenatide- are called short acting molecules.

Among long-active molecules, liraglutide shares 97 % sequence homology with human GLP-1 and is conjugated to a fatty acid chain, enabling non-covalent binding to albumin.

Semaglutide, by contrast, exhibits 94 % homology with human GLP1, with a structure similar to liraglutide, but includes a fatty acid molecule attached to lysine at position 26 via a γ-glutamate spacer. This modification enhances albumin binding and prolongs its half-life. All GLP-1 receptor agonists are metabolized by the kidneys, with the exception of liraglutide, which is excreted in the urine at a rate of approximately 6 %.

This GLP-1 is involved in several physiological processes, including enhancement of insulin synthesis and insulin sensitivity in peripheral tissues, and stimulation of pancreatic β-cell proliferation [2–3]. In addition, these actions counteract apoptosis, thereby preserving pancreatic β-cell mass.

Specifically, short-acting agents primarily influence postprandial glucose levels, whereas long-acting molecules exert minimal effects on gastric emptying and are more effective in reducing fasting glucose concentrations.

In extrapancreatic settings, several studies have reported beneficial extraglycemic renoprotective effects, including anti-albuminuric, antioxidant, and anti-inflammatory actions [4].

The principal cardiovascular benefits involve favourable cardiac remodelling and antihypertensive activity, mediated through mechanisms such as natriuresis, vasodilation of renal arterioles, modulation of catecholaminergic signalling in the brainstem, and suppression of angiotensin II activity within renal tissue [5–6-7]

GLP1-RAs and cardiometabolic syndrome

The promising effects of GLP-1 receptor agonists (GLP-1 RAs) in various clinical settings have recently broadened their indications in real-world practice. Initially introduced as antidiabetic agents, they are now approved for weight management and cardiovascular protection. Their efficacy in promoting weight loss, particularly in the context of obesity treatment, has extended their use to the prevention of obesity-related diseases such as cardiovascular disease, diabetes and osteoarthritis.

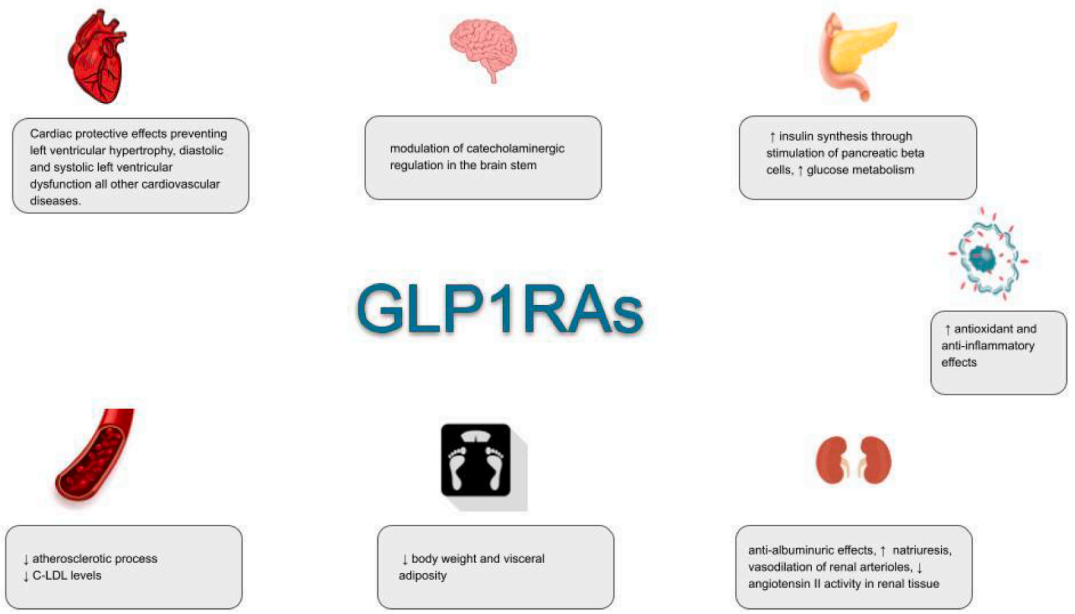

Fig 1. Summary of the pleiotropic effects of GLP1-RAs across major organ systems, including glucose regulation, cardiovascular remodeling, renal protection, appetite control, and neuroprotection.

Furthermore, several large randomized controlled trials have demonstrated pleiotropic effects beyond weight reduction and glycemic control. Notably, the reduction in major adverse cardiovascular events appears to be independent of weight loss [8] (Figure 1).

Strong evidence indicates that obesity increases the risk of developing type 2 diabetes by approximately 80–85 %, and that nearly one-third-of individuals with diabetes are affected by cardiovascular disease. Furthermore, epidemiologic evidence indicates that the majority of patients with heart failure with preserved ejection fraction are obese and characterized by increasing adipose tissue. Visceral adiposity, in particular, is associated with systemic inflammation, left ventricular hypertrophy, insulin resistance, both diastolic and systolic dysfunction of the left ventricle, as well as arterial, skeletal muscle, and overall physical impairment [9].

The last evidence supporting the use of GLP1-RAs in the cardiovascular field arises from the recognition of a complex health disorder characterized by the interconnections among obesity, diabetes, chronic kidney disease and cardiovascular disease (CVD) such as heart failure, atrial fibrillation, coronary heart disease, stroke and peripheral artery disease.

A recent document published in 2023 introduced the concept of cardiovascular-kidney-metabolic (CKM) syndrome, in which systemic inflammation plays a central role (10). While the bidirectional interactions between the kidneys and the heart have long been recognized, attention has only recently shifted toward the contribution of cardiometabolic disease. In this context, excess adipose tissue, especially in the visceral sites, can trigger a wide range of systemic effects including insulin resistance, cardiovascular disease, atherosclerosis and alterations in myocardial function, hemostasis and cardiac conduction. Furthermore, higher degrees of obesity are associated with progressively earlier mortality, with grade III obesity (BMI 40-45 kg/m2) linked to a reduction in median survival of 8 to 10 years [10].

In this context, GLP1-RAs not only improve insulin resistance and glycemia but also reduce weight and significant reduction in CVD mortality [11].

Cardiovascular-kidney-metabolic (CKM) syndrome can be categorized into distinct stages. Stage 0 indicates the absence of CKM risk factors. Stage 1 is characterized by excess dysfunctional adiposity, while stage 2 is defined by the presence of multiple metabolic risk factors together with a moderate-to-high risk of chronic kidney disease (CKD). Stage 3 corresponds to subclinical cardiovascular disease (CVD) or subclinical heart failure. Stage 4 reflects overt CKM, including clinical manifestations such as heart failure, established CVD, atrial fibrillation, stroke, and peripheral artery disease. This stage is further subdivided into 4a and 4b, according to the presence or absence of kidney failure [12]

This strong classification provides important clinical utility as recognizing patients at the earliest stages may prevent progression to subclinical or overt disease . Within this framework, therapeutic interventions such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) offer a rational strategy to address excess adiposity at stage 1 and to manage multiple metabolic risk factors at stage 2.

The close relationship between weight gain and cardiovascular disease is particularly evident in patients with obesity and heart failure with preserved ejection fraction (HFpEF). Several studies have demonstrated that these patients exhibit elevated inflammatory markers, reduced venous capacitance, increased exercise pulmonary wedge pressures, impaired response to diuresis, hypertension and decreased exercise tolerance [13–14-15–16]. All these features exert a substantial negative impact on patients' quality of life.

For instance, impaired physical function is recognized as an independent predictor of reduced quality of life, increased risk of hospitalization, loss of independence, and mortality. In addition, patients with obesity exhibit lower circulating levels of natriuretic peptides, which contribute to diminished vasodilatory and natriuretic capacity [17–18].

The strong evidence of the use of GLP1-RAs on cardiovascular diseases allowed their indication not only in the context of heart failure but also in coronary artery disease.

The last guidelines from the European Society of Cardiology for the management of chronic coronary syndrome (CCS) recommend the use of GLP1-RA in patients with diabetes and CCS regardless of baseline hemoglobin A1c or the concomitant use of other hypoglycaemic agents (Class I A) [19–20]

In patients who are overweight (body mass index [BMI] > 27 kg/m^2) or obese without diabetes, treatment with GLP-1 RAs should be considered to reduce the risk of cardiovascular events, myocardial infarction (MI), or stroke (Class IIa) [21]

This recommendation is supported by the SELECT trial, which evaluated the effects of semaglutide on major adverse cardiovascular events in 17,604 patients with overweight and established cardiovascular disease. The study demonstrated a significant mean weight reduction of 6.4 % over two years in the semaglutide group, compared with 0.88 % in the placebo group. Moreover, semaglutide therapy was associated with a significant reduction in the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (hazard ratio [HR] 0.80; 95 % confidence interval [CI] 0.72–0.90; $p < 0.001$) [21].

Long-term use of GLP1-RAs

The encouraging results from multiple clinical trials support the potential expansion of GLP-1 RA use to a broader patient population, with evidence suggesting that these agents may represent a long-term therapeutic option. In clinical practice, however, concerns remain regarding the potential adverse effects associated with prolonged treatment. Initial worries about pancreatic complications have been largely dispelled, as long-term follow-up studies have not demonstrated significant associations. Moreover, regarding renal impairment, a subanalysis of the SELECT trial evaluated the long-term kidneys outcomes of semaglutide against placebo with a median follow up of 182 weeks. The main kidney endpoint was a composite endpoint including specific death from kidney disease, initiation of dialysis or transplantation, onset of persistent eGFR < 15 mL/min/1.73 m2, reduction >50 % in eGFR and onset of persistent macroalbuminuria. The result at the end of the follow up demonstrated the significant reduction of incidence of kidney events in the semaglutide group instead of the placebo arm (HR 0.78,95 % CI, 0.63-0.96, $p = 0.02$). More specifically, despite the initial decline in eGFR during the first 8-10 weeks that was more pronounced in the semaglutide group, after this period semaglutide showed to be more effective in the renal protection [22]

Furthermore, a retrospective cohort study has analysed the long-term impact of GLP1-RA on thyroid, heart and kidney and adverse events in patients with obesity without type 2 diabetes and without other glucose-lowering drugs. An analysis of almost twenty-four thousand patients in eight years demonstrated the benefit of GLP1RAs treatment in reduction of all-cause mortality and several cardiovascular events such as ischaemic heart disease, heart failure, arrhythmias, hypertension, stroke and atrial fibrillation ($p < 0.05$). In addition, it was observed a significant reduction of urinary tract infections and pyelonephritis in the GLP1-RAs group. (HR 0.79; 95 % CI, 0.68–0.93; $p = 0.01$). For whom it concerns adverse events there were no significant differences between the two groups in hypoglycaemia, lactic acidosis, pancreatitis, liver injury and dyspepsia [23]

Moreover, a recent retrospective study analysed the effects of GLP1RAs in a population of 253 patients undergoing therapy with GLP1-RAs with an average follow-up of 8.15 years. The endpoints of the study were weight and glycemic outcomes while secondary endpoints were the occurrence of renal and cardiovascular events.

Comparing the data obtained from patients, it was found that the protective effect of these molecules increased over time. In fact, a reduction in HbA1c values was found to be 7.81 % at 6 years, 8.08 % at 8 years, and 8.26 % at 10 years, while weight reduction was 5.6 kg at 6 years and 6.8 kg at 8 years. In addition, a progressive reduction in ischemic events such as strokes/transient ischemic attacks and acute coronary syndromes was observed, with the latter showing a reduction in absolute terms, although not reaching statistical significance.

This study therefore confirms the beneficial effects of GLP-1 RA treatment on HbA1c and weight over time. Moreover, the reduction in atherosclerotic events, likely due to stroke protection, should help to strengthen the safety and the long-term use of these drugs in clinical practice [24]

Recently, a meta-analysis analysed the long-term effects of using GLP1RAs, comparing their risks and benefits. Fifty-five articles were analysed with 45 trials involving a total of over 70,000 patients, including studies comparing GLP1RAs with placebo or other anti-hyperglycaemic medications.

Compared to placebo, GLP1RAs reduced cardiovascular risk factors (such as systolic blood pressure, weight and BMI), microvascular complications (including renal events), macrovascular complications (stroke), and mortality.

Regarding adverse effects, GLP1RAs were associated with less hypoglycaemic events when compared to other anti-hyperglycaemic medications but were still liked with gastrointestinal events (nausea and vomiting) even if no differences were observed in terms of pancreatic cancer, medullary thyroid cancer, or pancreatitis [25]

In fact, a sub-analysis of the ELIXA study analysed the effects of lixisenatide on approximately 6,000 patients with type 2 diabetes mellitus and acute coronary syndrome. All patients were randomised to receive lixisenatide or placebo, and after a mean follow-up of 25 months, lixisenatide was not associated with serious adverse events such as severe hypoglycaemia, pancreatitis, pancreatic neoplasms, or allergic reactions [26]

Although not strictly related to long-term use, gastrointestinal effects are still one of the main reasons that can lead to discontinuation of the drugs.

The Table 1 summarizes the studies cited above (Table 1).

Discontinuation of GLP1-RAs

Adverse events

Despite the well-documented health benefits of GLP1-RAs, many patients still discontinue therapy, particularly once weight reduction has been achieved. In the SELECT trial, the prevalence of treatment discontinuation was approximately 30 %, whereas real-world estimates suggest discontinuation rates between 50 % and 75 % at 12 months [27]

As discussed later, discontinuation of GLP1-RA therapy is associated with worsening cardiometabolic parameters such as glucose levels, blood pressure, and cholesterol, resulting in a significant increase in cardiovascular risk. Moreover, lean muscle mass lost during GLP1-RA treatment may not be regained after discontinuation, leading to adverse changes in body composition and an increased risk of sarcopenia [28]

Several studies have investigated the reasons for treatment discontinuation. Structural factors such as out-of-pocket costs are important drivers of chronic therapy discontinuation and likely have a disproportionate influence on GLP1-RA discontinuation. However, adverse effects must also be considered. The most common side effects include gastrointestinal events such as nausea, vomiting, diarrhea, constipation, indigestion, dizziness, hypoglycaemia, and abdominal discomfort.

These may arise from activation of both peripheral and central GLP1 receptors, through direct or indirect interactions with the central nervous system. Other possible mechanisms include activation of afferent parasympathetic pathways or effects on brain regions unprotected by the blood–brain barrier [29–30]. Additionally, changes in the secretion of gastrointestinal peptides, delayed gastric emptying, or altered intestinal motility may contribute [31–32]

A recent cross-sectional study analysed common side effects and reasons for GLP1-RA discontinuation, with subgroup analyses based on treatment duration and patient age [33]. Almost 350 patients were evaluated, the majority female, with a median BMI of 32.4 kg/m^2. All patients had been prescribed liraglutide or semaglutide specifically for weight management, excluding other indications. Regarding treatment duration, >40 % had used GLP1-RAs for more than six months, 30 % for three to six months, and about 25 % for less than three months. In this study, nearly 70 % of patients discontinued therapy, most commonly by personal choice (45 %), followed by cost (22 %) and treatment schedule difficulties (20 %).

Adverse events affected >80 % of patients, with nausea reported in 77.5 %, followed by loss of appetite (36.6 %), vomiting (36.6 %), abdominal pain (33.8 %), and headache (19.0 %). Subgroup analysis by age revealed no significant differences in side effect

Table 1
Trials exploring the effects of long-term use of GLP1RAs.

Author	Follow-up	Population	Type of study	Outcomes	Results
Helen M. Colhoun, et al.	182 weeks	8803 overweight or obese pts, with established cardiovascular disease.	Prospective Study: semaglutide Vs placebo	Primary endpoint: Composite of death from kidney disease, initiation of chronic kidney replacement therapy, onset of persistent eGFR <15, persistent ≥50 % reduction in eGFR or onset of macroalbuminuria	Reduction in all pre-specified main composite kidney endpoint (**$p = 0.02$**)
Yu-Nan Huang, et al.	8 years	24246 obese pts without type 2 diabetes mellitus	Observational study	Primary endpoint: Safety, cardiovascular, thyroid and clinical biochemical profile	Lower risk of all-cause mortality and several cardiovascular complications, including ischaemic heart disease, heart failure, arrhythmias, hypertension, stroke and atrial fibrillation. Lower risk includes acute kidney injury and allergic reactions **(all $p < 0.05$)**
Piccini Sara, et al.	8.15 years	253 pts	Retrospective study	Primary endpoints: weight and glycaemic outcomes. Secondary endpoints: renal and cardiovascular events	Reduction in HbA1c and weight over time. Reduction in ischemic events such as strokes/transient ischemic attacks and acute coronary syndromes, even if not statistically significance **($p > 0.001$)**
Marc A Pfeffer, et al.	25 months	6,000 pts with type 2 diabetes mellitus and acute coronary syndrome	Prospective: lixisenatide Vs placebo	Primary composite endpoint of cardiovascular death, myocardial infarction, stroke or hospitalization for unstable angina. Secondary endpoint concerning adverse events	No significant association with serious adverse events such as severe hypoglycaemia, pancreatitis, pancreatic neoplasms, or allergic reactions **($p < 0.001$)**

Table 2
Discontinuation of therapy with GLP1RAs.

Study	Author	Follow-up	Population	Randomization	Outcomes	Results
STEP 1	John P.H. Wilding, et al.	120 weeks	1961 pts, without diabetes, BMI >= 30 or >= 27 with other comorbidities despite unsuccessful dietary efforts	Semaglutide 2.4 mg Vs placebo until week 68 then withdrawal (2:1)	Primary endpoint: Change in body weight Confirmatory endpoints: waist circumference, systolic blood pressure and quality of life	Body weight: Semaglutide Vs placebo (−14.9 % Vs −2.4 %) (95 % CI, −13.4 to −11.5; $\boldsymbol{p < 0.001}$) After withdrawal semaglutide Vs placebo (+11.6 % Vs +1.9 %)
STEP 4	Domenica Rubino, et al.	48 weeks	903 pts, without diabetes, BMI >= 30 or >= 27 with other comorbidities despite unsuccessful dietary efforts	Run-in of semaglutide 2.4 mg for 20 weeks. Than placebo Vs semaglutide (1:2) plus lifestyle interventions	Primary endpoint: Change in body weight Confirmatory endpoints: waist circumference, systolic blood pressure and quality of life	After withdrawal Semaglutide Vs placebo: body weight (−7.9 % Vs +6.9 %; 95 % CI, $\boldsymbol{p < 0.001}$); waist circumference (−9.7 cm, $\boldsymbol{p < 0.001}$), systolic blood pressure (−3.9 mmHg, $\boldsymbol{p < 0.001}$), and SF-36 physical functioning score (2.5, $\boldsymbol{p < 0.001}$)
AHED	Rena R Wing, et al.	13.5 years	5145 pts, BMI > 25 with diabetes 2 type	Decreased caloric intake and increased physical activity Vs support and education	Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina	↓ caloric intake and ↑ physical activity Vs support and education: 403 Vs 418(1.83 and 1.92 events per 100 person-years, 95 % CI, 0.83 to 1.09; $\boldsymbol{p = 0.51}$)
PCOS and Obesity	Mojca Jensterle, et al.	2 years	25 pts, PCOS and BMI > 27	Run-in of semaglutide 1 mg + metformin (Glucophage) 2000 mg for 16 weeks. Than only metformin (Glucophage) plus lifestyle interventions	Change in body weight, cardio-metabolic and endocrine parameters	Body weight decreased from 101 kg to 92 kg. Two years after semaglutide withdrawal, weight was 95 kg with similar results in total and LDL cholesterol and fasting glucose ($\boldsymbol{p = 0.003}$)

incidence ($p = 0.356$), although nausea was more common among younger patients compared with older groups ($p = 0.011$). Interestingly, adverse events were significantly less frequent in patients treated for more than six months compared with those treated for a shorter duration ($p < 0.001$). These findings suggest that while gastrointestinal adverse events are common, their prevalence declines substantially after the first few months of treatment. In this context, addressing potential side effects and adverse events during shared decision-making may help reduce discontinuation rates.

Mental health and GLP1-RAs

Another important aspect of treatment discontinuation relates to mental health. Previous studies have suggested that mental disorders may influence GLP1-RA discontinuation, and that these drugs could exacerbate pre-existing psychiatric conditions [34]. It is well known that individuals with severe obesity (BMI ≥ 40 kg/m^2) are at increased risk of depressive disorders compared with those with lower BMI.

With regard to the relationship between GLP1-RAs and mental health, a recent post hoc analysis investigated the psychiatric safety of these medications. Data from the phase 3a STEP 1, 2, and 3 trials and the phase 3b STEP 5 trial were included. Patients were randomized to receive subcutaneous semaglutide or placebo in addition to lifestyle intervention. Psychiatric and nervous system adverse events were evaluated, with particular attention to depressive symptoms and suicidal ideation assessed using validated scales. In over 3,000 patients, treatment with semaglutide was not associated with the development of psychiatric symptoms after long-term follow-up ($p < 0.001$).

Furthermore, treatment with semaglutide was associated with a lower likelihood of progression to more severe categories of depression or other psychiatric conditions ($p < 0.001$) [35]

Finally, a retrospective study investigated the prevalence of mental disorders and their impact on treatment adherence in obese patients receiving liraglutide [36]. The study included 54 individuals, in whom psychiatric symptoms were assessed using validated scales, while adherence was evaluated through achievement of maximum dosage and treatment duration. A high discontinuation rate of nearly 60 % was reported. Detailed analysis revealed a negative association between anxiety symptoms and attainment of maximum dosage, as well as between depressive symptoms and treatment duration. These findings indicate that, although mental health conditions do not affect the pharmacological efficacy of GLP1-RAs, they may play a critical role in reducing adherence.

While isolated case reports of mood changes have been described [34], pooled analyses from STEP trials and post-marketing data show no increased risk of depression or suicidality with semaglutide [35]. However, further prospective data are needed, particularly in patients with baseline psychiatric comorbidities

This highlights the importance of appropriate psychological support and comprehensive care in patients with mental disorders undergoing GLP1-RA therapy.

Effects of GLP-1 RAs discontinuation

Conversely, several trials have investigated the systemic consequences of discontinuing GLP-1 RA therapy.

Firstly, the STEP 1 trial extension randomized almost 2000 obese patients without diabetes receiving semaglutide or placebo, adding in both group lifestyle intervention (regular counselling and physical activity). After 68 weeks both groups discontinued their treatment, and it was conducted a follow up to week 120. From week 0 to week 68, there was a significant weight loss in the semaglutide group compared to placebo arm (17.3 % vs 2 %). After treatment withdrawal, both groups regained weight respectively of 11.6 % and 1.9 % in the semaglutide and placebo group.

Other endpoints included the analysis of cardiometabolic risk factors. After treatment withdrawal, mean systolic and diastolic blood pressure significantly increased with a similar increase in CRP (C reactive protein), HbA1c and lipids levels [37]

Prior to this study, the STEP 4 trial included a total of 902 patients who received semaglutide for 20 weeks. After this period, they were randomized to continue receiving subcutaneous semaglutide or switch to placebo, in addition to lifestyle interventions with a follow up of 48 weeks. The primary endpoint included change in body weight while secondary confirmatory endpoints were changes in waist circumference, systolic blood pressure and physical functioning. After the randomization there was a significant reduction of mean body weight in the semaglutide group Vs placebo (-7.0 % Vs $+ 6.9$ %, $p < 0.001$). For whom it concerned all three secondary endpoints there still was a significant benefit in the treatment arm compared to placebo (all $p < 0.001$) with no significant adverse events registered [38]

On the other hand, evidence suggests that the cardioprotective effects of GLP-1 RAs extend beyond weight reduction, underscoring their additional pleiotropic properties.

Another study tried to compare GLP1RAs with other pharmacological therapies in maintaining weight loss. A specific population of obese women with polycystic ovary syndrome were treated with semaglutide 1 mg/week plus metformin (Glucophage) 2000mg/day for 16 weeks. After that period semaglutide was discontinued continuing treatment with metformin (Glucophage) and other lifestyle interventions for 2 years. During the treatment period with semaglutide there was a significant reduction in body weight (90-106.8 Vs 83.3-100.8). After discontinuation, there was a slow increase in body weight, although it remained significantly lower than the initial pre-treatment values. ($p = 0.003$). For whom it concerns all cardiometabolic factors including total and LDL cholesterol and fasting glucose levels, a clear improvement in these parameters was observed during semaglutide treatment phase with a complete return towards baseline after two years of withdrawal [39]

The trials mentioned above have demonstrated interesting cardiovascular effects of GLP1RAs, with no evidence of serious adverse events related to long-term use. Notably, these effects almost disappear after the discontinuation of the therapy.

A recent systematic review and meta-analysis by Berg et al. [40] evaluated the effects of discontinuing GLP1-RAs on body habitus. The study included >2,300 participants from eight randomized controlled trials who discontinued treatment with liraglutide, semaglutide, or tirzepatide. All patients were overweight or obese (BMI $\geq$ 27 kg/m^2) and presented comorbidities such as type 2 diabetes, prediabetes, or non-alcoholic fatty liver disease. Treatment duration before discontinuation ranged from 20 to 160 weeks, with lifestyle interventions maintained throughout. The analysis showed that discontinuation was consistently associated with significant increases in body weight and BMI, with weight regain proportional to the initial weight loss ($p < 0.001$). Interestingly, the increase in waist circumference was less pronounced compared with overall weight and BMI, particularly among patients previously treated with semaglutide or liraglutide. These findings underscore the chronic nature of obesity and suggest that long-term pharmacological support may be required to maintain the benefits of GLP1-RA therapy, as discontinuation leads to substantial weight regain and potentially unfavourable redistribution of adipose tissue. In particular, fat may accumulate viscerally, leading to an apparent attenuation of weight regain while still contributing to adverse cardiovascular outcomes and unfavourable biomarker profiles.

However, it is important to mention that other therapeutic options, not only pharmacological, may have a positive impact on obesity-related cardiovascular diseases.

In fact, the AHED trial has studied the impact of intensive lifestyle intervention in obese patients with type 2 diabetes. The study included more than five thousand patients receiving an intensive lifestyle intervention promoted to decreased caloric intake and increased physician activity or just diabetes support and education. The primary outcome was a composite of major cardiovascular adverse events including death from cardiovascular causes, non-fatal myocardial infarction, nonfatal stroke or hospitalization for angina. After a long follow up of 13.5 years, it was possible to appreciate a great reduction of mean body weight in the intervention group. Similarly, the intervention group showed improvements in glycated hemoglobin levels and other cardiovascular risk factors (except for LDL cholesterol levels) in the first years with a slowing reduction over the years. For whom it concerns the primary outcome, the trial showed no significant differences between the two groups ($p = 0.51$) [41].

The Table 2 summarizes the studies cited above (Table 2)

Conclusions

Obesity is a chronic disease with an increasing prevalence worldwide. The association between visceral adiposity and other metabolic disorders is now well established and formally integrated into specific classifications. Within this framework, GLP-1 receptor agonists (GLP-1 RAs) have emerged as a novel class of agents with relevant cardiovascular consequences that go well beyond hypoglycemic effect. As cited above, multiple studies have demonstrated their pleiotropic effects, extending beyond weight loss to include significant cardiovascular benefits. Sustained therapy confers durable cardiometabolic protection, while discontinuation leads to rapid relapse of weight and risk factors. Ongoing research should define optimal treatment duration and strategies to enhance adherence.

Despite robust outcome data, most evidence derives from populations with type 2 diabetes; data in non-diabetic obesity and HFpEF remain limited. Real-world discontinuation rates and post-withdrawal metabolic trajectories warrant further investigation

Nowadays, the chronic nature of obesity highlights the importance of maintaining long-term drug therapy for weight management and all related cardiometabolic diseases, with no evidence of serious adverse events related to long-term use, thus allowing GLP1RAs to be a safe first line in the treatment of these patients.

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