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REVIEW

Therapeutic Potential of GLP-1 Receptor Agonists in Diabetes and Cardiovascular Disease: Mechanisms and Clinical Implications

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Abstract

Background Glucagon-like peptide-1 (GLP-1) is a crucial incretin hormone secreted by intestinal endocrine L cells. Given its pivotal physiological role, researchers have developed GLP-1 receptor agonists (GLP-1 RAs) through structural modifications. These analogues display pharmacological effects similar to those of GLP-1 but with augmented stability and are regarded as an effective means of regulating blood glucose levels in clinical practice.

Objective This review aims to comprehensively summarize the role of GLP-1 RAs in the management of diabetes mellitus (DM) and cardiovascular disease (CVD), with a particular emphasis on the underlying signal transduction pathways and their therapeutic potential.

Methods A comprehensive review was carried out through literature research.

Results and Discussion In pancreatic β-cells, GLP-1 RAs regulate the secretion of insulin and glucagon in a glucosedependent manner by influencing signaling pathways such as cAMP, PI3K, and MAPK. They also contribute to the regulation of blood glucose levels by promoting the proliferation of β-cells and inhibiting apoptosis in these cells. Recent comprehensive studies have also demonstrated the favorable impact of GLP-1 RAs on cardiovascular wellbeing. In addition to the cardiovascular protection afforded by glucose metabolism regulation, a large body of evidence from animal and cellular studies has corroborated the beneficial effects of GLP-1 RAs on conditions such as heart failure (HF), hypertension, and ischemic cardiomyopathy. These benefits are mainly attributed to the alleviation of inflammatory responses, reduction of oxidative stress, and prevention of cell apoptosis. Clinical data shows that GLP-1 RAs can reduce the risk of major adverse cardiovascular events (MACE) in diabetic patients.

Conclusion GLP-1 RAs play an important role in the management of both diabetes and cardiovascular diseases. They show potential therapeutic value through the modulation of multiple signal transduction pathways. However, there may still be some issues in practical applications that require further research and resolution.

Keywords GLP-1 RAs · Cardiovascular · Type 2 diabetes · Ischemic cardiomyopathy · Diabetic cardiomyopathy · Heart failure

Nonstandard abbreviations and acronyms

AC	Adenylyl cyclase
Akt	Protein kinase B
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CDK2	Cyclin-dependent protein kinase 2
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
EGFR	Epidermal growth factor receptor
Epac	Exchange protein directly activated by cAMP
ER	Endoplasmic reticulum
Ex-4	Exendin-4
GLP-1	Glucagon-like peptide-1
GLP-1 RAs	GLP-1 receptor agonists
GLUT1	Glucose transporter 1
HF	Heart failure

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HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
H/R	Hypoxia/reoxygenation
I/R	Ischemia/reperfusion
LV	Left ventricular
MACE	Major adverse cardiovascular events
MAPK	RAS/RAF/MEK1/2/ERK1/2
NLRP3	Nod-like receptor thermal protein domain associated protein 3
PAH	Pulmonary arterial hypertension
PCI	Percutaneous coronary intervention
PI_3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
SBP	Systolic blood pressure
STEMI	ST-segment elevation myocardial infarction
VSMCs	Vascular smooth muscle cells

Introduction

In recent years, the incidence of diabetes mellitus (DM) and cardiovascular disease (CVD) has surged significantly. These two conditions are closely interrelated, with DM representing a significant risk factor for CVD due to factors such as obesity, hypercholesterolemia, atherosclerosis, microcirculation disorders, and hypertension [1, 2]. Epidemiological studies have demonstrated a correlation between hyperglycemia and the severity of cardiovascular dysfunction and mortality in patients with DM [3, 4]. The results of both animal and cellular studies have demonstrated that in the context of hyperglycemia, the heart's capacity to utilize glucose is diminished, which in turn promotes oxidative stress and inflammation in myocardial cells. These factors alter myocardial mitochondrial function, induce apoptosis, and impact cardiac contractility [5]. Moreover, endothelial cell inflammation results in the proliferation, migration, and apoptosis of vascular smooth muscle cells (VSMCs), thereby fostering intimal thickening and vascular remodeling and accelerating the deposition of atherosclerotic plaques [6].

Cardiovascular ailments associated with diabetes have become the foremost cause of diabetes-related morbidity and mortality, imposing a significant economic burden on society [7]. The identification of potential therapeutic agents for diabetic cardiopathy remains a crucial area of research. GLP-1 is a gut-derived hormone secreted in response to oral nutrient intake, exhibiting potent insulinotropic activity across several species, including humans [8]. GLP-1 primarily acts by binding to the GLP-1 receptor (GLP-1 R), which is expressed in various tissues, including the heart, lungs, intestines, bones, and brain. GLP-1 RAs are known to regulate glycemic metabolism, mitigate myocardial and lung injury, inhibit gastric emptying, reduce bone destruction, and provide neuroprotective effects [9–11]. However, native GLP-1 has a short half-life of approximately 2–3 min, limiting its therapeutic potential [12]. To overcome this limitation, several GLP-1 RAs with longer half-lives have been developed to mimic the role of endogenous GLP-1 [13].

The protective effects of GLP-1 RAs on cardiovascular health have attracted considerable attention, with research focusing on several key areas. In models of heart failure (HF), GLP-1 RAs have been observed to alter energy substrate utilization, alleviate myocardial and endothelial inflammation, mitigate oxidative stress, and antagonize myocardial remodeling [14]. In hypertension models, GLP-1 RAs exert beneficial effects through multiple mechanisms including vascular vasodilation, diuresis, decreased sympathetic activity in the central nervous system, and reduced blood pressure variability (BPV) [15]. Furthermore, GLP-1 RAs play a pivotal role in the alleviation of oxidative stress, the maintenance of mitochondrial homeostasis, and the inhibition of cell apoptosis and pyroptosis in models of ischemic cardiomyopathy [16]. Furthermore, they inhibit vascular remodeling and enhance coronary blood flow in diabetic cardiopathy models [17]. In light of these benefits, GLP-1 RAs present a promising avenue for enhancing outcomes in patients with DM and CVD.

The Origin and Classification of GLP-1 RAs

GLP-1 is an incretin hormone secreted by L cells in the distal ileum, rectum, and colon. Its primary functions are to facilitate glucose-stimulated insulin release and to inhibit glucagon secretion. However, its relatively short plasma half-life of 2–3 min, due to rapid degradation by dipeptidyl peptidase-4 (DPP-4), has prompted structural modifications to enhance its pharmacological efficacy. These modifications serve to enhance the binding affinity of GLP-1 to the GLP-1 R and increase its resistance to DPP-4 degradation, thereby prolonging its half-life and enhancing its clinical utility. It is noteworthy that exendin-4 (Ex-4), a peptide derived from the saliva of the American Gila monster, exhibits pharmacological functions similar to those of GLP-1 and is resistant to DPP-4 degradation. This has led to the development of Ex-4 as a hypoglycemic drug. Drugs that activate GLP-1 R in a similar manner are collectively designated as GLP-1 RAs [18].

GLP-1RAs are classified according to their structural and pharmacokinetic properties. In terms of their structural composition, these agents can be divided into two main categories: modified versions of native GLP-1 that are resistant to DPP-4 and those that mimic Ex-4, activating GLP-1 R in a manner that is comparable to that of native GLP-1. In terms of pharmacokinetics, GLP-1 RAs can be classified as either short-acting or long-acting. Short-acting options include exenatide and lixisenatide, while long-acting ones include liraglutide, albiglutide, tirzepatide, dulaglutide, semaglutide, and polyethylene glycol loxenatide (PEX-168) [19]. Table 1 provides

Table 1 Classification, pharmacokinetic characteristics, and crucial aspects of clinical application of GLP-1RA

Drug	Exenatide	Benaglutide	Lixisenatide	Liraglutide	Dulaglutide	Albiglutide	Semaglutide	Polyethylene glycol loxenatide (PEX-168)
Classification	Short-acting formulations			Long-acting formulations				
Molecular structure	Exendin-4	Recombinant human GLP-1	Modified exendin-4	Modified human GLP-1	Modified human GLP-1	Modified human GLP-1	Modified human GLP-1	Chemically synthesized GLP-1
Half-life	2.4 h	11 min	3 h	13 h	4.7d	5d	7 d	144–155 h
Dosage	Initial dose: 5 μg Conventional dose: 10 μg	Initial dose: 0.1 mg Conventional dose: 0.2 mg	Initial dose: 10 μg Conventional dose: 20 μg	Initial dose: 0.6 milligrams Conventional dose: 1.2–1.8 mg	Initial dose: 0.75 mg Conventional dose: 1.5 mg	Recommended dose: 30 mg	Initial dose: 0.25 milligrams Conventional dose: 0.5–1 mg	Initial dose: 0.1 mg Conventional dose: 0.2 mg
Usage	Bid	Tid	QD	QD	QW	QW	QW	QW
Metabolic pathway	Kidney/protein catabolism	Kidney	Kidney/protein catabolism	Urine/feces/protein catabolism	Protein catabolism	Unknown	Urine/feces/protein catabolism	Kidney
Side effects								
Gastrointestinal adverse reaction	Common							
Hypoglycemia	Low							
Particular population								
Individuals with high risk of cardiovascular disorders	The safety remains uncertain	The safety remains uncertain	Safety	Priority of use rights	Safety	The safety remains uncertain	Safety	The safety remains uncertain
Overweight/obesity	There are significant effects on reducing body weight							The effectiveness is uncertain
Abnormal renal function	Caution: eGFR < 30 mL·min^{-1}	Unknown	Caution: eGFR < 30 mL·min^{-1}	Not recommended for end-stage patients	Not recommended for end-stage patients	No need for dose adjustment	Not recommended for end-stage patients	Patients with mild renal insufficiency: no need for dose adjustment Patients with moderate renal insufficiency: reduce the dose Patients with severe renal insufficiency: unknown

Table 1 (continued)

Drug	Exenatide	Benaglutide	Lixisenatide	Liraglutide	Dulaglutide	Albiglutide	Semaglutide	Polyethylene glycol loxenatide (PEX-168)
Abnormal liver function	Unknown	Unknown	No need for dose adjustment	Not recommended: severe patients	No need for dose adjustment	Unknown	Caution: patients with severe hepatic insufficiency	Unknown
History of pancreatitis disease	Caution							
Severe gastrointestinal diseases	Caution							
History of medullary thyroid carcinoma or a family history thereof	Not recommended							

a comprehensive overview of the characteristics of the most commonly used GLP-1 RAs [12, 20].

In clinical practice, GLP-1 RAs are primarily employed to stabilize blood glucose levels in patients with diabetes, with established efficacy. Furthermore, research suggests that GLP-1 RAs confer a range of advantages to individuals without diabetes but with CVD. This review examines the evidence pertaining to the mechanisms underlying the hypoglycemic and cardiovascular protective effects of GLP-1 RAs.

Beneficial Effects of GLP-1 RAs on DM

Effects of GLP-1 RAs on Insulin Secretion

GLP-1 enhances insulin secretion in a glucose-dependent manner, thereby primarily stimulating insulin release when blood sugar levels are elevated, thus reducing the risk of hypoglycemia. This characteristic renders GLP-1 RAs a promising area of focus in diabetes treatment research, as they facilitate effective blood sugar management without an increased risk of hypoglycemia.

Insulin secretion is biphasic, comprising an initial rapid release, followed by a slower, sustained phase. The second phase is dependent on ATP-producing secretagogues, which serves to underscore its energy dependence [21]. Upon binding to GLP-1 R on pancreatic β-cells, GLP-1 activates a G-protein complex, resulting in the release of the Gαs subunit. This subunit activates adenylyl cyclase, resulting in the production of cyclic adenosine monophosphate (cAMP). The primary effectors of cAMP, protein kinase A (PKA), and the cAMP-regulated guanine nucleotide exchange factor (Epac) play crucial roles in this process [22]. GLP-1 phosphorylates glucose transporter 2 (GLUT2) via the PKA pathway, thereby facilitating glucose transport into β-cells [23]. Upon entering into the cells, glucose is converted to glucose-6-phosphate, which in turn triggers the processes of glycolysis and the tricarboxylic acid (TCA) cycle, thereby increasing the levels of cytoplasmic ATP. This results in the closure of ATP-sensitive potassium (K_{ATP}) channels, which in turn leads to cell depolarization, the opening of voltage-dependent Ca^{2+} channels (VDCCs), and the subsequent influx of Ca^{2+}. Additionally, PKA and Epac modulate IP_3R and RyR on the endoplasmic reticulum (ER), thereby promoting Ca^{2+} release via Ca^{2+}-induced Ca^{2+} release (CICR). This results in an increase in the cytoplasmic calcium concentration, which enhances insulin secretion from β-cells [24–26] (Fig. 1).

The results of animal studies indicate that Ex-4 enhances glucose uptake, intracellular Ca^{2+} levels, and insulin secretion in β-cells. However, these effects are attenuated by PKA inhibitors or dominant-negative Epac overexpression [23, 25]. In the resting β-cells, the delayed rectifier potassium

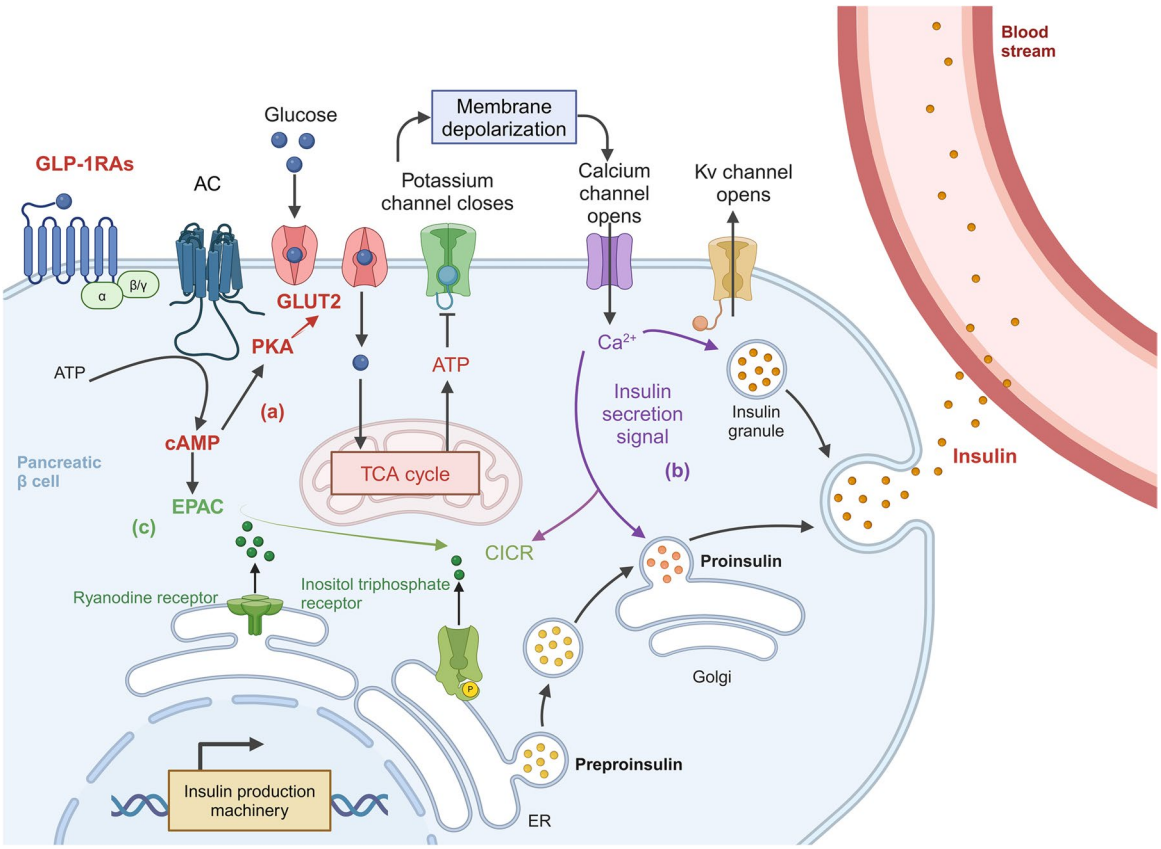

Fig. 1 GLP-1 RAs

channels (Kv) are typically closed; however, in response to glucose-induced depolarization, these channels open. It is proposed that Ex-4 acts to counteract potassium outflow, thereby delaying repolarization and increasing Ca^{2+} influx, which in turn enhances insulin secretion [27]. Furthermore, GLP-1 RAs have been demonstrated to enhance β-cell sensitivity to glucose by modulating K_{ATP} channel activity, as evidenced by observations in both animal and human studies [28, 29] (Fig. 1).

GLP-1 RAs are acknowledged for their role in maintaining glucose homeostasis and exerting a range of broader biological effects, including cardioprotective properties. They enhance myocardial glucose uptake, reduce inflammation and oxidative stress, and prevent apoptosis. For example, Ex-4 has been demonstrated to increase cardiac glucose uptake and ATP production by promoting GLUT1 translocation in H9c2 cells. GLP-1 R activation has been shown to elevate cAMP levels, activating PKA and Epac pathways, which offer antioxidant and anti-apoptotic protection against oxidative damage. In cardiac injury contexts, immune cells produce inflammatory mediators, impairing contractile function; however, liraglutide has been shown to significantly mitigate these effects [30, 31].

Effects of GLP-1 RAs on Promoting Pancreatic Islet β-Cell Proliferation and Inhibiting Its Apoptosis

GLP-1 RAs confer comprehensive benefits through the enhancement of glucose-stimulated insulin secretion, restoration of β-cell glucose sensitivity, and stimulation of insulin gene expression and biosynthesis. Clinical studies indicate that GLP-1 RAs promote β-cell proliferation, improve survival, and facilitate regeneration, thereby underscoring their potential for therapeutic intervention in cases of pancreatic β-cell dysfunction [32]. Ex-4 binds to receptors on pancreatic β-cell, activating adenylyl cyclase (AC) and cAMP, which in turn activate PKA and Epac [33]. In streptozotocin-induced diabetic mice, Ex-4 has been observed to regulate the cell cycle via the PKA/activating transcription factor 1 (ATF-1)/β-catenin/cyclin D1 pathway, thereby enhancing proliferation of β-cell [34]. Epac activates the MAPK pathway, thereby promoting the activity of cyclin-dependent kinase 2 (CDK2) and CDK4, which in turn facilitate β-cell differentiation and proliferation [35, 36] (Fig. 2).

It is postulated that GLP-1 RAs activate the GLP-1 R and transactivate the epidermal growth factor receptor (EGFR) via metalloproteinases. In C57BL/6 mice, the absence of

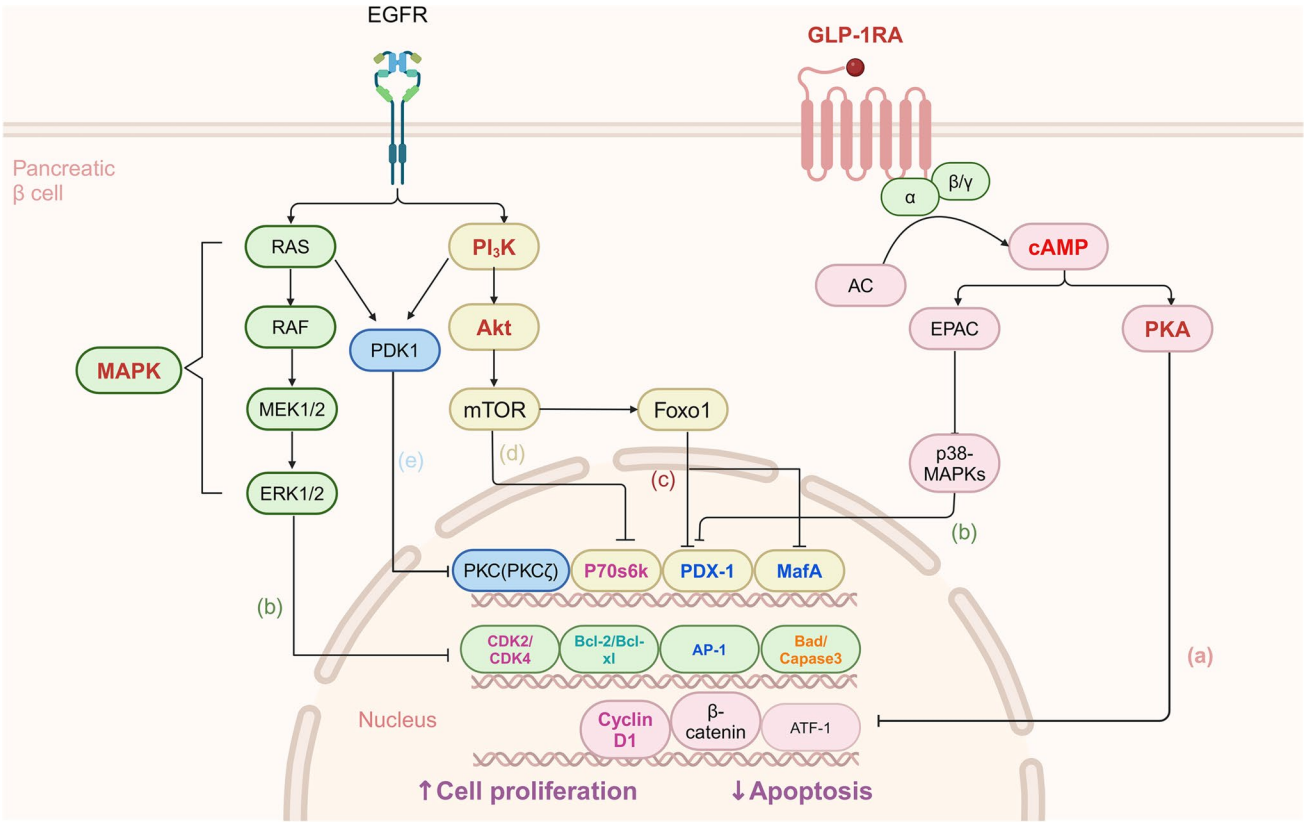

Fig. 2 PKCζ, a PI_3K effector, is essential for β-cell proliferation and differentiation

EGFR in β-cell results in glucose intolerance, underscoring the importance of EGFR in insulin secretion and β-cell proliferation [37]. Ex-4 exerts regulatory control over the PI_3K/Akt/Foxo1 pathway, impeding the nuclear entry of Foxo1 and consequently enhancing the expression of insulin gene transcription factors PDX-1 and MafA. These factors have been demonstrated to enhance both β-cell proliferation and α-to-β-cell trans-differentiation [38–40]. The activation of Akt by mTOR is essential for the phosphorylation of P70s6k, which plays a pivotal role in regulating the cell cycle and ensuring cell survival. Ex-4 exerts its influence on cell proliferation via the PKB/mTOR/p70S6K pathway [41]. PKCζ, a PI_3K effector, is essential for β-cell proliferation and differentiation (Fig. 2).

In the past decades, several groups have found that drugs that harmine and other dual specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) inhibitors are able to induce proliferation of human β-cell and increase islet mass in vitro and vivo, and its pro-proliferative effects primarily operate via translocation of nuclear factor of activated T-cells (NFAT) transcription factors to the nucleus, with the consequent transactivation of cyclins such as cyclin A, CDKs such as CDK1, and repression of CDK-inhibitors such as $p15^{INK4}$, $p21^{CIP1}$, and $p57^{KIP2}$ [42, 43]. It is noted that, whether in vitro or in vivo experiments, the combination of harmine and Ex-4 can significantly promote the proliferation of human β-cells compared with harmine alone, which may also be related to the promotion of trans-differentiation from α-cells to β-cells [44].

Studies have demonstrated that GLP-1 RAs inhibit β-cell apoptosis. They reduce caspase-3 mRNA activity and enhance the expression of anti-apoptotic genes, including Bcl-2 and Bcl-xl [45, 46]. Additionally, GLP-1 RAs have been demonstrated to activate AP-1, which regulates the expression of apoptotic genes, and to phosphorylate Bad, a pro-apoptotic factor, thereby reducing apoptosis [47] (Fig. 2). These pathways play a critical role in enhancing cell survival and inhibiting apoptosis in pancreatic β-cell, thereby showcasing multifaceted protective effects of GLP-1 RAs on β-cell viability.

Effects of GLP-1 RAs on Promoting Somatostatin Release and Inhibiting Glucagon Secretion

The effects of GLP-1 RAs on the release of somatostatin and the inhibition of glucagon secretion are complex and multifaceted. The precise mechanism through which GLP-1 RAs reduce glucagon secretion remains a topic

of contention and investigation. Some researchers posit that this effect occurs via an intrinsic mechanism, while others hypothesize that it may be mediated through the paracrine actions of insulin or somatostatin. Somatostatin, renowned for its potent inhibitory effects on both insulin and glucagon release, plays a pivotal role in the regulation of hormones. In perfused pancreas models, it has been observed that GLP-1 significantly inhibits glucagon secretion from pancreatic α-cells across various glucose levels. This reduction in glucagon secretion is consistently accompanied by an increase in somatostatin release. The specific blockade of somatostatin receptor 2 (SSTR2) resulted in a notable increase in glucagon secretion, effectively reversing the inhibitory effect of GLP-1 [48, 49]. The research conducted by J. de et al. demonstrated that in isolated rat pancreatic cells, the infusion of a highly selective SSTR2 antagonist entirely blocked the inhibitory effect on glucagon secretion, resulting in a swift increase in basal glucagon secretion levels. In contrast, the introduction of a monoclonal somatostatin antibody resulted in only partial inhibition [50, 51]. These findings provide compelling evidence in support of the hypothesis that GLP-1 RAs inhibit glucagon secretion by stimulating the release of somatostatin, an effect that is independent of insulin and the secretory products of β-cells.

However, Ramracheya et al. proposed that GLP-1 RAs might exert a direct effect on α-cells, as the inhibition was not reversed by the insulin receptor antagonist or the SSTR2 antagonist [52]. The dual actions of GLP-1 RAs, namely, the promotion of insulin secretion and the inhibition of glucagon release, exert a significant influence on the plasma ratio of these hormones, thereby contributing to the maintenance of glucose homeostasis in the body.

Beneficial Effects of GLP-1 RAs on Cardiovascular System

The Influence and Mechanism of GLP-1 RAs in Improving HF

HF is a clinical syndrome marked by rising incidence, prevalence, and high mortality [53]. Normally, myocardial energy metabolism relies mainly on fatty acids (70%), with glucose, ketone bodies, and lactate as supplementary sources. In failing heart tissue, the uptake and metabolism of these substrates are compromised, reducing oxidative phosphorylation and energy production [54]. In a model of non-ischemic HF in dogs (tachycardiomyopathy induced by pacemakers), IV infusion of GLP-1 increases left ventricular (LV) contractility (LV dP/dt increased by 98%, stroke volume by 102%, and cardiac output by 57%) and decreases LV end-diastolic pressure, heart rate, and systemic vascular resistance. In addition, GLP-1 also improves myocardial insulin sensitivity and myocardial glucose uptake [55]. These benefits are also present in the presence of active metabolite of GLP-1 [56]. Above all, these benefits of IV infusion of GLP-1 are confirmed in preliminary studies in humans [57, 58]. However, the short half-life of GLP-1 greatly precludes its clinical utilization. Therefore, microsphere sustained-release technology is being utilized to enable GLP-1 drugs to be released slowly and continuously, or GLP-1 molecules are being modified and optimized through structural modifications to develop GLP-1 RAs with longer half-lives. Various studies have shown the beneficial effects of GLP-1 RAs in HF treatment, primarily by enhancing the expression of glucose transporters GLUT1 and GLUT4 via the AMPK/cAMP/PKA pathway, which boosts glucose uptake and improves cardiac function [59].

Inflammation significantly contributes to HF pathogenesis and progression [60]. Zhang et al. found that liraglutide alleviates IL-1β-induced suppression of AMPK phosphorylation, increasing ACC, PGC-1α, CPT-1, and DGAT1 expression, which improves triglyceride deposition and reduces myocardial inflammation [30]. Moreover, liraglutide can activate ERK5 signaling in endothelial cells, mitigating endothelial dysfunction [61]. Oxidative stress, inflammation, and apoptosis are critical in HF progression. GLP-1 RAs such as exenatide and liraglutide modulate signaling pathways to reduce oxidative stress, reactive oxygen species (ROS) production, and apoptosis [62, 63] (Fig. 3). Ex-4 also restores SERCA2a expression and activity via the eNOS/cGMP/PKG pathway, reducing cytoplasmic Ca^{2+} levels and suppressing structural remodeling in HF rats [64].

While GLP-1 RAs are beneficial in reducing body weight and improving cardiovascular outcomes in type 2 diabetes mellitus (T2DM) patients, their effects vary in HF with differing ejection fractions [65]. In HF with preserved ejection fraction (HFpEF), GLP-1 RAs may not reduce HF hospitalization but might lower atherosclerotic event risks [66, 67]. However, it is especially remarkable that within the SUMMIT trial, among patients with HFpEF, the dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide agonist, tirzepatide, significantly reduces the combined risk of cardiovascular death or the exacerbation of HF. Specifically, it brings down the hospitalization rate for HF by 38% [68]. Additionally, it is demonstrated that it can improve multiple biomarkers (such as C-reactive protein, N-terminal prohormone B-type natriuretic peptide, and troponin T, among others), relieve systemic inflammation, and curtail myocardial injury [69]. In the cardiac magnetic resonance (CMR) sub-study of the SUMMIT trial, in comparison with the placebo, the treatment of obesity-related HFpEF with tirzepatide can lead to a reduction in LV mass and pericardiac adipose tissue. Notably, the variation in LV mass is

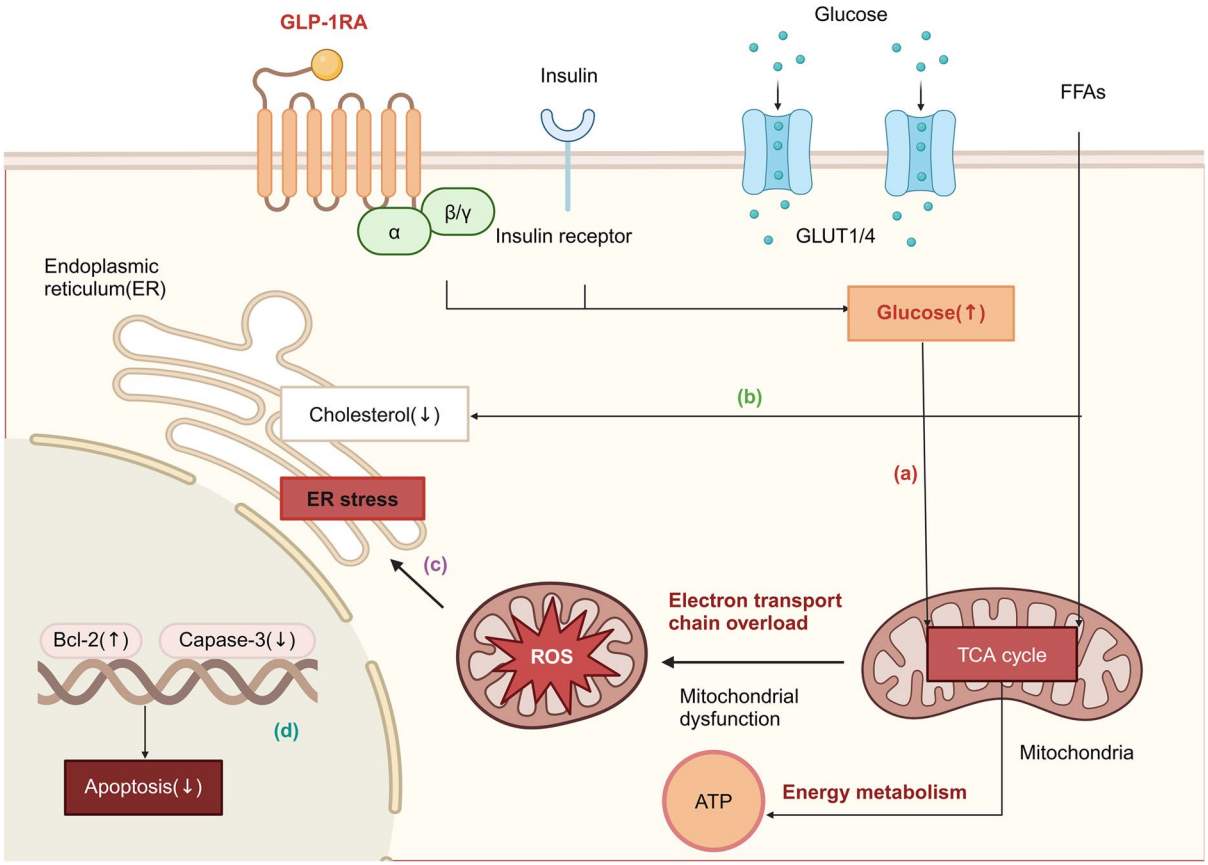

Fig. 3 GLP-1 RAs such as exenatide and liraglutide modulate signaling pathways to reduce oxidative stress, reactive oxygen species (ROS) production, and apoptosis

correlated with weight loss. The decrease in LV mass and pericardiac adipose tissue might be closely associated with the reduction in HF events that were observed in the main SUMMIT trial [70]. Conversely, in HF with reduced ejection fraction (HFrEF), especially in advanced stages, caution is necessary due to potential increases in heart rate and arrhythmic events [71]. Tailored therapy according to HF type and severity is advised for optimal management.

The Influence and Mechanism of GLP-1 RAs in Modulating Hypertension

Hypertension, a chronic cardiovascular disease, affects a large number of individuals, with its prevalence increasing, making it a major cause of mortality and disability [72]. Thus, finding effective treatments is crucial. Hypertension is multifactorial, influenced by genetics, environment, and other factors. Animal studies have shed light on the mechanisms by which GLP-1 RAs may benefit patients with hypertension. Recent research indicates that GLP-1 RAs reduce hypertension development in animal models like Dahl salt-sensitive (DSS) rats [73], spontaneously hypertensive rats (SHRs) [74], and angiotensin II-infused C57BL/6 J mice [75]. These studies reveal that GLP-1 RAs not only decrease oxidative stress and inflammation in endothelial cells but also inhibit cardiac hypertrophy and fibrosis by regulating myocardial proliferation and apoptosis [76]. The antihypertensive effects of GLP-1 RAs are due to several mechanisms: natriuretic effects, vasodilation, and reduced sympathetic activity. GLP-1 RAs promote diuresis and natriuresis by inhibiting sodium reabsorption in the renal proximal tubule through the Na^+/H^+ exchanger isoform 3 (NHE3) [77]. Vasodilation is achieved by activating endothelial nitric oxide synthase (eNOS) and increasing nitric oxide (NO) production via the cAMP/PKA, AMPK, and PI_3K/Akt signaling pathways [17]. Solitary tract neurons in the brainstem, reactive to dopamine beta-hydroxylase (DBH), play crucial roles in reducing sympathetic activity in response to GLP-1 RAs [78].

BPV is also crucial in hypertension development [79]. Xu et al. demonstrated that GLP-1 RAs could alleviate cytoplasmic Ca^{2+} overload in VSMCs in SHRs, improve the arterioles' systolic and diastolic functions, and reduce BPV by upregulating Na^+/Ca^{2+} exchanger 1 (NCX1) expression via

the Akt signaling pathway [80]. In pulmonary arterial hypertension (PAH), specific studies using monocrotaline (MCT)-induced PAH models suggest that liraglutide acts through the NO/sGC/cGMP pathway, increasing NO release, activating soluble guanylate cyclase (sGC), and enhancing cyclic guanosine monophosphate (cGMP) synthesis. This pathway regulates vascular tension, prevents remodeling, and alleviates PAH symptoms [81]. Current studies support that liraglutide can prevent and treat worsening PAH symptoms [82]. The United Kingdom Prospective Diabetes Study (UKPDS) shows that intensive blood pressure (BP) control reduces the risks of stroke, myocardial infarction, and other cardiovascular complications [83]. A 5.6 mmHg reduction in systolic blood pressure (SBP) in T2DM patients can decrease cardiovascular disease-induced mortality by 18% [84]. Several large randomized controlled trials highlight the benefits of GLP-1 RAs in lowering BP in T2DM patients. Liakos et al. noted that short-term liraglutide treatment favorably affected SBP based on 24-h ambulatory measurements, with minimal impact on diastolic blood pressure (DBP) [85]. A meta-analysis evaluating GLP-1 RAs, including exenatide and liraglutide, found these agents more effective in reducing both SBP and DBP compared to insulin and other oral antidiabetics, providing additional cardiovascular benefits [86].

However, the outcomes remain controversial. Gill et al. observed a non-significant trend towards lower SBP and DBP with exenatide compared to placebo in T2DM patients [87]. Muskiet et al. found exenatide did not significantly lower DBP compared to insulin glargine [88]. Similarly, Jendle et al. reported that 1.8 mg/day liraglutide did not effectively reduce SBP compared to 4 mg/day glimepiride (a sulfonylurea) [89]. These contradictory findings suggest that GLP-1 RAs' effects on DBP may vary across studies [90, 91]. This inconsistency might be due to most trials being small, short-term, and not specifically designed for hypertension assessment. As hypertension development typically takes longer, study durations might be insufficient to capture GLP-1 RAs' full effects on BP regulation. Consequently, large, long-term, and specifically designed randomized controlled trials (RCTs) are necessary to accurately evaluate GLP-1 RAs' impact on hypertension and determine their potential benefits and limitations [86].

The Influence and Mechanism of GLP-1 RAs in Ameliorating Ischemic Cardiomyopathy

Myocardial ischemia and reperfusion injury play a pivotal role in the onset and progression of myocardial infarction and heart failure. These processes are characterized by oxidative stress, mitochondrial dysfunction, and apoptosis. A substantial body of evidence from animal studies [92–95] and clinical trials [96–101] indicates that GLP-1 RAs have a marked effect in ameliorating myocardial ischemia, reducing reperfusion injury, decreasing infarct size, and enhancing cardiac function.

In a pioneering study conducted by Eid on male rats, it was revealed that the administration of Ex-4 just 10 min post-left anterior descending (LAD) coronary artery ligation activated the Sirt1/AMPK axis. This resulted in Sirt3 upregulation, sustained deacetylation of p53, PGC-1α, Foxo1, NF-κB, and the inhibition of oxidative stress and apoptosis in the infarcted myocardium. Ultimately, this led to a reduction in infarct size and the preservation of cardiac function and structure [92]. Recent research has identified mitochondrial dysfunction as a key feature of hypoxia/reoxygenation (H/R) models. Chang et al. proposed that exenatide upregulates uncoupling protein-3 (UCP-3) and nuclear respiratory factor-1 (Nrf-1) in cardiomyocytes subjected to ischemia/reperfusion (I/R) via the cAMP/PKA pathway, thereby facilitating mitochondrial homeostasis [93]. Furthermore, exenatide has been demonstrated to mitigate mitochondrial oxidative stress, reduce Ca^{2+} overload, inhibit fission, and close the mitochondrial permeability transition pore (mPTP), collectively preventing cardiomyocyte apoptosis by inhibiting the release of proapoptotic proteins such as cytochrome c and caspase-3 [94]. Furthermore, liraglutide was demonstrated to inhibit NLRP3 inflammasome-induced pyroptosis in ischemia–reperfusion rats via the Sirt1/NOX4/ROS signaling pathway, thereby providing additional myocardial protection [95] (Fig. 4).

Ischemic cardiomyopathy remains a significant global cause of mortality, with treatments focusing on medical or surgical reperfusion. However, restoration of acute myocardial blood flow can pose a risk to cardiomyocytes, resulting in reperfusion injury and a notable impact on infarct size and prognosis [96]. The study of Lazaros et al. firstly demonstrates the utility of a novel metabolic agent, GLP-1, in attenuating myocardial stunning after ischemia–reperfusion in canine models [97]. Moreover, in a porcine model, exenatide is ascertained to attenuate cardiomyocyte apoptosis and oxidative stress levels, which plays a role in curtailing the myocardial infarction area and precluding the impairment of cardiac systolic and diastolic functions [98]. These salutary effects seemingly pertain to humans as well. In clinical trials, with respect to patients diagnosed with STEMI who are undergoing primary percutaneous coronary intervention (pPCI), the administration of exenatide during the reperfusion period is capable of remarkably augmenting the myocardial salvage ratio and diminishing the ultimate infarct dimension [99, 100]. Notwithstanding the fact that the aforestated investigations have uniformly demonstrated that GLP-1 RAs are endowed with a multiplicity of cardioprotective efficacies, the consistency of such findings has not been ubiquitously maintained throughout all the research undertakings [101]. This highlights the necessity for larger studies to rigorously evaluate myocardial salvage and clinical outcomes.

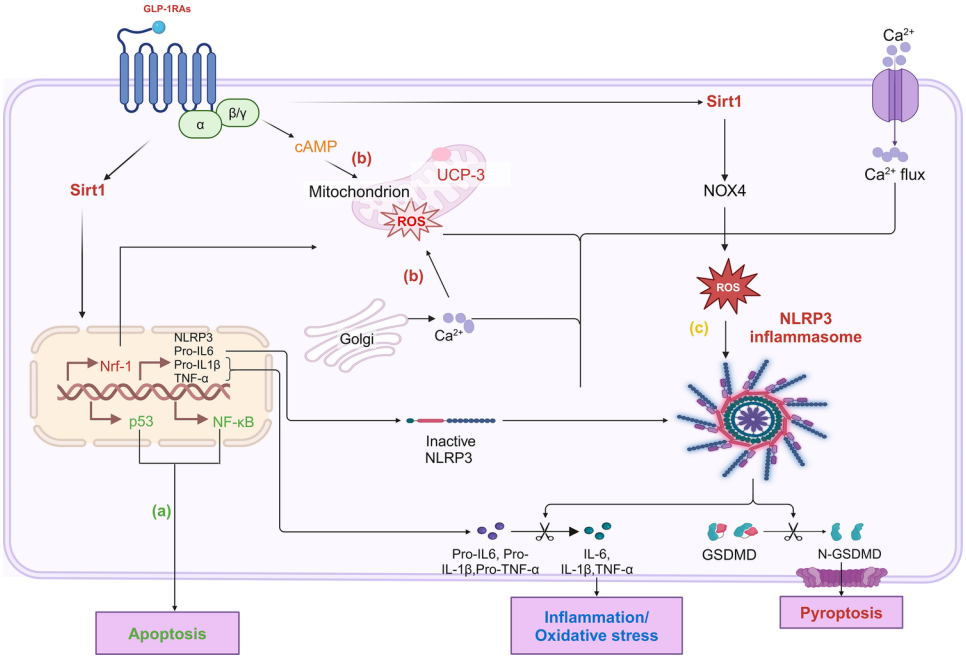

Fig. 4 Liraglutide was demonstrated to inhibit NLRP3 inflammasome-induced pyroptosis in ischemia–reperfusion rats

The Influence and Mechanism of GLP-1 RAs in Improving Diabetic Cardiopathy

At present, diabetic cardiopathy is acknowledged as a condition defined by cardiac dysfunction resulting from aberrant cardiac structure and function in diabetic patients, irrespective of other cardiac risk factors. Pathological changes typically manifest as myocardial interstitial fibrosis, peripheral vascular fibrosis, and cardiomyocyte hypertrophy. Diabetic cardiopathy can be classified into three categories: coronary atherosclerotic heart disease, diabetic cardiomyopathy, and cardiac autonomic neuropathy. The effects of GLP-1 RAs on cardiac structure and function have been examined in both animal models and human patients with DM.

Previous animal experiments have demonstrated that liraglutide could inhibit the proliferation and migration of VSMCs by suppressing the PI_3K/Akt and MAPK signaling pathways while activating the AMPK signaling pathway. The excessive proliferation of VSMCs could accelerate the deposition of atherosclerotic plaques in the vascular intima, leading to intimal thickening and vascular remodeling [102, 103]. Both short-acting and long-acting GLP-1 RAs have demonstrated beneficial effects by activating the AMPK-Sirt1 pathway, which has the potential to mitigate cardiac steatosis, oxidative stress, and apoptosis. Additionally, Ex-4 has been demonstrated to activate eNOS and inhibit Rho, an important signaling molecule in oxidative stress. This results in increased NO bioavailability, improved oxidative stress, and enhanced coronary blood flow in diabetic rats [104]. Moreover, mitochondrial dysfunction and ER oxidative stress have been identified as key factors in the induction of myocardial apoptosis in diabetic myocardial models. GLP-1 RAs have been demonstrated to effectively support cardiomyocyte survival by addressing a number of key mechanisms, including impaired mitochondrial Ca^{2+} processing, abnormal energy metabolism, structural abnormalities, increased oxidative stress, and ER stress mediated by NF-κB (Fig. 5). These mechanisms contribute to the cardioprotective effects of GLP-1 RAs in diabetic myocardial diseases [105].

Clinical evidence demonstrates that GLP-1 RAs are an effective means of reducing the risk of MACE in diabetic patients. This protective effect is attributed not only to their influence on systemic metabolism, which safeguards the heart, but also to their direct actions on cardiac tissues. The direct cardioprotective effects of GLP-1 RAs encompass the reduction of inflammation, the lowering of oxidative stress, the decrease of fibrosis, the regulation of lipids, and the preservation of mitochondrial function. For instance, in carotid endarterectomy procedures for diabetic patients, preoperative administration of GLP-1 RAs has been demonstrated to markedly enhance the expression of proteins that improve inflammatory pathways in diabetic atherosclerotic lesions, thereby promoting plaque stabilization [106]. Furthermore, clinical trials have indicated that GLP-1 RAs can reduce carotid intima-media thickness in patients with DM, suggesting a favorable impact on vascular health [107].

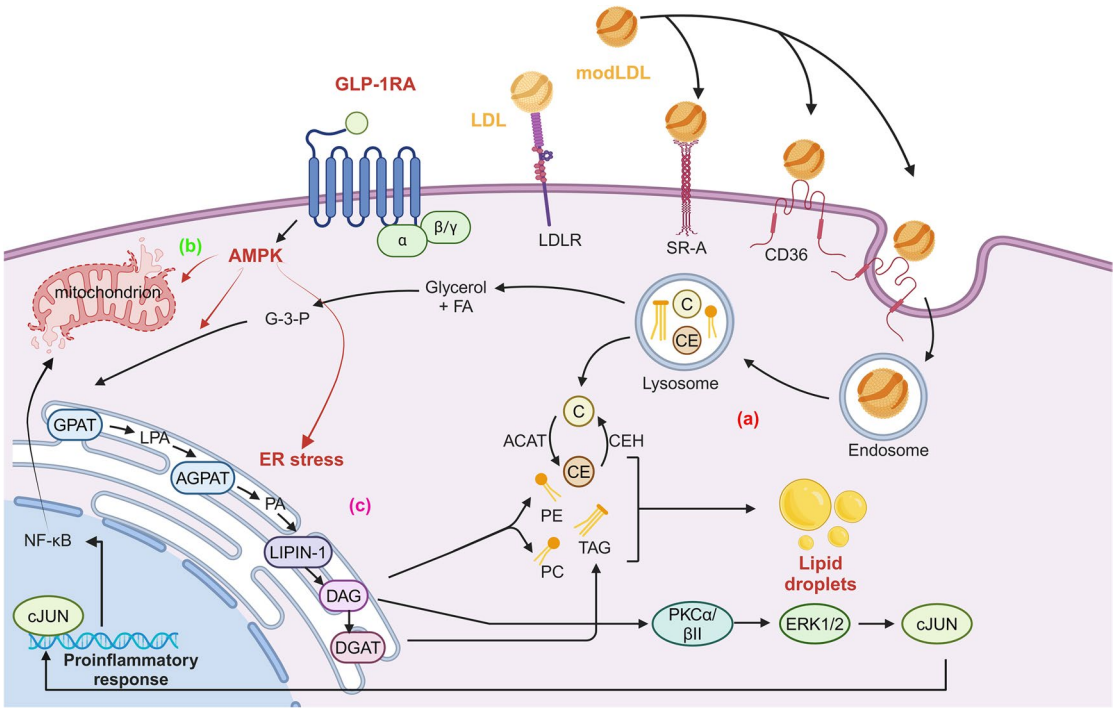

Fig. 5 GLP-1 RAs have been demonstrated to effectively support cardiomyocyte survival by addressing a number of key mechanisms

Conclusion and Future Perspective

The therapeutic benefits of GLP-1RAs in the management of DM extend well beyond glycemic control, offering a broad range of cardiovascular advantages. By promoting insulin secretion, enhancing pancreatic β-cell proliferation, and inhibiting β-cell apoptosis in a glucose-dependent manner, GLP-1 RAs effectively regulate blood glucose levels with a low risk of hypoglycemia. In addition to their glucose-regulating capabilities, GLP-1 RAs provide significant cardiovascular protective effects. They enhance cardiac function, combat heart failure, facilitate myocardial energy uptake, reduce inflammation, alleviate oxidative stress, and inhibit myocardial structural remodeling. Moreover, GLP-1 RAs contribute to the management of hypertension by lowering BP and reducing variability. Additionally, they facilitate recovery from ischemic cardiomyopathy by mitigating ischemia–reperfusion injury and ameliorating diabetic cardiopathy through multiple pathways.

In light of the substantial in vivo and in vitro evidence supporting the efficacy of GLP-1 RAs, further research into their protective mechanisms is imperative. Such studies may facilitate the identification of novel therapeutic targets and the development of innovative treatment options. To resolve the current controversies regarding the use of GLP-1 RAs in treating hypertension and ischemic cardiomyopathy, large-scale clinical RCTs or real-world studies should be designed to provide more robust evidence.

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Declarations

Ethics Approval Not applicable.

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Consent for Publication Not applicable.

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