

Review

Semaglutide and the Heart: Focus on Their Love–Hate Relationship

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Abstract

Semaglutide, a recombinant DNA-derived long-acting GLP-1 receptor agonist, has emerged as a key player for patients with or without T2DM and obesity. It exerts pleiotropic effects by modulating glycemic regulation and energy homeostasis. Mechanistically, it stimulates glucose-dependent insulin secretion and suppresses glucagon while enhancing satiety through POMC/NPY modulation in the arcuate nucleus and delaying gastric emptying. Beyond its metabolic utility, semaglutide is cardioprotective, leveraging the PI3K/Akt and eNOS pathways to improve vasodilation, reduce reactive oxygen species (ROS), and stabilize atherosclerotic plaques by inhibiting pro-inflammatory cytokines like TNF- α . While it improves cardiac output via PKA-mediated inotropy, potential cardiotoxicity, including resting tachycardia and autonomic-driven arrhythmias, requires clinical vigilance, particularly regarding electrolyte imbalances in heart failure patients. Ultimately, its robust vasculoprotective profile reinforces its potential as a cornerstone in cardiovascular pharmacotherapy. Further research is needed to better understand the effects of semaglutide on cardiac function and pathologies as it advances as a cardiac drug. This review discusses multiple molecular targets of semaglutide on the heart.

Keywords: semaglutide; GLP-1 receptor agonist; cardioprotection; cardiotoxicity; cardiovascular pharmacotherapy; arrhythmia; atherosclerosis; heart failure; obesity; type 2 diabetes mellitus



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1. Introduction

Semaglutide is a widely used glucagon-like peptide 1 (GLP-1) receptor agonist initially approved for the management of type 2 diabetes mellitus (T2DM); according to current ADA/EASD guidelines, GLP-1 receptor agonists including semaglutide may be considered early in therapy, particularly in patients with obesity, established cardiovascular disease, or chronic kidney disease [1]. Semaglutide has recently received approval in higher dose formulations as management for obesity due to its effectiveness in weight loss [2] in diabetic and non-diabetic populations [3,4]. Cardiovascular outcome trials, most notably

SUSTAIN-6 and the SELECT trial, have demonstrated significant reductions in major adverse cardiovascular events (MACEs) with semaglutide, establishing its cardioprotective profile prior to any discussion of adverse effects [5,6].

Semaglutide is a modified version of the endogenous hormone GLP-1. GLP-1 works by binding to GLP-1 receptors, which are GPCRs (G-protein-coupled receptors). Activation of GPCRs leads to increases in cAMP and initiation of the protein kinase A (PKA) signaling cascade as the principal pathway for the GLP-1 effect [7]. PI3K/Akt activation is generally considered a downstream or indirect signaling event rather than a primary canonical GLP-1R pathway; it is recruited via secondary messengers and crosstalk with growth factor receptors [7]. GLP-1 is released post-prandially, and it stimulates insulin release, inhibiting glucagon release, and is responsible for satiety through neuromodulation [8]. These effects contribute to its use in cases of T2DM and weight management. Increased feelings of satiety over long periods of time naturally lead to decreased appetite, causing decreased food intake. In addition, its stimulation of insulin and suppression of glucagon leads to a net anti-hyperglycemic and catabolic state, creating an ideal environment for diabetic and bariatric patients [2].

Semaglutide's related pathologies mainly include T2DM and obesity. T2DM is a polytropic and multifactorial disease involving genetic and environmental factors. The pathophysiology involves developed insulin resistance and eventual β -cell exhaustion. Genetic predispositions from family histories mainly relating to TCF7L2 and IRS1 variants play a role in T2DM development [9]. Nutritional concentrations of sugary foods, refined carbohydrates, and ultra-processed foods also aid in its development and lead to hyperinsulinemia, a key finding in T2DM and obesity. These dietary choices also integrate into obesity along with its own respective genetic proclivity, such as in LEP or POMC mutations causing leptin resistance [10]. These diseases account for over 54% of the US population, with 12% of U.S. adults considered diabetic, 42% obese, and nearly 10% suffering both conditions [11]. Semaglutide has made major strides in these pathologies with ~15% weight loss over a 68-week program in obese patients and a ~1.5-point reduction in A1c in T2DM patients [5,6].

Cardiac effects of semaglutide have recently provoked considerable interest, showing both cardioprotective and cardiotoxic properties. Studies have suggested significant cardioprotective benefits of semaglutide including increased cardiomyocyte contractility, vasculoprotective effects, and anti-inflammatory properties. Enhanced L-type calcium channel activity resulting from semaglutide's PKA activation raises intracellular calcium, which in isolated cardiomyocytes and human atrial trabeculae produces stronger contraction and, in principle, could increase ejection fraction and cardiac output [12,13]. However, this positive inotropic effect has been demonstrated primarily in preclinical and experimental preparations rather than in humans; direct clinical evidence that semaglutide improves cardiomyocyte contractility or ejection fraction *in vivo* remains limited. The large cardiovascular outcome trials (SUSTAIN-6 and SELECT) did not measure contractility as an endpoint. The experimentally supported pathway requires direct clinical validation rather than an established *in vivo* effect of the drug [5,6]. Anti-atherosclerotic and endothelial regenerative capabilities of semaglutide originate from its vasodilative nature as an indirect nitric oxide (NO) producer via the Akt pathway [14]. As an inhibitor of NF- κ B, major inflammatory cytokines are prevented from being released, promoting an anti-inflammatory state beneficial to reducing risk for myocardial infarction (MI), ischemia, fibrosis, and hypertrophy [14]. The cardiotoxic effects of semaglutide are not negligible, with risks of arrhythmia, hypovolemia, and lipotoxicity requiring consideration in predisposed populations. Acute tachycardia has been observed in semaglutide use due to GLP-1 receptors modulating the sinoatrial (SA) node [15]. Vasodilative effects can be acute in hy-

potensive patients and GI-related hypovolemia causes considerable electrolyte imbalances in magnesium and potassium [16]. Hypovolemia also furthers shock risks in patients with reduced perfusion such as congestive heart failure (CHF) or ventricular arrhythmias. Rapid lipolysis with semaglutide use can reduce both body and visceral fat, risking lipotoxicity via TAG surge and RAAS suppression [17]. Epicardial fat also plays a major role as cardiac energy storage, loss of which produces concerns of further cardiac dysfunction.

2. Semaglutide

2.1. Structural Modifications, Pharmacokinetics, and Mechanism of Action of Semaglutide

Semaglutide [Kalundborg, Denmark] follows the structure of endogenous GLP-1, a 141-amino-acid peptide hormone, with modifications. GLP-1 agonists, including semaglutide, use modifications to add biochemical properties to improve the half-life in vivo and ensure its pharmacological efficacy [Figure 1].

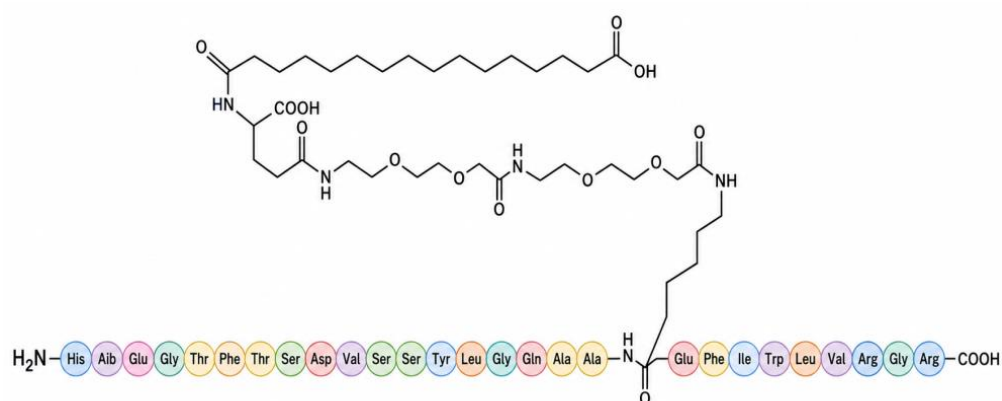


Figure 1. Modified by C. Peck: approximate structure of semaglutide. Residue colors are for visual distinction only and do not encode chemical properties. Structural concept design credited to Biosynth [18,19].

A crucial distinction between semaglutide and endogenous GLP-1 is their respective half-lives in the body. Semaglutide is generally prescribed at one dose per week, while the half-life of endogenous GLP-1 in vivo is 2–3 min [20]. The short half-life of endogenous GLP-1 is explained by a combination of the rapid degradation by dipeptidyl peptidase-4 (DPP-4) and a metabolic clearance rate of 23 mL/kg/min [18]. The longer half-life of semaglutide can be explained by two key modifications that are made to the hormone for use as a drug. The first important modification made to GLP-1 to give it a longer half-life is the replacement of an alanine residue at position 8 on the polypeptide chain with a synthetic amino acid, α -aminoisobutyric (Aib) [21]. The replacement of the alanine residue with Aib yields a resistance to DPP-4, which is normally responsible for breaking down endogenous GLP-1 by recognizing the eighth alanine [22]. With the Aib in place, DPP-4 has a lower affinity for the drug and thus semaglutide has a longer half-life. The second modification made to GLP-1 to increase the half-life is the addition of a fatty acid side chain to the lysine residue at position 26. The addition of the side chain allows semaglutide to bind to albumin, increasing its half-life in the body further [22]. These factors together lead to semaglutide having a clearance rate of 1.6 mL/kg/h [23], yielding a half-life of approximately one week in vivo.

The modifications that increase the half-life of semaglutide in the body are precisely what separates them from other subclasses of drugs that are GLP-1 agonists. One such subclass of GLP-1 agonists is prandial (short) agonists [24]. Prandial agonists are designed to bind the same receptors that endogenous GLP-1 does, but they only act for a few hours while semaglutide acts for roughly one week [25]. Examples of prandial agonists include

exenatide and lixisenatide [26]. These drugs are meant to be taken before or after a meal, and aid in the slowing of gastric emptying and feelings of satiety. Semaglutide's mechanism as an appetite suppressant stems from the vagal and enteric nervous pathways. By activating the GLP-1 receptors in the arcuate nucleus and solitary nucleus, semaglutide decreases the rate of gastric emptying and overall enhances appetite suppression [20]. This modulates POMC and NPY to produce satiety [27]. Due to their acute nature, these drugs are meant to prevent post-prandial hyperglycemia rather than long-term weight loss [26]. Semaglutide belongs to a category of longer-lasting GLP-1 agonists termed basal (long) agonists. The basal agonist class itself has different drugs associated with it, including semaglutide, dulaglutide, and liraglutide [25]. Although all three drugs have similar applications in reducing fasting blood glucose levels and managing A1c levels, the differences in design approaches lead to semaglutide having the longest half-life of the class. Liraglutide and dulaglutide respectively have half-lives of 13 h and 5 days, which makes semaglutide the longest-lasting solution for their shared indication.

Compared with semaglutide, other GLP-1 agonists offer a shorter half-life in vivo due to their distinct modifications. Like semaglutide, the commonly used GLP-1 agonists Exenatide, Liraglutide, and Dulaglutide share a similar GLP1-like backbone. Exenatide is derived from and modeled after the peptide exendin-4 from *Heloderma suspectum* (Gila monster) saliva, which has greater resistance to enzymatic degradation by DPP-4 than endogenous GLP-1 [28]. Exenatide has a plasma half-life of 2.4 h and an action time of about 8 h, and so it is a much shorter-acting GLP-1 analog compared to alternatives [29]. Liraglutide features a shorter single C16 fatty acid, and thus has a shorter half-life of about 13 h and needs to be administered daily instead of weekly [30]. Dulaglutide is composed of a GLP-1 analog fused to an IgG4 Fc fragment which makes it a larger molecule [28,31]. Dulaglutide has a similar half-life to semaglutide of about a week, which is primarily due to its bulky size with protein addition which causes slower renal clearance [32].

Semaglutide and other GLP-1 agonists work by binding to GLP-1 receptors in the body. There are four effects of GLP-1 that are physiologically relevant. First, it binds to receptors on β -cells in the pancreas, increasing insulin release, which aids in the absorption of glucose from newly digested food [33]. Second, GLP-1 binds to receptors on α -cells and inhibits them [33]. α -cells work in direct opposition to β -cells, and inhibition of α -cells leads to a decrease in glucagon release, which in turn reduces hepatic release of glucose [34]. The third important action of GLP-1 is that it slows gastric emptying by influencing vagal afferent nerves which then in turn act on the enteric nervous system [35]. Lastly, GLP-1 binds receptors in the arcuate nucleus in the hypothalamus. The direct interaction of GLP-1 in the arcuate nucleus of the hypothalamus simultaneously increases the action of anorexigenic neurons while decreasing the action of orexigenic neurons, thus causing the sensation of fullness [7]. Together, these effects work to lower hemoglobin A1c and explain the use of semaglutide as a weight management and diabetes drug [36]. Semaglutide has been shown to lower the blood glucose level (BGL) by 60 mg/dL post-prandially [37]. Another important mechanism of semaglutide is a PKA activation-related rise in intracellular calcium in conjunction with PKA-mediated phosphorylation of phospholamban and ryanodine receptor (RyR2) activation, which drives sarcoplasmic reticulum (SR) release of calcium, meaning sarcomere contraction is produced [13]. In cardiac muscle, this has been shown to produce a dose-dependent positive inotropic effect (PIE) [Figure 2] in semaglutide-specific preclinical and ex vivo human atrial tissue studies [7,13,36].

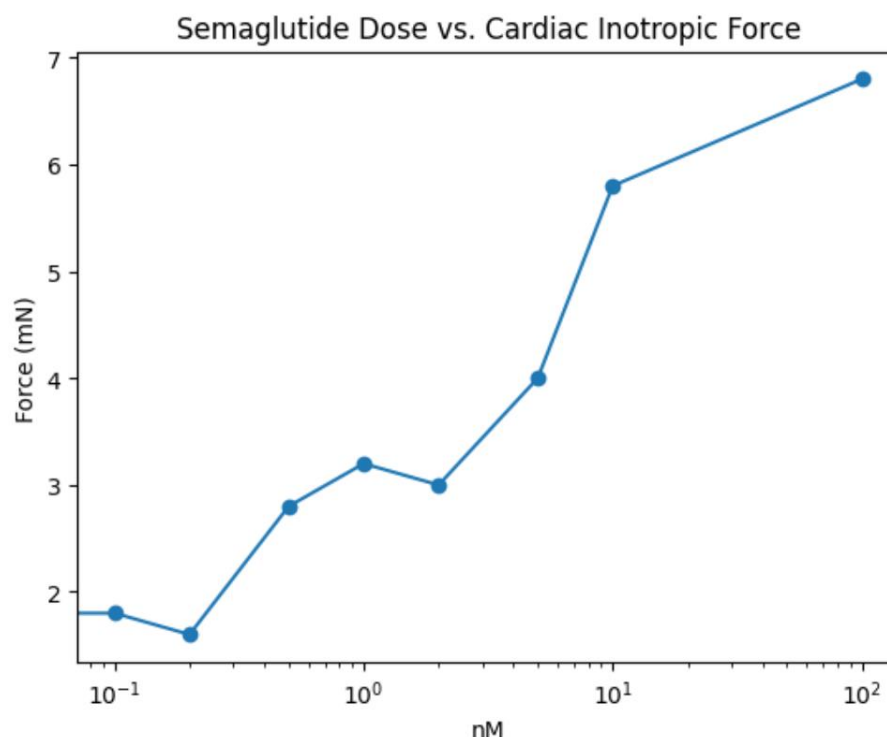


Figure 2. Modified by E. Khan: progressive dosing of semaglutide shows increasing cardiac contractility or positive inotropic effect (PIE) [13].

2.2. Therapeutic Applications and Related Disease States

Over recent years, semaglutide has been investigated as a therapy for treatment of T2DM by acting as an agonist for GLP-1 receptors [38]. T2DM is marked by a gradual development of insulin resistance and decreased glucose uptake from the blood. T2DM remains among the most significant contributors to cardiovascular disease, primarily through chronic hyperglycemia, insulin resistance, and systemic inflammation [38]. Persistent elevation of glucose leads to endothelial dysfunction, oxidative stress, and the formation of advanced glycation end products, all of which accelerate atherosclerosis [5]. Patients with T2DM have a 2–4× increased risk of coronary artery disease and stroke, and nearly 5× for heart failure [6]. These pathophysiologic mechanisms are especially relevant when considering therapies like semaglutide, which not only improve glycemic control but also demonstrate a cardiovascular risk reduction in large clinical trials such as SUSTAIN-6 and SELECT [5,6]. Semaglutide remains a top drug of choice in chronic treatment of T2DM as it is proven to sustain a 1% HbA1c reduction over a year and a 40 mg/dL reduction in the acute glucose level [39].

Obesity, another primary indication for semaglutide, is closely linked to cardiovascular pathology through both mechanical and metabolic pathways. Excess adipose tissue promotes a chronic pro-inflammatory state characterized by elevated cytokines such as TNF-α and IL-6 [39]. These cytokines overall contribute to endothelial dysfunction and vascular remodeling, most notably cardiac muscle hypertrophy [40]. Additionally, obesity is associated with increased cardiac workload, left ventricular hypertrophy, and diastolic dysfunction [40]. Obesity increases the risk of HF with preserved ejection fraction by over 40% [40]. Epidemiologic data consistently show that obesity independently increases the risk of hypertension, coronary artery disease, and arrhythmias [40]. Studies show nearly 30% increased risk of coronary artery disease in individuals with obesity [41]. Semaglutide's role in significant weight reduction has therefore been positioned as a key mechanism through which it exerts indirect cardioprotective effects [5].

It also demonstrates increased total cholesterol levels, and decreased amounts of high-density lipoproteins (HDL). These features in the context of diabetes are considered atherogenic dyslipidemia, which further bolsters the increased cardiovascular risk most T2DM patients are predisposed to. Hyperlipidemia is found in ~70% of patients with T2DM and obesity [42]. Worldwide incidence of hypertriglyceridemia remains prevalent at 28% and hypercholesterolemia at 24% [43]. Semaglutide brings resolution to many of these dyslipidemias with a 15% reduction in TG levels and a ~10% LDL-C reduction [43]. While statins remain the first-line treatment for dyslipidemia, semaglutide offers meaningful adjunctive benefit to patients with dyslipidemia and concurrent cardiometabolic disease [43].

3. Cardioprotective Mechanisms of Semaglutide

Before detailing individual mechanisms, an important scope clarification is warranted. Much of the cellular and molecular evidence for GLP-1-mediated cardioprotection has been understood using other GLP-1 receptor agonists (GLP-1RAs) or native GLP-1 in preclinical systems. Delineations between semaglutide-specific evidence, GLP-1RA class-wide evidence, and proposed mechanisms awaiting validation are made for clarification. Important clinical trials and their information are summarized in Table 1.

Table 1. Modified by E. Khan: major clinical trials of semaglutide relevant to cardiovascular outcomes [5,6,44,45].

Trial (Ref)	Population	Dose/Route	Primary CV Outcome	Key Efficacy Result	Major Adverse Events
SUSTAIN-6 [6]	3297 adults with T2DM at high CV risk	0.5 or 1.0 mg weekly	MACE (CV death, non-fatal MI, non-fatal stroke)	26% relative reduction in MACE vs placebo (HR 0.74)	GI effects (nausea, vomiting, diarrhea), increased retinopathy complications
SELECT [44]	17,604 adults with overweight/obesity and established CVD, without diabetes	2.4 mg weekly	MACE (CV death, non-fatal MI, non-fatal stroke)	20% relative reduction in MACE vs placebo (HR 0.80): ~9–10% weight loss	GI effects, higher discontinuation for GI intolerance (16.6% vs 8.2%)
STEP program [5]	Adults with overweight/obesity ($\pm$ T2DM)	2.4 mg weekly	Weight loss (CV risk factors secondary)	~15% mean weight loss: improved BP, lipids, inflammatory markers	GI effects most common (nausea, diarrhea, vomiting), gallbladder events
FLOW [45]	3533 adults with T2DM and chronic kidney disease	1.0 mg weekly	Composite kidney failure/kidney or CV death	24% relative reduction in primary composite events vs placebo	GI effects, increased treatment discontinuation vs placebo

3.1. Cardiomyocyte Modulation

Although semaglutide is primarily known for its role as a diabetes and weight management drug, important cardioprotective effects have since been elucidated. Several cells pertinent to heart health have been shown to express GLP-1 receptors, including cardiomyocytes, vascular endothelial cells, and primary immune cells [13,46]. Consistent with the evidentiary framework outlined above, each mechanism below is identified as semaglutide-specific, GLP-1RA class level, or proposed, with semaglutide-specific data emphasized wherever available [5,6,44].

Cardiomyocytes are responsible for the bulk of cardiac metabolism due to their high energy demand and thus are an important binding site for semaglutide when consid-

ering its cardioprotective features. Cardiomyocytes generate contractile force through sarcomere-mediated excitation contraction coupling, a process which is highly dependent on calcium influx through L-type calcium channels [46]. Activation of GLP-1 receptors on cardiomyocytes demonstrated for semaglutide in ex vivo human atrial tissue and for the GLP-1RA class more broadly in preclinical models stimulates cyclic AMP-dependent protein kinase A (PKA) signaling, which enhances the activity of L-type calcium channels and promotes increased intracellular calcium availability [47]. This augmented calcium handling contributes to improved myocardial contractility and cardiac performance; however, direct clinical evidence of improved cardiomyocyte contractility in vivo remains limited and warrants further investigation [13,43] (Figure 3). Furthermore, binding GLP-1 receptors on cardiomyocytes activates a separate pathway involving protein kinase B (Akt). Downstream, Akt stabilizes mitochondria by reducing electron leakage from the electron transport chain, inhibiting pro-apoptotic signaling, and indirectly promoting activation of Nrf2, all of which reduce instances of reactive oxygen species (ROS) generation [13]. It should be noted that Akt activation represents a downstream or indirect signaling event in GLP-1R biology rather than a primary pathway. The parallel PKA (contractile) and PI3K/Akt branches of GLP-1 receptor signaling, and their convergence on net cardioprotection, also play a significant role in semaglutide's downstream impacts [Figure 4]. Enhanced cardiomyocyte contractility increases stroke volume and ejection fraction, improving cardiac output and reducing end-systolic volume [48]. This leads to improved systemic perfusion and decreased ventricular wall stress.

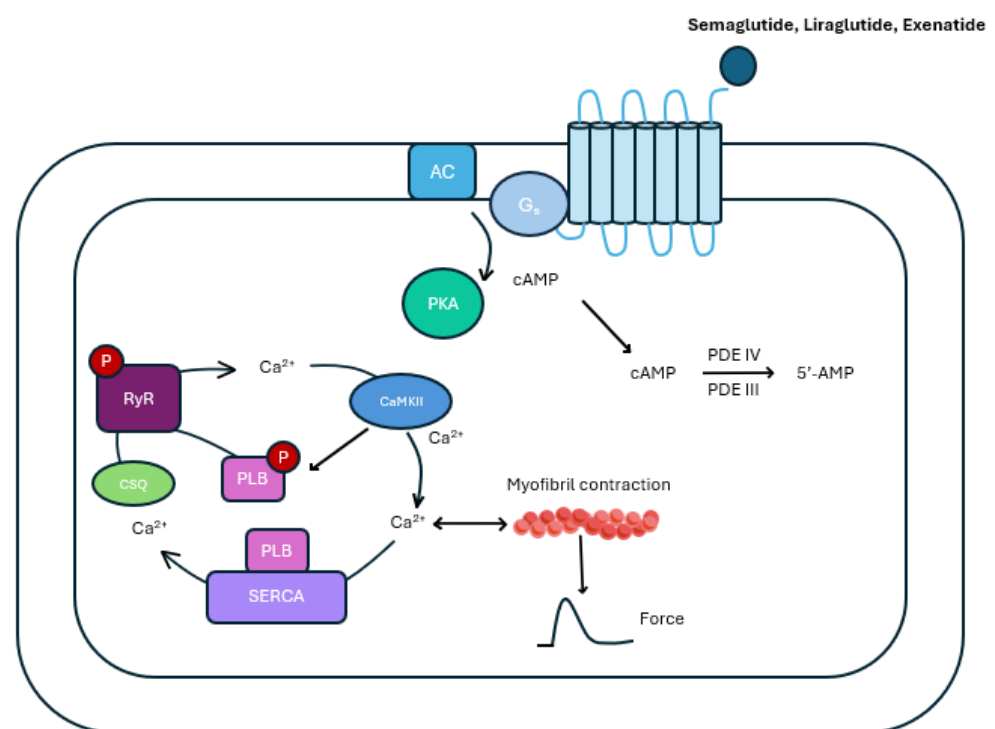


Figure 3. Modified by J. Fernandes: mechanism of action of GLP-1 agonists in cardiomyocytes. The GLP-1 agonists binding to the GTP-binding proteins (Gs) activate adenylyl cyclases (ACs) to form cAMP. This in turn activates cAMP-dependent protein kinases (PKA), which activate L-type Ca^{2+} channels and ryanodine receptors. The activation of the L-type Ca^{2+} channels and the ryanodine receptors allow for an influx of Ca^{2+} , causing myocardial contraction [49]. Colors are for visual distinction only and do not encode specific properties.

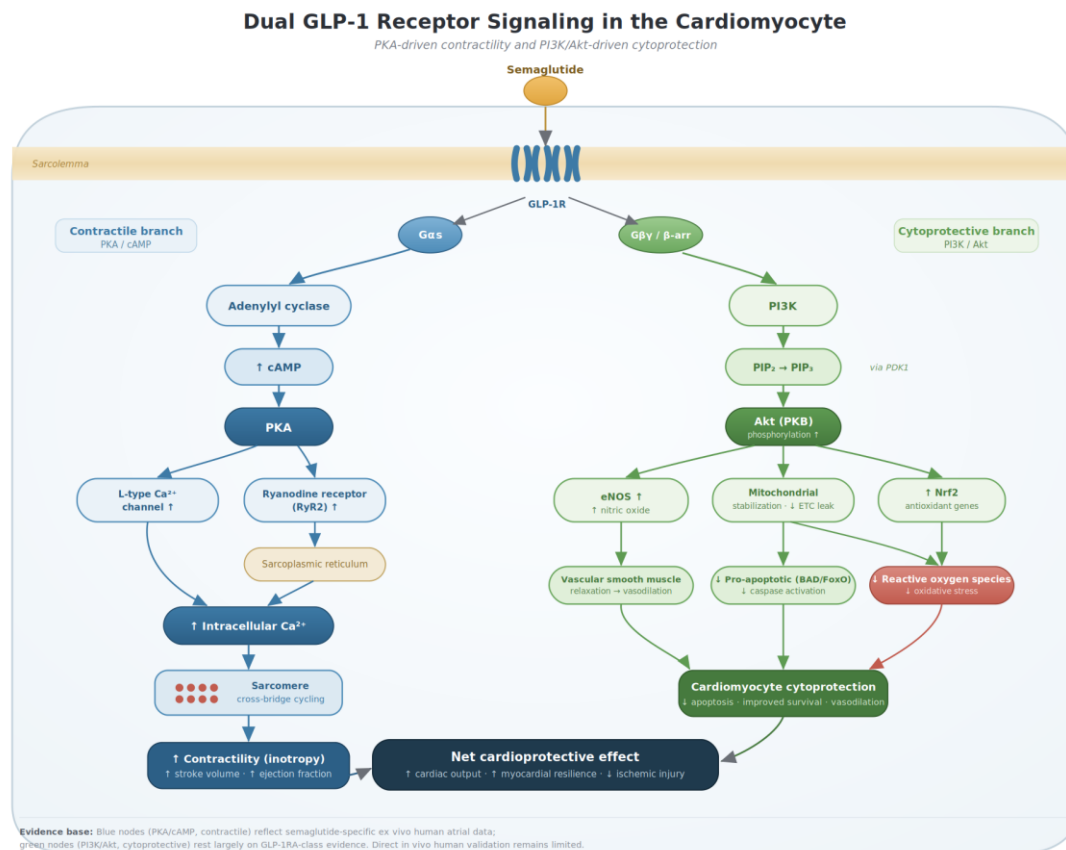


Figure 4. Modified by E. Khan: integrated model of dual GLP-1 receptor signaling in the cardiomyocyte. One path demonstrates ligand binding to the GLP-1 GPCR engages $G_{\alpha s}$, activating adenylyl cyclase (AC) to generate cAMP. cAMP activates protein kinase A (PKA), which phosphorylates L-type Ca^{2+} channels and the ryanodine receptor (RyR2), resulting in a rise in intracellular Ca^{2+} which drives sarcomere cross-bridge cycling and a positive inotropic effect. In parallel, receptor activation recruits $G\beta\gamma$, leading to a downstream PI3K/Akt cascade which phosphorylates endothelial nitric oxide synthase (eNOS) to increase nitric oxide and vasodilation, stabilizes mitochondria, upregulates Nrf2-driven antioxidant genes, and suppresses pro-apoptotic signaling. Together, they reduce reactive oxygen species (ROS) and promote cardiomyocyte survival. The two major branches converge on a net cardioprotective effect. Contractile (PKA/cAMP) effects are supported by semaglutide-specific ex vivo human atrial data, whereas the PI3K/Akt cytoprotective arm rests largely on GLP-1RA-class evidence; direct in vivo human validation remains limited [13,49,50]. Colors are for visual distinction only and do not encode specific properties.

3.2. Vasculoprotective Function

In addition to cardiomyocytes, GLP-1 receptors are found on endothelial cells lining the coronary vasculature [50]. Activation of the GLP-1 receptors provides two relevant effects. Similar to the mitochondrial effects seen in cardiomyocytes, the coronary vasculature relies on the Akt pathway. Activation of Akt in this case leads to phosphorylation and thus activation of endothelial nitric oxide synthase (eNOS). eNOS is the enzyme responsible for producing nitric oxide (NO), which increases vascular smooth muscle relaxation and thereby promotes vasodilation; this Akt–eNOS axis has been characterized largely in GLP-1RA-class endothelial models [50]. In the coronary vasculature specifically, increased vasodilation results in improved myocardial perfusion, enhanced oxygen delivery, and reduced afterload, collectively decreasing cardiac workload and protecting against ischemic injury [51]. Furthermore, GLP-1-mediated pathways are responsible for coronary vessel support. In addition to production of nitric oxide (NO), GLP-1-class agonists have also been shown to increase endothelial progenitor cell (EPC) function and angiogenic signal-

ing [50], with EPC proliferation and angiogenesis occurring via VEGF upregulation [52]. Semaglutide-specific evidence for these vascular effects is supported by SELECT trial data showing reduced cardiovascular events, independent of glycemic status [44]. Additionally, GLP-1-class effects include suppression of lipid peroxidation and restoration of endogenous antioxidant activity in endothelial cells [53]. These effects maintain coronary vessel integrity, increase cardiac perfusion, and decrease thrombosis risk.

Prevention of endothelial dysfunction is important for the heart due to its propensity to be affected by atherosclerosis. At the class level, GLP-1RAs can also reduce atherosclerosis risk indirectly by acting on immune cells [50]. Specifically, some primary immune cells such as macrophages express GLP-1 receptors which, when activated, act to confer anti-inflammatory effects [50]. Studies demonstrate that semaglutide use, irrelevant of baseline HbA1c and diabetic history, reduced cardiovascular risk in patients with atherosclerosis [44].

3.3. Anti-Inflammatory Effects

A major effect of GLP-1 receptor activation on immune cells, described across the GLP-1RA class, is inhibition of the pro-inflammatory transcription factor NF- κ B, which normally drives pro-inflammatory gene expression [54]. Inhibition of NF- κ B results in a reduction in TNF- α , IL-6, and MCP-1, all of which are downstream pro-inflammatory mediators [54]. Thus, the net result of NF- κ B suppression by GLP-1 receptor activation, demonstrated across the GLP-1RA class and in semaglutide, is a reduction in acute inflammation, especially on endothelial cells. This leads to decreased plaque growth as well as stabilization of existing plaques, secondary to decreased thrombosis [55]. Collectively, these anti-atherosclerotic effects show a reduction in major cardiovascular events.

In the case of metabolic endotoxemia, elevated LPS causes inflammation via the activation of different TLRs, commonly TLR-4 [56]. At the GLP-1RA class level, these agonists have been shown to reduce inflammation by lowering expression of the selectins V-CAM1 and E-selectins, which are generally elevated due to TNF- α and LPS stimulation [56]. This leads to reduced monocyte adhesion, which reduces the formation of foam cells in the disease process of atherosclerotic lesion formation. GLP-1 analogs have also been found to reduce inflammation in endothelial cells by increasing intracellular Ca²⁺ and AMPK. Specifically, liraglutide, rather than semaglutide, was demonstrated to increase intracellular calcium in a concentration-dependent manner, so this particular mechanism is being extrapolated to semaglutide from class data and awaits direct confirmation [57]. AMPK signaling is activated by the calmodulin-dependent protein kinase kinase- β , which is activated by increased intracellular calcium levels. AMPK has been shown to decrease NF- κ B, resulting in a decreased inflammation response [58]. AMPK in endothelial cells also causes activation of eNOS, which increases nitric oxide synthesis, which increases vasodilation via non-inflammatory pathways [59]. The clinical cardiovascular benefits of semaglutide, including the ~20% reduction in MACE demonstrated in SUSTAIN-6 and SELECT, are well established [5,6,44]. However, the precise molecular mechanisms connecting these anti-inflammatory pathways to semaglutide's *in vivo* cardioprotective effects remain incompletely characterized at a mechanistic level, representing an important direction for future research.

3.4. Metabolic Cardioprotection: Improvement in Insulin Resistance and Hyperinsulinemia

Beyond its direct actions on cardiomyocytes and the vasculature, semaglutide confers indirect cardioprotection by improving insulin resistance and the compensatory hyperinsulinemia that characterize both type 2 diabetes and obesity. Chronic insulin resistance is a potent driver of cardiovascular injury: hyperinsulinemia promotes sympathetic acti-

vation, sodium retention, and renin–angiotensin–aldosterone system (RAAS) stimulation. Impaired insulin signaling in the endothelium reduces PI3K/Akt-dependent eNOS activity and shifts the vasculature toward a vasoconstrictive, pro-inflammatory, and pro-atherogenic state [38,60,61]. The resulting endothelial dysfunction, dyslipidemia, and left ventricular hypertrophy contribute substantially to the excess coronary artery disease and heart failure risk observed in insulin-resistant patients [38,40]. By enhancing glucose-dependent insulin secretion, suppressing glucagon, and by producing weight loss and a reduction in visceral adipose, semaglutide improves peripheral insulin sensitivity, thereby relieving the hyperinsulinemic effects on the cardiovascular system [5,39,62]. This improvement in insulin resistance plausibly contributes to the favorable changes in blood pressure, lipid profile, and systemic inflammation as reported in the STEP and SUSTAIN programs, and may represent an important mechanistic link underlying the cardiovascular benefit observed in SELECT [39,44,63,64]. Whether improvement in insulin resistance is a direct causal mediator of semaglutide's cardiovascular benefit, as opposed to a correlate of weight loss and glycemic control, remains to be established by dedicated mechanistic studies [65].

4. Cardiotoxic Mechanisms of Semaglutide

The potential cardiotoxic effects described are, in the great majority of patients, subclinical, transient, or readily manageable, and they must be interpreted against the background of semaglutide's well-established and clinically dominant cardiovascular benefit. With appropriate patient counseling, these considerations do not constitute a meaningful clinical problem in routine practice. The mechanisms below are therefore presented primarily for mechanistic completeness and are most relevant to specific vulnerable subgroups, such as patients with advanced heart failure, significant electrolyte disturbance, or marked volume depletion, rather than to the typical patient receiving semaglutide for diabetes or obesity [5,6,44].

4.1. Arrhythmic Risk

Semaglutide can also exert several adverse effects on the cardiovascular system. Although semaglutide exerts cardioprotective effects by working to regulate glycemic control and reduce weight, it can also play a role in the elevation of heart rate, arrhythmia, and other hemodynamic alterations [15,66].

Semaglutide has been shown to increase resting heart rate by an average of 2–4 bpm, with meta-analytic data reporting increases of approximately +3.4 bpm in obese populations [15,66]. These chronotropic effects are attributed to direct GLP-1R-mediated sympathomimetic activity at the sinoatrial node rather than reflex responses alone [15]. The drug works indirectly by modulating the autonomic nervous system by influencing vagus nerve tone via GLP-1 receptors on afferent vagus nerves [5,6]. Semaglutide has been shown to inhibit vagal output to cardiac muscle, leading to anti-cholinergic tachycardia while increasing vagal output to the GI system, slowing gastric emptying [5,6]. Baroreceptive effects of semaglutide from NO-induced vasodilation cause hypotension and slight reactive hypertension [5,6]. Although this may seem benign to most healthy individuals, slight changes in heart rate can increase risk for tachyarrhythmia-prone and elderly patients along with patients with heart failure [5,6]. Although no trials have studied the electrophysiological toxicity of semaglutide, evident adverse GI effects such as nausea, diarrhea, and vomiting lead to significant electrolyte imbalances [5,6] (Figure 5). In total, 60% of patients experienced at least one GI side effect across the STEP and SUSTAIN trials with vomiting and diarrhea being experienced in 24% and 34% of patients respectively in STEP 1 trials [5,6]. Although uncommon, patients on semaglutide with adverse GI effects have been found to be hypokalemic, hyponatremic, hypomagnesemic, and hypovolemic,

increasing the risk of PVCs, ventricular tachycardia, ventricular fibrillation, and Torsades de Pointes [67]. Patients with chronic kidney disease or heart failure (HF), or diuretic users, are at further risk for these arrhythmias when on semaglutide due to these imbalances [5,6]. The shorter diastole of HF patients leads to reduced ventricular filling and increased oxygen demand on myocytes, which can be exacerbated by the mild tachycardia and hypotension induced by semaglutide. Volume depletion also causes reduced cardiac output, putting patients with HF under considerable risks when taking semaglutide [5,6]. Although semaglutide moves forward as a future cardiac pharmacotherapy, studies have shown no significant benefit to arrhythmic outcomes of supraventricular tachycardia (SVT), ventricular tachycardia, bradycardia, and atrial tachycardia [66]. Semaglutide has also shown no significant effect on the treatment of unstable angina, CHF, MI, or coronary artery disease [15].

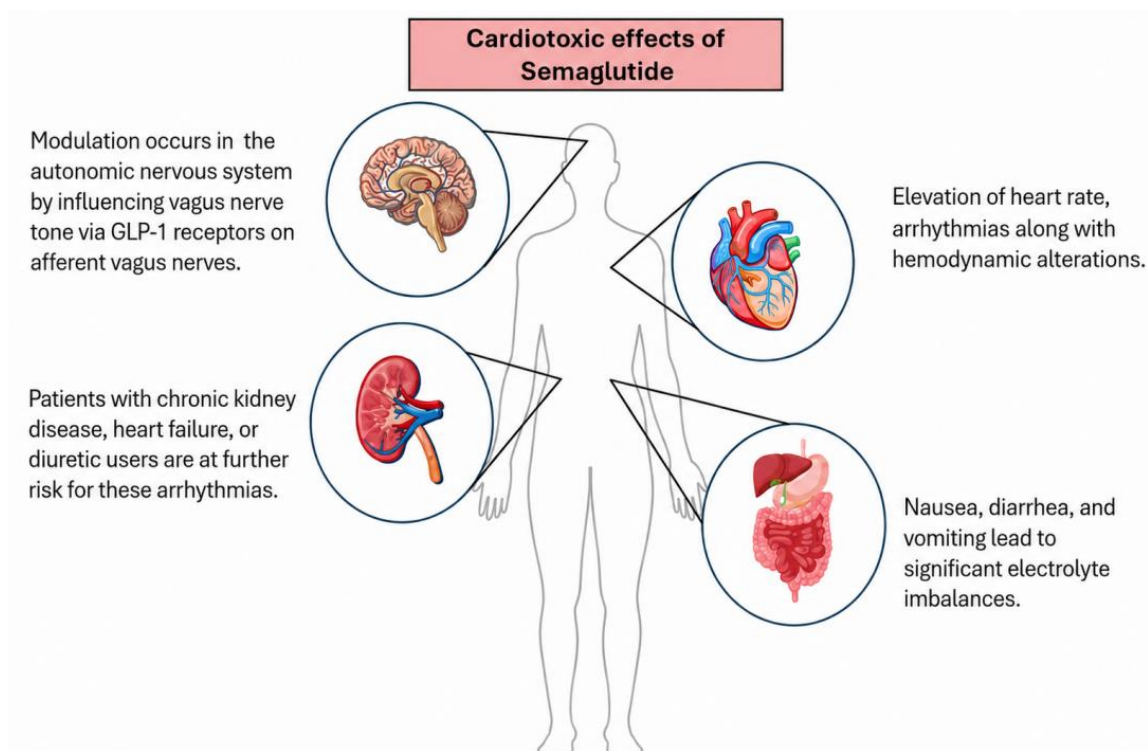


Figure 5. Modified by J. Fernandes: cardiotoxic effects of semaglutide. The systemic effects of semaglutide induce several pathologies to the cardiovascular system along with other organ systems [66].

4.2. Hypovolemia and Lipolytic Concerns

Hypovolemia induced by GI side effects under semaglutide also raise concerns for hemodynamic instability. Fluid loss from nausea and vomiting leading to hypovolemia can cause orthostatic hypotension [68]. Hypovolemia commonly causes reflexive tachycardia which produces reduced preload. Dehydration from reduced appetite and fluid intake furthers these effects [68]. Additionally, semaglutide acts on GLP-1 receptors in the vascular epithelium by modulating vascular tone and leading to vasodilation, thereby lowering blood pressure by an average of 5 mmHg systolic or more in patients with cardiac histories [63]. This reduction in blood pressure can lead to imperfusion to cardiac muscle and ischemia, which causes myocardial injury and can worsen hypovolemia [42].

Semaglutide's decisive role in fat reduction causes loss of visceral fat along with body fat [62]. Visceral fat plays a key role as metabolically and hormonally active tissue by mediating inflammatory response and activating the renin–angiotensin–aldosterone

system (RAAS), causing an increase in cardiac and hepatic workload [60,69]. Rapid loss of visceral fat has been observed in semaglutide with ~25% loss of visceral fat being observed within 12 weeks in STEP trials [5]. Although trials did not observe lipotoxicity, harmful disruptions to visceral fat functions do remain a risk, especially in overuse of semaglutide or in conjunction with metabolic issues which have not been studied. A common result of rapid visceral fat loss is cholelithiasis, which has been reported in semaglutide users [70]. Across the GLP-1RA class, up to 31% of patients have reported cholelithiasis, inducing systemic strain seen in the heart as tachycardia and hypertension [70]. These changes can also induce lipotoxic cardiomyopathy due to triglyceride surges through systemic circulation [71]. TAG surge can overload cardiac myocyte mitochondria, producing toxic lipid intermediates such as ceramide and DAG.

5. Discussion

Semaglutide is a powerful GLP-1 agonist used in the management of type 2 diabetes and in chronic weight management. It demonstrates complex actions on the cardiovascular system which can be both cardioprotective and cardiotoxic. Semaglutide is unique from other subclasses of the GLP-1 agonist family due to modifications that increase its half-life in the body. This review delineates semaglutide's therapeutic cardioprotection across metabolic, vascular, and immunomodulatory pathways, balanced against its cardiotoxic profile.

It is established that hyperglycemia is a cause of endothelial dysfunction and atherosclerosis, generally due to the increased oxidative stress. GLP-1 agonists reduce blood glucose and, in turn, oxidative stress, mitigating vascular injury. These effects are most evident in patients with type 2 diabetes mellitus, who carry an elevated risk of coronary artery disease, stroke, and heart failure; for semaglutide specifically, this translates into a significant MACE reduction in the SUSTAIN-6 and SELECT trials [5,6,72].

With its ability to target receptors across various organ systems and its anti-inflammatory properties, the versatility of semaglutide has allowed clinicians to optimize care for their patients. Semaglutide primarily exerts its cardioprotective mechanisms via improvement in glycemic control by enhancing insulin secretion from pancreatic β -cells and suppressing glucagon release from α -cells. By mimicking the GLP-1 hormone, semaglutide also acts to enhance feelings of satiety [8]. Additionally, by slowing gastric emptying through the vagal and enteric nervous system, it overall enhances appetite suppression [20].

In the cardiovascular system, GLP-1 receptor activation acts directly on cardiomyocytes to increase L-type channel activity, an effect shown for semaglutide in ex vivo human atrial tissue and supported more broadly by GLP-1RA-class data, increasing intracellular calcium and ultimately causing increased contractility [73]. In fact, it has been noted that the right atrium exerts positive inotropic effects (PIE) due to this mechanism, leading to possible concerns in patients with heart failure [13]. All of this leads to increased stroke volume and EF [48,73]. Another cardioprotective mechanism is how GLP-1 activates PKB (Akt), which acts to stabilize mitochondrial function by reducing ETC leakage, thus inhibiting the formation of ROS. Together, these effects support myocardial functions and increase resistance to metabolic stress, and may be utilized in future treatments.

At the opposite end of the spectrum, semaglutide and other GLP-1 agonists have been shown to exhibit direct cardiotoxic properties. They are shown to increase heart rate by 2–4 bpm by acting on the autonomic nervous system, specifically by acting on the SA node via the GLP-1 receptors. This mechanism may be detrimental to patients who are susceptible to arrhythmias, heart failure and/or other cardiac pathologies, as well as CKD and those on diuretics. Semaglutide also acts on the vascular epithelium to modulate vascular tone, causing vasodilation and leading to decreased blood pressure.

These negative effects should be considered in geriatric populations, due to their increased risk of cardiac compromise. Semaglutide has been shown to cause side effects such as hypovolemia via dehydration and nausea/vomiting, leading to electrolyte abnormalities, worsening hypotension, and arrhythmia [15,74]. It has also been shown that the GLP-1R agonist dulaglutide decreases fluid intake [75]. Furthermore, rapid loss of visceral fat due to GLP-1s has also been indicated in lipotoxic cardiomyopathy due to triglyceride surges. These are induced via toxic intermediates produced by cardiomyocyte mitochondria.

While the efficacy of semaglutide has consistently shown a ‘benefits outweigh the risks’ pattern for the management of type 2 diabetes and weight loss, it requires further research to be independently considered as a cardioprotective drug. Notably, though, the FDA has approved semaglutide usage in overweight and obese patients with cardiac indications [76]. However, studies have shown that a high dose of semaglutide in obese patients increases the risk of ventricular arrhythmias [15].

Knowledge Gaps, Limitations, and Future Directions

Several important gaps and controversies exist in the context of semaglutide. First, much of the mechanistic evidence, particularly for the PI3K/Akt-eNOS, Nrf2, and anti-inflammatory pathways, derives from preclinical models or from other GLP-1 receptor agonists rather than from semaglutide directly; the extent to which these class-level mechanisms operate in the human heart at clinically used doses remains uncertain. Second, the relationship between semaglutide’s well-documented clinical cardiovascular benefit and its proposed molecular mechanisms is associative and the modest resting heart rate increase of 2–4 bpm represents a genuinely conflicting signal whose long-term arrhythmic significance is still being researched. Finally, long-term cardiovascular safety data beyond the SUSTAIN-6 and SELECT trials are limited, and the cardiac consequences of rapid visceral and epicardial fat loss, RAAS suppression, and rebound cardiometabolic risks require dedicated study. Adequately powered, semaglutide-specific mechanistic and long-term outcome studies, ideally incorporating direct human myocardial data, are needed to establish causal cardioprotective pathways and to define the drug’s safety in patients with cardiovascular disease.

6. Conclusions

There remain limited research and testing on the impact of semaglutide on specific cardiac pathologies, especially in patients with complex medical histories [38]. Given the drug’s negative side effects on the cardiovascular and GI systems, its direct and indirect mechanisms of action need to be researched further in the context of the cardiovascular system exclusively. Furthermore, long-term studies are required to assess the drug’s cardiotoxic qualities before it can be prescribed as a cardiac drug. However, despite these considerable risks, meta-analysis shows that, overall, semaglutide enacts greater cardioprotective benefits [77].

Documented AEs of semaglutide include resting tachycardia, potential arrhythmogenic fluctuations, and hemodynamic or metabolic stress from drug-induced hypoglycemia. Discontinuation frequently precipitates rebound cardiometabolic risks, abruptly terminating its cardioprotective attributes. Less common reported complications include acute cholecystitis, anaphylaxis, acute kidney injury (AKI), and exacerbations of diabetic retinopathy. Although acute pancreatitis has historically been regarded as a theoretical concern for the GLP-1RA class, patients with a prior history were excluded from pivotal trials as a precaution and current prescribing information advises caution in this population. Importantly, current evidence does not support a causal association between semaglutide and an increased risk of pancreatitis. Furthermore, cases of non-arteritic anterior ischemic

optic neuropathy (NAION) have been observed in vulnerable cohorts, alongside potential risks of thyroid C-cell neoplasms and elevated circulating levothyroxine levels [77,78].

It should be emphasized that semaglutide represents a major therapeutic advance in the management of diabetes and obesity, and that its established cardiovascular benefits clearly outweigh the largely theoretical and subgroup-specific risks discussed here. Overall, understanding semaglutide's direct and indirect mechanisms is vital for assessing its potential as a cardiac pharmacotherapy as its cardiovascular effects remain minimally researched. While semaglutide shows exceptional promise when appropriately prescribed for patients with metabolic diseases, additional research is needed to ascertain both its cardioprotective and cardiotoxic impacts in both normal and pathological hearts. Particular care should be taken to research its effects in patients with cardiovascular compromise. Semaglutide and the heart share a love–hate relationship throughout this review, reflecting both its therapeutic promise and its potential for harm.

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