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Review

Potential Role of GLP-1 Based Therapeutics in Coronary Artery Disease

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Abstract

Glucagon-like peptide-1 (GLP-1), an incretin hormone primarily secreted by intestinal L cells, regulates glucose metabolism by increasing insulin synthesis and secretion, decreasing plasma glucagon levels, reducing food intake, and slowing gastric emptying. This has led to the development of GLP-1 receptor (GLP-1R) agonists as a treatment for diabetes and obesity. In addition to being present in beta cells, GLP-1R has also been identified in blood vessels and the heart, suggesting that GLP-1R agonists may have an impact on cardiovascular health. There is now substantial evidence supporting GLP-1's protective effects on the cardiovascular system. This review summarizes the current research on GLP-1-based therapy for coronary artery disease (CAD) by examining its protective effects against inflammation and ischemia/reperfusion injury and analyzing clinical trials on GLP-1-based therapies for CAD. Although results from various studies were inconsistent, the challenge of transitioning GLP-1-based therapies from the laboratory to the clinical setting remains. Further well-designed and high-quality studies are necessary to determine the efficacy and safety of GLP-1 for patients with CAD.

Keywords: glucagon-like peptide-1; GLP-1 receptor agonists; coronary artery disease; acute/chronic coronary syndromes; ischemia/reperfusion injury; inflammation

1. Introduction

The close relationship between coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) has been established by current research. Patients with T2DM are more likely to experience CAD earlier in life and in a more severe and widespread manner compared to non-diabetic patients [1]. The progression of arteriosclerosis in this population occurs earlier and at a faster rate compared to non-diabetic individuals [2]. The significant public health impact caused by ischemic heart disease is projected to rise as the population ages and the incidence of comorbidities such as obesity and diabetes increases. According to projections, the global prevalence of diabetes among adults aged 20–79 years is expected to surge in the coming decades, reaching 783.2 million by 2045 [3].

Two significant trials have been reported: DCCT (the Diabetes Control and Complications Trial) [4] in type 1 diabetes (T1DM) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) [5] in T2DM. The results from both trials showed that improved glycemic control reduces microvascular disease and can effectively lower long-term cardiovascular complications. The United Kingdom Prospective Diabetes Study [6] suggested that intensive glycemic control can significantly reduce the occurrence of diabetes-related events. However, the impacts on cardiovascular events and mortality were not substantial. Another study revealed that the intensive-therapy regimen resulted in an unexpected increase in mortality [7]. As a result, the Food and Drug Administration (FDA) established guidelines that any anti-hyperglycemic prescription medications must demonstrate the safety of their effects on the heart and blood vessels before they can be marketed. This policy was revised and strengthened in March 2020 [8].

Fortunately, several new pharmacological agents, such as glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors have obtained acceptance among medical practitioners and patients due to their reliable cardiovascular profiles as demonstrated in cardiovascular outcome studies (CVOTs) [9,10]. Despite this, controversies surrounding their risk of cardiovascular events persist. In this review, we aim to summarize and evaluate the available evidence from pre-clinical studies and clinical trials regarding the effects and underlying mechanisms of GLP-1-based therapies on CAD.

Table 1. Comparison of GLP-1-receptor agonist products approved by the FDA for treatment of T2DM.

Generic	Proprietary	Dosing regimen	Half-life	Sponsor	Year approved by FDA
Exenatide	Byetta	Subcutaneous injection twice-daily	2.5 h	AstraZeneca	2005
Liraglutide	Victoza	Subcutaneous injection once-daily	12 h	Novo Nordisk	2010
Exenatide extended-release (ER)	Bydureon	Subcutaneous injection once-weekly	n/a	AstraZeneca	2012
Albiglutide*	Tanzeum	Subcutaneous injection once-weekly	120 h	GlaxoSmithKline	2014
Dulaglutide	Trulicity	Subcutaneous injection once-weekly	90 h	Eli Lilly	2014
Liraglutide	Saxenda	Subcutaneous injection once-daily	12 h	Novo Nordisk	2014
Lixisenatide	Adlyxin	Subcutaneous injection once-daily	3~4 h	Sanofi	2016
Semaglutide	Ozempic	Subcutaneous injection once-weekly	160 h	Novo Nordisk	2018
Oral semaglutide	Rybelsus	Oral once-daily	160 h	Novo Nordisk	2018
Semaglutide	Wegovy	Subcutaneous injection once-weekly	160 h	Novo Nordisk	2021

*Albiglutide was discontinued in 2017 due to a decrease in sales. GLP-1, Glucagon-like peptide-1; FDA, Food and Drug Administration; T2DM, type 2 diabetes mellitus. n/a: not applicable.

2. The Properties of GLP-1 and GLP-1 Receptor Agonists

GLP-1 was first discovered as a hormone that stimulates insulin production and is secreted by intestinal endocrine L-cells. GLP-1 is released within minutes of consuming food and helps to speed up the metabolism of nutrients. One of the defining characteristics of GLP-1 is its extremely brief half-life of approximately 2 minutes, making it highly susceptible to decomposition by DPP-4. The predominant biologically active variant of GLP-1, known as GLP-1 (7-36), initiates signaling cascades through the GLP-1 receptor (GLP-1R). Yet, it undergoes rapid conversion into GLP-1 (9-36) [11]. The GLP-1R is a protein consisting of 463 amino acids belonging to the Class B family of 7-transmembrane-spanning receptors [12]. GLP-1 and GLP-1 receptor agonists exert multiple physiological effects, including increased insulin production and release, decreased glucagon secretion, delayed gastric emptying, and increased satiety by acting on the GLP-1R.

The initial approval of the first GLP-1R agonist for the management of T2DM in 2005 was attributed to the therapeutic impact of GLP-1 on glucose metabolism [13]. Since then, the FDA has approved various GLP-1R agonist products with diverse structures and pharmacokinetics (as shown in Table 1). These drugs are commonly recommended as combination therapy in addition to metformin for patients who have not achieved their glycemic goals, particularly those who need to lose weight and reduce the risk of hypoglycemia [14]. The expression of GLP-1R is not limited to pancreatic islet cells but is also observed in multiple other anatomical locations, including the lung, brain, kidney, stomach, and liver. Considerable evidence suggests that the expression of GLP-1R has been further localized in cardiomyocytes, microvascular endothelium, the endocardium, the coronary arteries, and the smooth muscle cells [15].

While GLP-1R agonism is primarily recognized for its insulin-stimulating and weight-reducing properties, studies have also demonstrated its several positive effects on the cardiovascular system in animal models [16]. Importantly, the improvement in cardiovascular function brought about by GLP-1 is not solely dependent on its ability to enhance energy metabolism and reduce body weight. GLP-1 may enhance cardiovascular function through direct action on GLP-1R and indirect mechanisms that are unrelated to its mode of action in the heart.

3. Pre-Clinical Evidence for the Anti-Inflammation Effects of GLP-1

Inflammation, especially in those with diabetes, plays an important role in the development of atherosclerosis. Systemic inflammation can speed up the advancement of the disease and heighten the susceptibility to other CAD, such as acute coronary syndromes (ACS) and myocardial infarction (MI). Proinflammatory stimuli can cause atherosclerosis, which is marked by elevated levels of Tumor Necrosis Factor-α (TNF-α), Interleukin 6 (IL-6), C-Reactive Protein (CRP), or endotoxin [17]. Anti-inflammatory drugs were postulated to have beneficial effects on the natural progression of CAD by slowing down plaque expansion, reducing the risk of acute plaque changes, and improving the outcome of MI events [18].

Both endogenous GLP-1 and GLP-1R agonists can diminish cardiovascular inflammation via direct and indirect means. GLP-1 infusion decreases the elevation in microvascular permeability during inflammation caused by lipopolysaccharide (LPS), and the positive impact may be due to GLP-1R/cAMP pathways [19]. Liraglutide has a protective effect against TNFα-induced inflammation in human aortic endothelial cells by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, Protein kinase C (PKC-α), Nuclear factor-kappaB (NF-κB) signaling [20].

Sirtuin 6 (SIRT6), a histone deacetylase, has been recognized as a promising therapeutic target for the treatment of inflammatory vascular diseases due to its effects on NF-

κB in HUVECs [21]. Plaques in individuals with diabetes have more inflammation and higher collagen content, along with increased SIRT6 expression, compared to those in non-diabetic individuals. GLP-1-based therapy can reduce the inflammation in diabetic plaques by regulating SIRT6/NF-κB signaling [21].

Liraglutide reduces the level of E-selectin and vascular cell adhesion molecule (VCAM-1) in response to endotoxin stimulation. This inhibitory effect was nullified by inhibiting calmodulin-dependent protein kinase kinase-β (CAMKKβ). In addition, knocking down 5 adenosine monophosphate-activated protein kinase (AMPK) abolished the liraglutide-stimulated phosphorylation of AMPK and its anti-inflammatory effect. This finding indicates that the activation of CaMKKβ and AMPK is correlated with the anti-inflammatory effect of liraglutide in endothelial cells [22]. A one-week administration of liraglutide had an anti-inflammatory effect in C57BL/6 mice with obesity produced by a high-fat diet, independent of changes in body weight. These obese mice exhibited a decrease in the level of phosphorylated AMP-activated protein kinase (pAMPK), along with cardiac insulin resistance. Additionally, there was an increase in the expression of TNF-α and NF-κB [18]. Our previous research also showed that recombination of GLP-1 and liraglutide can suppress the expression of matrix metalloproteinase 1 (MMP1) by inhibiting the ERK1/2-NF-κB signaling pathway, reversing vascular remodeling [23]. Additionally, studies have demonstrated that the administration of exenatide elicits a strong and rapid anti-inflammatory action, regardless of weight loss, and this effect becomes evident within the first two hours of treatment [24]. These findings suggest that the direct anti-inflammatory properties of GLP-1 may be separate from its hypoglycemic effects.

Intriguingly, in a mouse model of atherosclerosis, it has been demonstrated that GLP-1 (9-37) and (28-37), which are breakdown products of GLP-1 (7-37), have the potential to decrease inflammation within plaques and enhance their stability, despite their inability to control glucose metabolism [25]. Future studies are required to clarify the exact impact of GLP-1-based treatment on atherosclerosis and coronary plaque stability. It is speculated that the mechanism may be associated with the indirect control of weight loss, glucose levels, blood pressure, inhibition of inflammation, and platelet activation [26]. However, a more detailed analysis of these elements falls outside the scope of this review.

4. GLP-1-Based Therapies and Coronary Blood Flow

Abnormal coronary blood flow is believed to contribute to ischemic heart disease. Insufficient coronary blood flow leads to fibrosis and necrosis of the heart muscle. Reviving the balance between oxygen consumption and demand is critical to preserving heart muscle in the face of obstructed coronary arteries [27]. While coronary intervention is an effective solution, finding effective drugs is also important.

Previous research has demonstrated that GLP-1R agonists can increase coronary flow in aerobically perfused mouse hearts through GLP-1R-dependent and GLP-1R-independent mechanisms [28]. The administration of GLP-1 through infusion has been observed to result in an augmentation in microvascular blood volume and flow velocity. This effect is believed to be facilitated by a process that relies on nitric oxide, as evidenced by the utilization of contrast-enhanced ultrasound imaging [29]. Additionally, another study has demonstrated that GLP-1 administration leads to an augmentation of coronary blood flow in conscious dogs with dilated cardiomyopathy produced by rapid pacing [30].

In a post-resuscitation swine model, continuous GLP-1 infusion increased coronary flow reserve, as estimated by intracoronary Doppler flow measurements [31]. Another study found that the administration of human GLP-1 by intravenous infusion following cardiac arrest and resuscitation resulted in enhanced coronary microvascular function via reducing oxidative stress [32]. Our team has also reported that GLP-1 exhibits a dosage-dependent inhibition of thromboxane receptor agonist-induced contraction in rat coronary artery rings, and this effect may be due to stimulation of potassium-ATP currents in the vascular endothelium [33]. Additionally, the presence of the relaxant effect of GLP-1 was not detected following the removal of the endothelial layer, indicating the potential involvement of the vascular endothelium. Putative mechanisms may include stimulation of the potassium-ATP currents [33]. A study on a rat model of metabolic syndrome found that chronic administration of liraglutide improved the capacity for nitric oxide-mediated dilation in coronary vessel internal diameter. These improvements were observed irrespective of any changes in body mass or control of blood glucose levels [34].

Clinical studies, however, have produced mixed results. A small, short-term clinical study revealed that infusion of GLP-1 resulted in a notable enhancement of resting myocardial blood flow (MBF) by about 24% in patients with T2DM but without heart failure or CAD, as seen by quantitative positron emission tomography (PET) [35]. Comparable findings were found in healthy participants using semi-quantitative contrast-enhanced echocardiography [36]. Conversely, a study of patients with non-diabetic chronic heart failure found that liraglutide administration for 24 weeks did not affect myocardial blood flow despite reducing weight, HbA1c, and 2-hour glucose values compared to placebo [37].

Although the relationship between GLP-1 and its receptor agonists and the nature of coronary arteries has been studied, the exact mechanisms linking GLP-1 to improved coronary blood flow are still unclear. One possible explana-

Table 2. The effect of GLP-1 on Ischemia-reperfusion (I/R) injury and its underlying mechanisms.

Authors	Agent	Subjects	Results or potential mechanisms	Ref
Ban *et al*.	GLP-1 (7-36), GLP-1 (9-36)	Mice	Both GLP-1 (7-36) and GLP-1 (9-36) reduced ischemic damage after I/R and increased cGMP release in wild-type and Glp1r(-/-) mice	[28]
Bose *et al*.	GLP-1	Rat	Activation of cAMP and PI3K	[42]
Bose *et al*.	GLP-1	Rat	Activation of mTOR/p70s6	[44]
Huisamen *et al*.	GLP-1 (7-36)	Rat	Activation of AMPK and PKB/Akt	[45]
Noyan-Ashraf *et al*.	Liraglutide	Mice	Activation of PKB, GSK3beta, PPARbeta/delta, Nrf-2, and HO-1	[47]
Sonne *et al*.	Exendin-4, GLP-1 (9-36)	Rat	Exendin-4 protect against I/R injury by activating GLP-1R	[52]
Eid *et al*.	Exendin-4	Rat	Activation of SIRT1, SIRT3 and AMPK	[51]
Bao *et al*.	Albiglutide	Rat	Increasing both glucose and lactate oxidation	[48]
Wohlfart *et al*.	Lixisenatide	Rat	Independent of GLP-1R	[50]
Kavianipour *et al*.	GLP-1	Pig	GLP-1 does not limit infarct size	[53]
Kristensen *et al*.	liraglutide	Pig	Liraglutide has a neutral effect on myocardial infarct size	[54]
Ekström *et al*.	liraglutide	Pig	Liraglutide does not reduce infarct size	[55]
Timmers *et al*.	Exenatide	Pig	Exenatide reduces infarct size by increasing the expression of PKB and Bcl-2	[56]
Siraj *et al*.	GLP-1 (28-36)	hcaECs, hcaSMCs	Activation of MTPα and sAC	[57]
Ban *et al*.	Exendin-4, GLP-1 (9-36)	Rat, CMs	cAMP and phosphorylation of ERK1/2 and the phosphoinositide 3-kinase target protein kinase B/Akt	[58]
Besch *et al*.	Exenatide	Patients admitted for CABG	Exenatide does not exert any additional cardioprotective effect compared to insulin in patients undergoing scheduled CABG surgery	[59]

Abbreviations: AMPK, AMP-activated protein kinase; Bcl-2, B-cell lymphoma 2; CMs, cardiomyocytes; cAMP, cyclic adenosine 3′,5′-monophosphate; CABG, coronary artery bypass graft; GLP-1-Tf, GLP-1 to human transferrin; GSK3beta, Glycogen synthase kinase-3; HO-1, heme oxygenase-1; hcaECs, human coronary artery endothelial cells; hcaSMCs, human coronary artery smooth muscle cells; sAC, soluble adenylyl cyclase; SIRT6, sirtuin 6; mTOR, mammalian target of rapamycin; MTPα, mitochondrial trifunctional protein-α; Nrf-2, NF-E2-related factor 2; PI3K, phosphoinositide 3-kinase; PKB, Protein kinase B; PPARbeta/delta, Peroxisome proliferator-activated receptor beta/delta; p70s6, 70-kDa ribosomal protein S6 kinase; sAC, soluble adenylyl cyclase.

Table 3. Overview of studies reporting on GLP-1-based therapies for CAD.

Authors	Year	Subjects	N	Agent	Result	Ref
Read *et al*.	2011	Patients with normal LV function and single-vessel coronary disease within the LAD artery undergoing elective PCI	20	GLP-1 (7-36)	GLP-1 improved recovery of LV systolic and diastolic function at 30 minutes after balloon occlusion compared with control	[62]
McCormick *et al*.	2015	Patients with preserved LV function and single-vessel coronary disease within the LAD artery undergoing elective PCI	20	GLP-1 (7-36)	Pre-treatment with GLP-1 (7-36) protects the heart against ischemic LV dysfunction and improves the recovery of function during reperfusion	[63]
Read *et al*.	2012	Patients with CAD and good LV function awaiting revascularization	14	GLP-1	Global LV function was greater at peak stress during GLP-1 infusion compared with control	[64]
McCormick *et al*.	2015	Patients with obstructive CAD (at least one proximal stenosis $>$70% and diabetes	10	GLP-1 (7-36)	GLP-1 improved both global and regional myocardial performance at peak stress and at 30-min recovery	[65]
Kumarathurai *et al*.	2016	Patient with T2D and stable CAD	41	Liraglutide	Liraglutide did not improve LV ejection fraction when compared to placebo	[66]
Kumarathurai *et al*.	2021	Patients with CAD and newly diagnosed T2DM	40	Liraglutide	Liraglutide did not improve diastolic function parameters in subjects with T2DM, CAD, and preserved LVEF	[67]
Myat *et al*.	2021	Patients with chronic stable angina	22	Liraglutide	Liraglutide did not improve exercise tolerance or hemodynamics compared with saline placebo during serial treadmill testing	[68]
Suhrs *et al*.	2019	Female overweight patients with CMD and angina symptoms	29	Liraglutide	Liraglutide did not alleviate angina and improve coronary microvascular function	[69]
Chen *et al*.	2016	Patients with STEMI undergoing PCI	210	Liraglutide	Liraglutide lowers the prevalence of no-reflow as compared with the control group, and the incidence of MACE is no different	[70]
Lønborg *et al*.	2012	Patients with STEMI and TIMI flow 0/1	148	Exenatide	Exenatide reduces infarct size only when the duration of ischemia before primary PCI is less than 132 mins	[71]
Nikolaidis *et al*.	2004	Patient with AMI and LVEF $<$40% after successful reperfusion	21	GLP-1 (7-36)	GLP-1 significantly improved LVEF (from $29 \pm 2\%$ to $39 \pm 2\%$, $p < 0.01$) compared with control subjects	[73]
Chen *et al*.	2016	Patient with STEMI undergoing PPCI	77	Liraglutide	Liraglutide increases salvage index and reduces infarct size	[74]
Chen *et al*.	2015	Patient with STEMI undergoing PPCI	85	Liraglutide	Liraglutide increases LVEF at 3 months	[75]
Chen *et al*.	2016	Patient with NSTEMI	90	Liraglutide	Liraglutide increases LVEF at 3 months	[76]
Lønborg *et al*.	2012	Patients with STEMI and TIMI flow 0/1	172	Exenatide	Exenatide increases salvage index	[72]
Woo *et al*.	2013	Patients with STEMI and TIMI flow 0	116	Exenatide	Exenatide reduces infarct size, and biomarkers rise	[77]
Roos *et al*.	2016	Patients with STEMI and TIMI flow 0/1. T2DM was excluded.	91	Exenatide	No difference was found in infarct size	[78]
Pfeffer *et al*.	2015	Patients with T2DM and recent ACS	6068	Lixisenatide	No significant between-group differences in the rate of hospitalization for heart failure or the rate of death	[79]

Abbreviation: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CMD, Coronary microvascular dysfunction; LAD, Left anterior descending artery; LV, left ventricular; LVEF, left ventricular ejection fraction; NSTEMI, non-ST- elevation myocardial infarction; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; T2DM, Type 2 diabetes mellitus; TIMI, thrombolysis in myocardial infarction.

tion is that GLP-1 may indirectly improve myocardial capillaries through the inhibition of myocardial hypertrophy [38,39]. Currently, large randomized controlled trials investigating the influence of GLP-1 on coronary blood flow in CAD patients are lacking, and the available data is derived from small-sample studies with varying inclusion criteria. Additional studies are warranted to examine the role of GLP-1-based therapies in addressing issues such as coronary spasm, slow flow, and no flow, which are increasingly becoming angiographic phenomena in the treatment of CAD [40].

5. GLP-1-Based Therapies and Ischemia-Reperfusion Injury

Ischemia-reperfusion (I/R) injury is the main pathological manifestation of CAD that causes myocardial damage. Currently, there is no effective medication to defend the cardiovascular system against I/R. Rapid increases in intracellular cAMP and calcium levels brought on by GLP-1 activation trigger PKA activation and phosphorylation of cyclic AMP response element binding protein (CREB). GLP-1R agonists can modulate the activity of CREB by stimulating cytoplasmic-to-nuclear translocation of target of rapamycin (TOR) complex-2 (TORC2) [16]. Moreover, GLP-1 receptor activation also activates PKC, extracellular regulated kinase 1/2 (ERK1/2), AMPK, and phosphoinositide 3-kinase (PI3K) [41]. These pro-survival intracellular signaling pathways and proteins protect against I/R injury.

The impact of GLP-1-based therapy on ischemia-reperfusion (I/R)-induced cardiac damage has been largely demonstrated in animal models [28,42–52]. However, these studies have exhibited variable findings, with some reporting positive outcomes, while others have shown neutral or negative effects (as shown in Table 2, Ref. [28,42,44,45,47,48,50–59]). For example, Kavianipour *et al.* [53] showed that the administration of recombinant GLP-1 did not limit infarct size during I/R when utilizing a porcine heart model. Similarly, in other studies using porcine ischemia-reperfusion models induced by balloon occlusion, liraglutide also exerts neutral properties on infarct size [54,55]. Timmers *et al.* [56] demonstrated that exenatide treatment reduced myocardial infarct size in Dalland Landrace pig I/R models. The variation in the consequences of GLP-1 on I/R injury may also be attributed to variations in dosing times, whether it was given before or after the injury or the duration and methods used to artificially obstruct coronary blood flow.

Moreover, the protective effects of GLP-1 seem to be independent of its receptors [28]. In the C57BL/6J mice I/R model, pre-treatment with GLP-1 (28-36) reduces myocardial infarct size through the suppression of inhibiting mitochondrial trifunctional protein-α, and the protective property was preserved in Glp1r$^{-/-}$ mice [57]. Ban and colleagues [58] revealed that the protective effects of exendin-4 were abolished in cardiomyocytes treated with exendin (9–39), as well as in cardiomyocytes isolated from GLP-1r$^{-/-}$ mice. Also, GLP-1 (9-36), a GLP-1 metabolite made by enzymatic cleavage that was thought to be biologically inactive at first, reduced the size of an infarct after I/R in a rat model and protected cardiomyocytes from GLP-1r$^{-/-}$ mice. In a clinical trial conducted by Besch *et al.* [59], the researchers did not observe additional cardioprotective effects on I/R injury with exenatide versus insulin in patients undergoing coronary artery bypass grafting (CABG) surgery.

The disparities between the results mentioned above can be attributed to several factors. Firstly, different dosing phases may have led to varying results. Several studies have suggested that early drug administration exhibits the greatest protection against myocardial I/R injury. Secondly, differences in results may be due to inadequate doses. Clinical studies of drugs often use off-label doses, which presents challenges in establishing comparability between clinical and pre-clinical studies. Finally, other interfering or confounding factors may have overshadowed the beneficial impact of GLP-1-based therapy. For instance, the aforementioned randomized controlled trial utilized insulin in both the control and study groups, and it is well-established that insulin protects against I/R injury [60,61]. Therefore, more research is needed to evaluate the potential benefits of various GLP-1R agonists in the context of I/R damage.

6. Clinical Data on Coronary Artery Disease from GLP-1-Based Therapies.

6.1 Chronic Coronary Syndromes

Evidence on the impact of GLP-1RAs on outcomes in chronic coronary syndromes (CCS) is still minimal (as shown in Table 3, Ref. [62–79]), particularly from clinical trials. Research has demonstrated that GLP-1 protects against ischemic dysfunction as evaluated by left ventricular (LV) conductance catheter in patients with CAD [62,63]. Read *et al.* [64] did a study that backs up this claim. They found that GLP-1 therapy protects the heart against ischemic LV dysfunction in patients with CAD who are waiting for revascularization. Furthermore, the benefits were found to be sustained even during a hyperglycemic hyperinsulinemic clamp (HHC), indicating that they are independent of glycemic control [65].

In a randomized controlled trial (RCT) with patients who had stable CAD, preserved LVEF, and T2DM, giving liraglutide for 12 weeks failed to show a significant improvement in left ventricular ejection fraction (LVEF) [66]. However, no decline in cardiac function was observed, suggesting that liraglutide appears to be a safe therapeutic alternative when used in combination with metformin therapy in these patients. In another RCT conducted by the same research team, it was concluded that liraglutide did not have any impact on diastolic function [67]. In the LIONESS study [80], patients with chronic stable angina were given liraglutide for 3 plus 3 weeks to see how

it affected exercise hemodynamics during exercise stress testing. Results showed that liraglutide had no effect on any improvements in parameters of hemodynamic performance during exercise or the magnitude of ST-segment depression seen at peak exercise [68]. Another open-label study that enrolled women with coronary microvascular dysfunction in which participants were treated with liraglutide for 3 months showed liraglutide failed to produce any improvements in symptoms or coronary flow velocity reserve (CFVR) [69].

6.2 Acute Coronary Syndromes

Despite having a cardioprotective effect, the impact of GLP-1 based therapies on ACS has not been as strong as anticipated from pre-clinical studies. However, recent research indicates that GLP-1R agonists have a favorable cardiovascular safety profile for patients with T2DM. A prospective study reported that pre-treatment with liraglutide demonstrated a significant association with a reduced occurrence of no-reflow in patients with ST-elevation myocardial infarction (STEMI) as compared to placebo (5% *vs*. 15%, $p = 0.01$) [70]. However, the primary endpoint of the study was to determine the prevalence of angiographic no-reflow as assessed by subjective TIMI flow. Other objective assessment techniques might provide a clearer understanding of microvascular injury. Following a 3-month period of observation, there was no significant difference in the occurrence of major adverse cardiovascular events (MACE) between the liraglutide group and the control group (8% *vs*. 15%, $p = 0.12$) [70].

Studies indicate that administering cardioprotective medications early during reperfusion provides optimal protection from I/R injury [81]. In a randomized trial conducted by Lønborg *et al*. [71,72], the administration of exenatide during the period of ischemia and continuing for 6 hours reduced final infarct size among patients with STEMI and a brief ischemic duration ($\leq$132 minutes). However, patients with a prolonged ischemic delay (>132 minutes) did not exhibit any cardioprotective effect. Nikolaidis *et al*. [73] demonstrated that administering recombinant GLP-1 by continuous infusion for 72 hours after successful reperfusion improved LV function in patients who had experienced acute myocardial infarction (AMI).

Another clinical trial conducted to evaluate the role of liraglutide on reperfusion injury in patients with STEMI who underwent primary PCI found that administering liraglutide before intervention and maintaining it for one week resulted in an increased salvage index and improved infarct size after 3 months. Similarly, there was no difference noted in the incidence of MACE during the half-year follow-up period [74]. Moreover, one week of subcutaneous liraglutide treatment in both STEMI and non-STEMI patients revealed an enhancement in LVEF during a subsequent 3-month follow-up period [75,76]. Two studies conducted in a population of patients with STEMI who underwent primary PCI suggested that adjunctive exenatide therapy could also limit infarct size and increase salvage index [72,77]. The findings of these abovementioned studies differ from those of a similar randomized clinical trial examining exenatide, with no apparent difference in final infarct size (18.8 ± 13.2 *vs*. 18.8 ± 11.3% of left ventricular mass, $p = 0.965$) [78].

The ELIXA trial (The Evaluation of Lixisenatide in Acute Coronary Syndrome) [82] provided high certainty evidence that treatment with lixisenatide has a neutral cardiovascular profile for patients with T2DM who recently experienced ACS. The agent had no substantial impact on the rate of MACE or any other adverse events, including hypoglycemia, pancreatitis, pancreatic neoplasms, or allergic reactions. Although there were only 2 years of follow-up in this clinical setting, enough cardiovascular events were observed to rule out a significant non-glycemic cardiovascular benefit [79]. Clinical evidence also suggests that GLP-1-based treatments have a protective impact on cardiovascular outcomes in diabetics with either STEMI or non-STEMI [83,84]. A meta-analysis including six RCTs suggested that GLP-1R agonists improved LVEF by 2.46 [95% CI: 0.23–4.70%] and reduced infarct size in both grams and as a percentage of the area at risk [WMD –5.29, 95% CI: –10.39 to –0.19; WMD –0.08, 95% CI: –0.12 to –0.04, respectively] when compared to placebo [85].

7. Cardiovascular Outcomes of Liraglutide and Semaglutide

In the LEADER trial (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes), liraglutide 1.8 mg (Victoza) reduced the risk of the primary outcome (cardiac death, myocardial infarction, or stroke) by 13% in diabetics with high cardiovascular risk compared to placebo [86]. Based on these significant cardiovascular benefits, in 2017, the European Medicines Agency incorporated the outcomes derived from the LEADER trial into the prescription label for the 3 mg dosage of liraglutide (Saxenda) [87]. Although some studies suggest GLP-1 receptor agonists demonstrate a dose-response relationship in HbA1c reduction [88] and weight loss [89], whether higher doses can further reduce cardiovascular events needs further investigation.

Results from the SUSTAIN 6 trial (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) demonstrated that injectable semaglutide, when compared to placebo, resulted in a 26% relative and a 2.3% absolute reduction in the risk of the 3-points MACE composite endpoint in diabetics with CAD or at high atherosclerotic cardiovascular disease (ASCVD) risk [90]. In the PIONEER 6 trial (Peptide InnOvatioN for Early diabEtes tReatment), treatment with oral semaglutide in diabetics with high cardiovascular risk reduced the occurrence of MACE by 21% and significantly reduced cardiovascular death by 53% compared to placebo [91]. With the FDA approval of Wegovy (semaglutide) injection for chronic

weight management in obese or overweight adults in 2021 [92], semaglutide appears to have the trend of becoming one of the most widely used GLP-1 receptor agonists. Another ongoing SOUL (Semaglutide cardiOvascular oUtcomes triaL) trial enrolled 9650 participants, with 70.7% having a history of coronary heart disease, the results of which will provide evidence on the cardiovascular effects of oral semaglutide in patients with T2DM and established ASCVD [93].

8. Conclusion and Future Perspective

A multitude of studies of GLP-1-based interventions have shown beneficial effects on cardiovascular parameters that go well beyond its classical identification as a hypoglycemic drug. Several GLP-1R agonists, such as liraglutide, albiglutide, semaglutide, and dulaglutide, have been recommended to reduce the risk of major adverse cardiovascular events in patients with T2DM and established ASCVD or multiple risk factors for ASCVD [94]. Therefore, larger and longer-term randomized trials with clinical endpoints, such as cardiovascular morbidity and mortality, should be performed to verify the cardioprotective benefit of adjunctive GLP-1-based therapies during all periods of heart attack. However, the translation of experimentally promising results into clinical therapy has proven to be challenging. A new paradigm is required to overcome the barrier of translating pre-clinical findings on GLP-1-based therapies into practical applications.

Three elements are more crucial. First, patients, especially with STEMI, must be able to survive malignant arrhythmias. GLP-1 may provide an anti-arrhythmic effect, including in ischemia/reperfusion-induced ventricular arrhythmias [95]. Secondly, infarct size must be restricted. The best way to treat STEMI is with primary percutaneous coronary intervention to get the blood flow back to the coronary artery as soon as possible. However, this is paradoxically associated with reperfusion injury due to the generation of reactive oxygen metabolites and proinflammatory neutrophil infiltrates, which can exacerbate apoptosis and cell death. There is no standard therapy for myocardial protection following reperfusion in acute myocardial infarction. Even though different ways that GLP-1 protects the heart are biologically plausible and have shown promising results in experiments, they still need to be confirmed in large-scale clinical trials. Thirdly, the prognosis and quality of life of patients with CAD must be improved. A general goal in management includes improved symptoms with hemodynamic stabilization and increased use of evidence-based therapies to reduce recurrent hospitalization and mortality. Due to their inotropic and chronotropic properties [96], GLP-1R agonists might be selected as an add-on therapy to improve myocardial function and remodeling in CAD patients with or without diabetes.

In conclusion, currently, GLP-1 is a promising option with benign cardiovascular safety for the treatment of T2DM and coexistent CAD. Nevertheless, larger and longer-term well-designed randomized control trials of both cardiovascular morbidity and mortality are needed to evaluate GLP-1R agonist as a cardioprotective agent and the population in whom it will work best.

Author Contributions

QX and JW prepared the manuscript and tables. KH helped with references collection. LZ and WL designed manuscript outline and revised manuscript. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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