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Obesity, cardiovascular and cerebrovascular disease: the role of GLP-1 receptor agonists

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Abstract

Obesity prevalence is increasing dramatically worldwide, representing an important economic burden for our society. The treatment of obesity is quite challenging, potentially due to the fact that different phenotypes of the disease exist. Considering "obesities" rather than "obesity" and therefore considering different metabolism pathophysiology might help to better identify more tailored treatments. Glucagon-like peptide-1 receptor agonists (GLP-1RA), such as dulaglutide and semaglutide, are routinely prescribed for the treatment of type 2 diabetes mellitus (T2DM) in obese patients or those at high cardiovascular (CV) risk. Indeed, despite being developed for T2DM, GLP-1RA are increasingly recognized as anti-obesity treatments due to their weight loss effects. Furthermore, recent evidence showed that the CV prevention exerted by these molecules goes beyond that due to the weight loss and

pleiotropic effects are reported. For instance, these drugs hold anti-inflammatory properties on vessels, enhance atherosclerotic plaque stability, reduce local advanced glycated end products receptor expression, lower monocyte-macrophages adhesion, and antagonize the effect of angiotensin-II. On the heart, GLP-1RA ameliorate cardiomyocyte survival and myocardial contractility, reduce cardiac hypertrophy, and are one of the few drugs that can reduce epicardial fat thickness. In this review, we summarize recent evidence concerning obesity/dysmetabolism and cardio-/cerebrovascular health. We further highlight the possible role of GLP-1RA as a treatment for obesity-related cardiovascular diseases by describing the principal molecular mechanisms known from current literature.

Key words

cardiovascular diseases, glucagon-like peptide-1 receptor agonists, GLP-1RA, obesity

Introduction

Although the efforts of health systems worldwide in promoting healthy lifestyle to counteract cardio and cerebrovascular diseases, the prevalence of obesity has increased worldwide over the last few decades [1] and is forecasted to increase even more in the coming years [2]. As a result, obesity represents an important social and economic burden, especially due to obesity-related pathologies [3]. Therefore, a deep understanding of obesity pathophysiology and a correct treatment are of foremost importance to improve patients' quality of life and healthcare sustainability.

Inflammation has emerged as the central core of obesity-related diseases [4]. Considering obesity as a condition related to a persistent low-grade inflammatory state of the whole body can explain how an obese subject is predisposed to the development of several cardiovascular diseases (CVDs), such as hypertension [5], left ventricular hypertrophy [6], heart failure [7], arrhythmias [8], atherosclerotic plaque formation [9], epicardial fat deposits [10], and

myocardial infarction [11]. Intertwined with inflammation other mechanisms linking metabolic alteration with CV conditions are insulin resistance [12] and altered adipokines balance [13]. In obesity, pro-inflammatory immune cells infiltrate the dysfunctional adipose tissue and promote the release of pro-inflammatory adipokines (such as leptin) while reducing the release of anti-inflammatory ones (such as adiponectin) [14].

The quest for novel treatment to reduce the social and health burden of obesity is running faster than ever. A recent therapeutic strategy is represented by glucagon-like peptide-1 receptor agonist (GLP-1RA), also known as glucagon-like peptide-1 (GLP-1) agonists or incretin mimetics, molecules developed for the treatment of type 2 diabetes mellitus (T2DM). Given the fact that beside lowering glucose levels, GLP-1RA also lead to important weight loss they are currently the gold standard for treating overweight patients with T2DM. Of interest, these drugs showed beneficial effects concerning CVD prevention in T2DM in recent clinical trials (Table 1) and are currently indicated as first choice treatment for T2DM patients at high/very high CV risk or with proven atherosclerotic cardiovascular disease by 2023 Guidelines for the management of cardiovascular diseases in patients with diabetes released by the European Society of Cardiology [15].

In this review, we summarize recent evidence concerning obesity and dysmetabolism and their implications on CV health. We highlight the role of GLP-1RA as a treatment for obesity and obesity-related CVDs by describing the principal molecular mechanisms that are known from current literature.

Different phenotypes of obesity

The most common clinical method for assessing obesity is the use of body mass index (BMI), which is calculated by dividing weight (in kilograms) by the square of height (in meters). Obesity is still defined as a BMI value equal or above 30 kg/m² [16]. However, BMI has

several limitations. For instance, it cannot distinguish between muscle and fat mass, which means that very fit athletes might be considered overweight or even obese when they are not. Conversely, cachectic patients might have a normal or low BMI but show clinically relevant metabolic alteration and obesity-related diseases. This condition is known as sarcopenic obesity [17]. To date, other clinical measurements can implement the value of BMI in obesity, such as waist girth [18]. This is probably because most visceral fat is found in the abdomen. Increased and dysfunctional visceral fat has emerged as the hallmark of obesity and its related dysmetabolic conditions. Indeed, obesity should be considered as a complex metabolic disease rather than a mere phenotypic expression of fat mass. As a result, the characterization of body fat distribution together with an appropriate depiction of the metabolic profile (including glucose and lipids) lead to the reporting of 4 different phenotypes: i) metabolic unhealthy normal weight (MUNW), ii) metabolically healthy overweight/obese (MHO), iii) metabolically unhealthy overweight/obese (MUO), and iv) sarcopenic obesity (SO) [4]. Therefore, understating the different pathophysiological mechanisms of obesity phenotypes can be useful to better predict their impact on the cardiovascular (CV) system.

Impact of obesity on CV diseases

Inflammation is considered as a central process in the development of CV diseases in obesity and insulin has been identified as one of the main factors stimulating adipose tissue and systemic inflammation during this condition [4, 19, 20]. Indeed, insulin has a strong impacts on lipid profile, i.e., stimulating the over-metabolization of free fatty acids or triglycerides in adipose tissue and resulting in the production of a high number of fatty acid intermediates. These molecules may in turn trigger intracellular pathways, such as c-Jun N-terminal kinase, IκB kinase, and protein kinase C, leading to insulin receptor phosphorylation and signaling inhibition [13]. On the other hand, hypertrophic adipocytes and macrophages in adipose tissue

of obese subjects tend to produce and release tumor necrosis factor (TNF)-α, which causes serine-phosphorylation and tyrosine-dephosphorylation of insulin receptor substrates, leading to their inactivation and degradation. Furthermore, the concomitant presence of a hyperglycemic [21] and inflammatory state [22] creates a detrimental loop that leads to pro-atherosclerotic conditions as well as cardiovascular dysfunction. Atherosclerosis is accelerated by hyperinsulinemia, dyslipidemia and hyperglycemia, which are known to induce endothelial oxidative stress via several pathways, including advanced glycation end product production, protein kinase C and polyol/hexosamine pathway activation, and endoplasmic reticulum and mitochondrial dysfunction [23]. Moreover, reactive oxygen species are at the center of both vascular smooth-muscle cell proliferation and apoptosis, which is a mechanism involved in plaque instability and potential rupture.

Of interest, recent studies showed that patients with very high BMI, i.e. morbid obese patients, show better CV outcomes including stroke [24] and myocardial infarction [25] when compared with normal weight or underweight subjects. Such unexpected finding is known as the “obesity paradox” and should be interpreted with caution [26]. Indeed, most of these studies did not differentiate between metabolically healthy or unhealthy subjects and markers of fat distribution such as waist to hip ratio (WHR) seems to have better prognostic ability rather than BMI alone [27, 28]. Even though no universal definition of metabolically healthy obesity is available at the moment, this group would include people with high BMI and healthy metabolic profile: preserved insulin sensitivity, favorable lipid profile and low plasma levels of pro-inflammatory cytokines (typically young and physically active individuals with low visceral or ectopic fat) [29]. On the opposite the unhealthy obesity phenotype is characterized by insulin resistance, high prevalence of CV risk factors other than body weight and increased visceral fat [29]. Focusing on the incidence of CVDs and differentiating the

outcome between different phenotypes of obesity would still highlight that metabolically unhealthy obesity is related with more detrimental effects rather than benefits.

Treating obesity with glucagon-like peptide-1 receptor agonists

GLP-1 is a 30 amino-acid-long peptide that is cleaved from proglucagon. It is synthesized and secreted from intestinal enterocytes known as L cells [30]. Together with the gastric inhibitory peptide (GIP), GLP-1 is part of the incretin hormones with several metabolic functions. Pancreatic β cells express the GLP-1 receptor and respond to stimulation by increasing intracellular calcium eventually leading to a higher exocytosis of insulin-containing granules [31]. GLP-1 also improves the insulin resistance of adipocytes by up-regulating insulin receptor- β, insulin receptor substrate 1, and glucose transporter type 4 expression [32]. In muscles, GLP-1 activates sirtuin 1 via the protein kinase A/cyclic adenosine monophosphate pathway, resulting in higher glucose transporter type 4 activity [33]. Furthermore, GLP-1 reduces gastric emptying by blunting vagal activity through GLP-1 receptors expressed by myenteric neurons [34]. Delayed gastric emptying further reduces post-prandial glycemia [34]. GLP-1 is then degraded by the proteolytic enzyme dipeptidyl peptidase-4, which is found in several tissues in the human body. The plasma half-life of GLP-1 after secretion is about 1.5-5 min [35]. Two classes of drugs are available to increase GLP-1 signaling: dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists.

GLP-1RA are commonly used in clinical practice for the treatment of T2DM. GLP-1RA class includes semaglutide, liraglutide, dulaglutide, albiglutide, exenatide, lixisenatide, and tirzepatide. GLP-1, secreted after meals, control glucose metabolism through different mechanism: (i) by increasing β-cells insulin secretion; (ii) by reducing glucagon secretion; (iii) by blunting gastric motility and emptying, and decreasing appetite; (iv) by improving insulin sensitivity. According, GLP-1RA treatment results in lower levels of glucose [36]. Of

interest, these drugs have shown a better safety profile with less risk of hypoglycemia with respect to other antidiabetics such as sulfonylureas or glinides [37]. Other side effects include nausea, vomiting, and diarrhea due to the binding to GLP-1 receptor expressed in the central nervous system. The same mechanism is also responsible of the main "good" side effects consisting in weight loss (up to 20%) due to the reduction of appetite and delayed gastric emptiness with slower glucose absorption [36, 38]. As a results, these drugs have shown promising results as a possible anti-obesity treatment [39, 40].

Treatment with GLP1-RA is associated with beneficial effects on the cardiovascular system

GLP-1RA effects on the CV system seem to go beyond the mere prevention of CVDs due to the reduction of weight. The main effects of GLP-1RA on the CV system are summarized in *Figure 1*.

Considering direct cardiac effects of these compounds, cardiomyocytes express GLP-1 receptor, especially near the sinoatrial node [41]. Also, treatment with GLP-1RA protects these cells toward interleukin-1β-induced reactive oxygen species (ROS) production [42]. Indeed, treatment with GLP-1RA associates with reduced mitochondrial ROS production in animals model treated with oxidized low-density lipoproteins [43]. Among mediators of such effects, studies have identified the deleterious scavenger receptor lectin-type oxidized low-density lipoprotein receptor 1 (LOX-1) [44]. Furthermore, GLP-1RA attenuates cardiac hypertrophy via 5' AMP-activated protein kinase (AMPK)/mTOR signaling pathway [45]. As an effect, GLP-1RA favor cardiomyocyte survival and ameliorate cardiac contractility [46].

A potential beneficial effect of GLP-1RA on visceral/ectopic fat deposit formation has been recently hypothesized. In particular, the use of GLP-1RA might be promising for reducing epicardial fat thickness. Epicardial fat express GLP-1 receptor in both diabetic and non-

diabetic subjects [47]. Recent studies showed that treatment with GLP-1RA can reduces up to 20-30% of epicardial fat thickness [48, 49], confirming the promising effect of these drugs in preventing possible CVDs. Regarding the effects on the vessels, endothelial cells express the GLP-1 receptor [50] and GLP-1RA favor vascular relaxation via AMPK/Akt pathway [51] and via endothelial nitric oxide synthase activation [52-54]. Also GLP-1R prevent the dysfunctional activation of endothelial cells by inhibiting NF-κB phosphorylation [55] and blunting the expression of pro-inflammatory mediators such as edothelin-1 and interleukins [56]. Furthermore, GLP1RA reduce the production and activation of angiotensin-II (Ang-II) [57, 58], with beneficial effects on both endothelial and vascular smooth muscle cells [54, 59]. Furthermore, through their anti-diabetic effects they reduce levels of advanced glycated end products as well as their receptor, preventing endothelial cell apoptosis [60, 61].

As previously mentioned, GLP-1RA treatment associates with direct anti-inflammatory properties [62]. In atherosclerosis model, they showed ability to prevent immune cells accumulation in the arterial wall by blunting levels of TNF-α, monocyte chemoattractant protein-1 [63], intercellular adhesion molecule 1 [53], vascular cell adhesion protein [55, 64], and metalloproteinases [65]. GLP-1RA also reduce systemic levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) [66, 67], while increasing anti-inflammatory mediators, such as adiponectin [66]. As a consequence, GLP1-RA treatment reduces atherosclerotic inflammation, foam cells formation and improve plaque stability by blunting matrix metallopeptidase-9 and facilitating the formation of plaque collagen and fibrous cap [61, 68-70].

Evidence from recent Clinical Trials of treatment with glucagon-like peptide-1 receptor agonists to reduce cardiovascular outcomes

Over the last decade, several controlled randomized trials have demonstrated the beneficial role of GLP-1RA in preventing CVDs in T2DM patients (Table 1). The main primary endpoints of these studies were myocardial infarction, CV death, or stroke. The majority of these studies showed a reduction in primary endpoints in the group treated with GLP-1RA, with the exception of the ELIXA (The Evaluation of Lixisenatide in Acute Coronary Syndrome) trial [71] that showed almost no difference between treated and untreated patients (Lixisenatide: 13.4% vs. Control: 13.2%). This might be due to several factors, including the fact that this trial had a short follow-up time (up to 1.1 years) and that enrolled patients had previous coronary events within 180 days, increasing the risk of secondary events. The most promising results were reported in the Harmony Outcomes [72] (Albiglutide: 7.0% vs. Control: 9.0%) and AMPLITUDE-O [73] (Efpeglenatide: 7.0% vs. Control: 9.2%). The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) [74] study enrolled the largest sample size (up to 14,752 patients), and the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) [75] study had the longest follow-up period (5.4 years). The clinical reduction of events showed in the REWIND study (Dulaglutide: 12.0% vs. Control: 13.4%) highlights the importance of continuing drug assumption for an extended period. To now, PIONEER-6 (Peptide Innovation for Early Diabetes Treatment) [76] was the only one specifically evaluating CV effects of oral GLP-1RA formulation (i.e. semaglutide 14 mg/die) with the result of reduced CV events in the treated group (Semaglutide: 3.8% vs. Control: 4.8%). Having confirmation of beneficial CV effects even for oral administration of GLP-1RA was important since oral drug intake is generally preferred for both simplicity and ensuring patient therapy maintenance.

Tirzepatide acts as an agonist for both GLP-1 receptors and GIP receptors. RCTs show that tirzepatide outperformed others GLP1-RA in terms of glucose control and was able to induce up to 20.9% of weight reduction in the SURMOUNT-1 trial [77]. Although to date there is no direct trial available, tirzepatide seems to cause higher weight loss than any other available medication based on post-hoc analysis [78, 79]. For this reason, the American Diabetes Association now consider tirzepatide together with semaglutide as “very highly efficacious for weight loss” [80]. With regards to its efficacy on CV outcomes, available trials only explored safety endpoints and proved its CV safety [81]. The ongoing SURPASS-CVOT enrolling patients with BMI ≥25 and T2DM will compare tirzepatide with dulaglutide for non-inferiority and superiority against the composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction, or nonfatal stroke over a period of 54 months. For this reason, to date, tirzepatide is not included among incretin mimetics with cardiovascular benefit.

Yet, evidence on the potential effect of GLP-1RA in patients with heart failure with preserved ejection factor is limited to date to the STEP-HFpEF trial. Up to 529 non-diabetic patients were enrolled in the study and randomly assigned to receive semaglutide 2.4 mg subcutaneously once a week for 13 months. Of interest, semaglutide met both primary endpoints i.e. body weight loss and reduction of HF symptoms assessed by the Kansas City Cardiomyopathy Questionnaire [82]. Furthermore, the treated group showed greater improvement in the 6-minute walking tests. The mean percentage reduction of circulating C-reactive protein was also greater in the treated group (-43.5% vs. -7.3%, respectively), indicating that GLP-1RAs can effectively reduce body inflammation and confirm their promising use in the treatment of dysmetabolism beyond T2DM treatment.

Based on the 2023 guidelines from the American Diabetes Association indicated GLP-1RA as first line therapy for T2DM patients that are obese or at high risk of CVD [83]. Later this year

such recommendations have been also implemented in the guidelines of the European Society of Cardiology [15].

In November 2023, the results of the SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) trial were published in The New England Journal of Medicine [84]. SELECT is the first study specifically designed to assess the role of GLP-1RA in preventing CV and CBV outcome in patients with preexisting cardiovascular disease and overweight or obesity. The primary endpoint was the composite of CV death, nonfatal myocardial infarction, or stroke. The trial enrolled 17604 patients aged at least 45 with a pre-existing CV disease and a BMI of 27 or higher. The trail included two harms: semaglutide 2.4 mg once a week subcutaneously and placebo. The mean follow-up was 39.8 months. The mean age was 62 years old with a higher prevalence of male subjects in both groups (72.2% vs. 72.5% in semaglutide and placebo groups, respectively). The majority of the enrolled patients were obese according to the BMI categories (BMI: 33.3 vs. 33.4, respectively). The treatment met the primary endpoint showing 20% less CV and CBV events when compared to placebo (6.5% vs 8.0%, hazard ratio: 0.80; 95% confidence interval: 0.72 – 0.9; $p < 0.001$) [84]. However, adverse effects that caused discontinuation of the treatment were higher in the treated group (16.6% vs. 8.2%), mostly due to gastrointestinal disorders. Collaterally, the trial reported a reduction of 3.3 mmHg in systolic blood pressure and a 37.8-percentage-point decrease in the high-sensitivity C-reactive protein levels in patients treated with semaglutide [84]. These data support the use of GLP-1RA for CV and CBV protective effects in obese patients, even in non-diabetic subjects.

Conclusions GLP-1RA are established drugs for the treatment of T2DM. Given their striking effects on body weight, GLP1-RA is increasingly regarded as a possible anti-obesity treatment with effects on weight loss and on CV and CBV complications. While the Food and Drug Administration already approved GLP1-RA for the treatment of obesity (with or without

diabetes) in the United States, this class of drugs cannot be prescribed in the absence of diabetes in Europe. The recent data from the SELECT trial confirmed the beneficial CV and CBV effects for semaglutide in non-diabetic patients and will pave the way for its broader use.

Conflict of Interest: LL is coinventor on the International Patent WO/2020/226993 filed in April 2020; the patent relates to the use of antibodies which specifically bind interleukin-1a to reduce various sequelae of ischemia-reperfusion injury to the central nervous system. LL has received financial support from the Swiss Heart Foundation and the Novartis Foundation for Medical-Biological Research outside of this work. All other authors declared no conflict of interest.

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Table 1 GLP1-RA trials with cardio- or cerebrovascular outcome

Trial	**Primary endpoints**	**Drug regimen**	**Sample size**	**Follow-up**	**Primary endpoints occurrence; HR (95%CI)**
ELIXA, 2015 [71]	MI, stroke, CV death, or hospitalization for UA	Lixisenatide up to 20 μg SC q.d.	6068	1.1 yrs	Lixisenatide: 13.4% vs. Control: 13.2% HR: 1.02, 95% CI: 0.89–1.17 $p < 0.001$ for non-inferiority

					p: 0.81 for superiority
LEADER, 2016 [85]	Non-fatal MI or stroke, CV death	Liraglutide 1.8 mg SC q.d.	9340	3.8 yrs	Liraglutide: 13.0% vs. Control: 14.9% HR: 0.87, 95% CI: 0.78–0.97) $p < 0.001$ for non-inferiority *p*: 0.01 for superiority
SUSTAIN-6, 2016 [86]	Non-fatal MI or stroke, CV death	Semaglutide 0.5 or 1.0 mg SC q.wk.	3297	2.1 yrs	Semaglutide: 6.6% vs. Control: 8.9% HR: 0.74, 95% CI: 0.58–0.95) $p < 0.001$ for non-inferiority
EXSCEL, 2017 [74]	Non-fatal MI or stroke, CV death	Exenatide 2 mg SC q.wk.	14752	3.2 yrs	Exenatide: 11.4% vs. Control: 12.2%

					HR: 0.91, 95% CI: 0.83–1.00) $p < 0.001$ for non-inferiority $p = 0.06$ for superiority
Harmony Outcomes, 2018 [72]	MI, stroke, or CV death	Albiglutide 30 mg SC q.wk. for 5 wks, then possible increment to 50 mg q.wk.	9463	1.6 yrs	Albiglutide: 7.0% vs. Control: 9.0% HR: 0.78, 95% CI: 0.68–0.90) $p < 0.0001$ for non-inferiority $p = 0.0006$ for superiority
PIONEER-6, 2019 [76]	Non-fatal MI or stroke, CV death	Semaglutide up to 14 mg q.d. oral	3183	1.3 yrs	Semaglutide: 3.8% vs. Control: 4.8%

					HR: 0.79, 95% CI: 0.57–1.11) $p < 0.001$ for non-inferiority
REWIND, 2019 [75]	Non-fatal MI or stroke, CV death	Dulaglutide 1.5 mg SC q.wk.	9901	5.4 yrs	Dulaglutide: 12.0% vs. Control: 13.4% HR: 0.88, 95% CI: 0.79–0.99) $p = 0.026$
AMPLITUDE-O, 2021 [73]	Non-fatal MI or stroke, CV or other causes of death	Efpeglenatide 4 or 6 mg SC q.wk.	4076	1.8 yrs	Efpeglenatide: 7.0% vs. Control: 9.2% HR: 0.73, 95% CI: 0.58 – 0.92 $p < 0.001$ for non-inferiority $p = 0.007$ for superiority

SELECT, 2023 [84]	Non-fatal MI or stroke, CV death	Semaglutide 2.4 mg SC q.wk.	17604	3.3 yrs	Semaglutide: 6.5% vs. Control: 8.0% HR: 0.80, 95% CI: 0.72 – 0.90 $p < 0.001$

CV: cardiovascular; ELIXA: The Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL Exenatide Study of Cardiovascular Event Lowering; LEADER: The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI: myocardial infarction; PIONEER-6: Peptide Innovation for Early Diabetes Treatment; q.d.: once a day; q.wk.: once a week; REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SC: subcutaneous; SELECT, Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity; UA: unstable angina

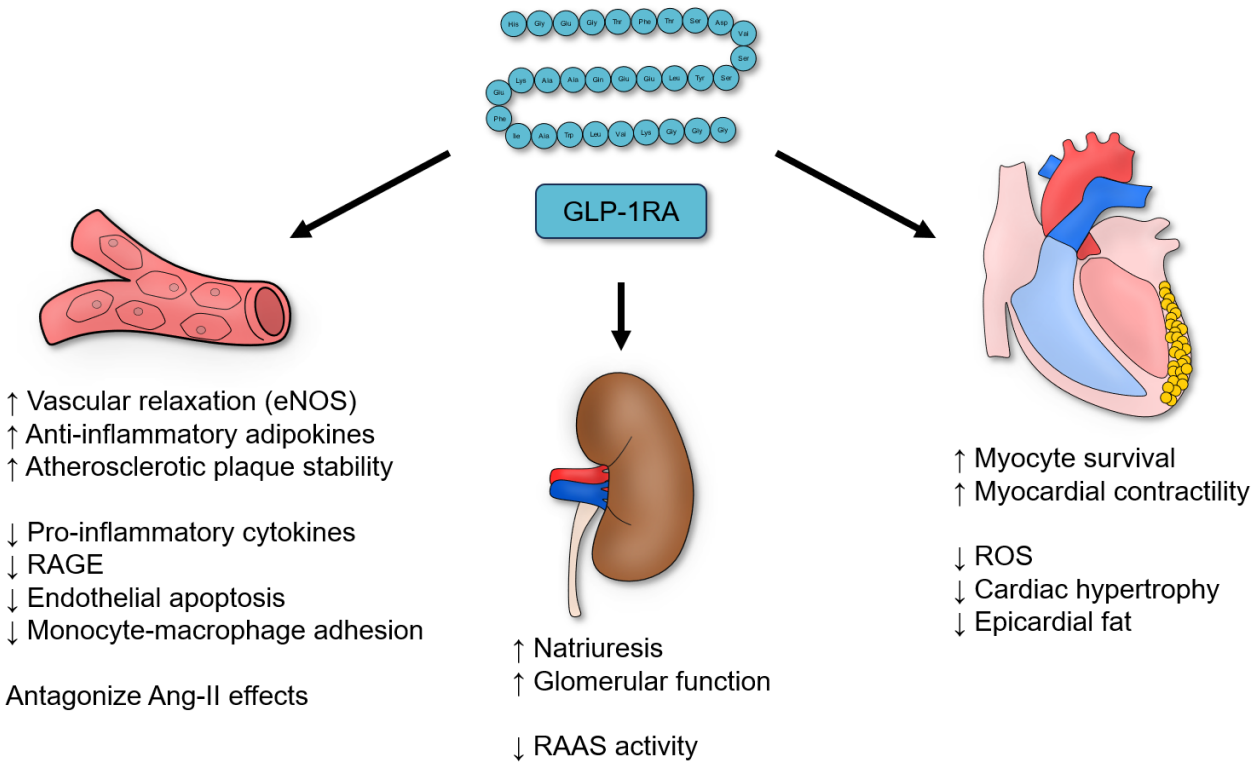

Figure 1 CV effects of GLP1RA in obese patients. GLP-1RA have pleiotropic effects on the CV system that goes beyond the mere reduction of weight. Specifically, this class of drugs directly acts on CV cells including cardiomyocyte, vascular smooth muscle cells and endothelial cells to reduce inflammation and oxidative stress, known mechanisms underlying most cardio and cerebrovascular conditions.

Abbreviations: eNOS: endothelial nitric oxide synthase; GLP-1RA: glucagon-like piptide-1 receptor agonist; RAAS: renin-angiotensin-aldosterone system; RAGE: receptor for advanced glycated end products; ROS: reactive oxygen species.