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The Efficacy and Safety of GLP-1 Receptor Agonists in the Treatment of Chronic Heart Failure with Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Keywords: Chronic heart failure; Type 2 diabetes mellitus; GLP-1 receptor agonists; Efficacy; Safety

Abstract: The efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in chronic heart failure (CHF) and type 2 diabetes mellitus (T2DM) patients were evaluated by performing a systematic review. Search of relevant literature was performed using five databases: PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, and VIP, up to February 1, 2026, and filtered based on the pre-established inclusion and exclusion criteria. Randomized controlled trials (RCTs) were also incorporated, and the efficacy and safety of GLP-1RAs were analyzed in all aspects of fasting blood glucose, glycated hemoglobin, left ventricular ejection fraction (LVEF), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and adverse reactions. Six RCTs were finally selected to be included in the systematic review and meta-analysis. The findings indicated that GLP-1 RAs could significantly lower fasting blood glucose and glycated hemoglobin levels among patients with CHF and T2DM. Simultaneously, after treatment, LVEF had a tendency to go up, and NT-proBNP levels had a tendency to decline, implying possible advantages in enhancing the functioning of the heart and minimizing the burden of heart failure. None of the included studies reported any serious safety concerns, and the most frequent adverse events were mild-to-moderate gastrointestinal symptoms. The GLP-1 receptor agonist has shown good glucose-lowering effects in patients with chronic heart failure and type 2 diabetes mellitus, and can have positive effects on heart function, which is a promising aspect of its clinical application. Nevertheless, due to the small number of existing studies and differences in the size of the samples and the quality of the studies, more large-scale, multi-center, high-quality RCTs should be conducted to verify their effectiveness and safety.

1. Introduction

Chronic heart failure (CHF) is a multifactorial clinical state, which is caused by structural or functional cardiac disorders that compromise ventricular filling or ejection capacity and is accompanied by such symptoms as dyspnea, tiredness, water retention, and limited physical activity

tolerance [1]. Type 2 diabetes mellitus (T2DM) is a frequent and relevant comorbidity among patients with CHF, and the two diseases are closely related in terms of pathophysiological processes, risk factors, and clinical outlooks [2]. As epidemiological investigations have demonstrated, people suffering from T2DM have much greater chances of developing congestive heart failure, which suggests that diabetes can be a strong contributor to the development of heart failure [3]. Coexisting diabetes in patients with CHF has been linked with poorer adverse clinical results such as hospitalisation due to heart failure, cardiovascular events, and mortality [4]. Moreover, patients with CHF and T2DM usually have concomitant obesity, kidney dysfunction, vascular disease, and metabolic disorders, which add to the disease burden [5]. The factors contribute to not only making treatment more complicated but also decreasing the level of exercise, repeated hospitalizations, restricting daily activities, and thus having a significant impact on quality of life and long-term prognosis [6].

Multiple factors contribute to the development and progression of CHF with T2DM, such as aging, obesity, hypertension, coronary atherosclerotic heart disease, chronic kidney disease, and long-term poor glycemic control [5]. Diabetic myocardial fibrosis, myocardial energy metabolism disorder, and myocardial remodeling are promoted by diabetes through various mechanisms, including insulin resistance, glucotoxicity, lipotoxicity, oxidative stress, and chronic inflammation [2]. Conversely, persistent sympathetic nervous system activity and activation of the renin-angiotensin-aldosterone system in the state of CHF may also worsen insulin resistance and glucose metabolism disturbances, which creates a vicious circle wherein CHF and diabetes feed on one another [5]. In this regard, incretin hormones and associated peptide hormones have received an increasingly significant amount of interest, and one of these is glucagon-like peptide-1 (GLP-1), a crucial endogenous peptide hormone that controls glucose homeostasis, insulin secretion, glucagon release, and gastric emptying and appetite [7]. Earlier mechanistic investigation has indicated that the GLP-1 and its receptor signaling pathway does not only play the role in regulating glucose metabolism, but it might also influence vascular functions, myocardial energy metabolism, inflammatory responses, and myocardial protection after ischemic damage [8]. Thus, the management of CHF with T2DM cannot be restricted to only glycemic control but should be holistic to address heart failure signs as well as cardiovascular risk, renal function, weight management, and drug safety [9]. Over the last several years, diabetes treatment consensus and cardiovascular guidelines have also highlighted the importance of choosing glucose-lowering drugs that have proven cardiorenal metabolic advantages based on the presence of coexisting CHF, atherosclerotic cardiovascular disease, or chronic kidney disease [10]. Under these circumstances, GLP-1 receptor agonists (GLP-1 RAs) have become a prominent medicine category as a result of their ability to reduce blood sugar, lose weight, and possibly protect the heart in a patient with cardiovascular risk who has type 2 diabetes mellitus [1].

GLP-1 receptor agonist is a type of glucose-lowering medication that was based on the research of the incretin system, and its major effects are glucose-dependent stimulation of insulin production, blocking of glucagon release, slowing of gastric emptying, and reduction of appetite [11]. Since endogenous GLP-1 has a low half-life, initial development of drugs focused on extending the duration of action of GLP-1 analogues, increasing resistance to degradation by dipeptidyl peptidase-4 and enhancing ease of administration [12]. The development of GLP-1 RA has shifted in terms of drug structure modification and formulation technology, where short-acting formulations have been replaced with long-acting formulations, weekly formulations, and oral formulations, with examples being exenatide, liraglutide, lixisenatide, dulaglutide, albiglutide, and semaglutide [13]. GLP-1 RAs have been found effective in reducing glycated hemoglobin levels in patients with T2DM in clinical use, and they also have some benefits in regulating weight [14]. Head-to-head RCTs have indicated that various GLP-1 RAs vary in terms of glucose-lowering strength, extent of

weight loss, regimen of dosage, and gastrointestinal side effects, implying that the drug class has an inherent heterogeneity [15]. Cardiovascular outcome trials have also shown the ability of GLP-1 RAs like liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide to minimize the occurrence of major cardiovascular events in the high-risk T2DM population [16]. Nevertheless, it is not clear whether GLP-1 RAs cause changes in the outcomes related to CHF and their cardiovascular effects are more evident in regard to atherosclerosis and some renal outcomes [17]. Early research had indicated that GLP-1 infusion could help to enhance LVEF and functional performance in patients with CHF [18]. Nonetheless, later RCTs that have specifically focused on patients with CHF have shown inconsistent findings, e.g., Liraglutide did not clearly enhance left ventricular systolic function in patients with stable CHF [19]. In patients with end-stage heart failure with diminished ejection fraction, liraglutide also did not demonstrate significant improvement in clinical stability, and its safety profile should be carefully evaluated [20]. Furthermore, albiglutide has not adequately shown significant changes in cardiac performance, myocardial metabolism, and exercise tolerance in patients with chronic heart failure with reduced ejection fraction in studies [21].

To sum up, the use of GLP-1 RAs has gathered considerable clinical data in the treatment of T2DM and cardiovascular disease risk reduction, but it is not yet clear whether they are effective and safe in people with CHF and T2DM [22]. Previous studies indicate that GLP-1 RAs might confer possible advantages in terms of glycemic control, weight loss, anti-inflammatory action, and myocardial metabolism; nevertheless, there have been no uniform findings concerning how they affect the hospitalization rates of heart failure, left ventricular function, exercise capacity, and adverse events related to heart failure [23]. Consequently, the objective of the current study was to perform a systematic review and meta-analysis on the basis of RCTs to thoroughly assess the effectiveness and safety of GLP-1 RAs in patients with CHF and T2DM with particular regard to outcome indicators such as glycemic control, LVEF, NT-proBNP, exercise tolerance, hospitalization due to heart failure, cardiovascular events, and adverse reactions in order to offer evidence-based assistance in individualized drug choice and medical care in individuals with CHF and diabetes.

2. Materials and methods

2.1 Search strategy

The given systematic review has been done based on the PRISMA 2020 statement. To find appropriate literature, the following five databases were explored: PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang. The deadline for the search was February 1, 2026. The search keywords that were used are as follows: chronic heart failure with diabetes, ischemic chronic heart failure with diabetes, stroke, GLP-1 agents, rosuvastatin, atorvastatin, and randomized controlled trial.

2.2 Inclusion and exclusion criteria

Inclusion criteria:

(1) Original studies published in peer-reviewed journals;

(2) Subjects were adults diagnosed with ischemic stroke;

(3) Included studies were randomized controlled trials (RCTs);

(4) The control group was given usual care for strokes as well as atorvastatin, whereas the experimental group was given usual care for strokes as well as rosuvastatin.

Exclusion criteria:

(1) Study types including meta-analyses, reviews, conference abstracts, and case reports;

(2) Studies with insufficient data that could not be obtained after contacting the authors;

(3) Patients with metal implants, cardiac pacemakers, or cochlear implants;
(4) Patients with contraindications to GLP-1 drugs.

2.3 Study selection

The obtained records of the databases were loaded into EndNote 9.0 reference management software. The screening was done after removing duplicates. The titles, abstracts, and full texts were reviewed independently, and the articles were included based on the inclusion and exclusion criteria, and the reasons for exclusion were recorded per article.

2.4 Quality assessment

The Cochrane Risk of Bias (ROB) tool was applied to evaluate the methodological quality of the included RCTs. The evaluation of evidence was done based on the context of the study aim, study design, study subjects, observation or measurement, outcome analysis, quality control, and results presentation. Following the quality assessment, Review Manager 5.3 software was applied to create a quality summary figure and the individual quality assessment findings.

2.5 Data extraction and analysis

The studies that passed the quality assessment underwent the procedure of extraction and analysis of their data. The extracted study properties were: clinical properties (i.e., first author and the year of publication, sample size (experimental/control), treatment results); and measurements of outcomes (lipid levels, carotid intima-media thickness (IMT) score, and National Institutes of Health Stroke Scale (NIHSS) score). Following the quality assessment, forest plots were constructed with the help of the Review Manager 5.3 program.

3. Results

3.1 Study selection results and characteristics of included studies

The systematic search has produced a total of 79 records. When deduplicated, 69 records were available to be screened initially. After eliminating 20 records that were not eligible, 49 full-text articles were evaluated according to eligibility criteria. Finally, 6 randomized controlled trials [19,24-28] were included in the review, where the sample sizes were between 15-4,732 patients. The controls used were placebo, acarbose, or conventional treatment, whereas the interventions used were liraglutide, semaglutide, and albiglutide. Outcome measurements that were primary included blood glucose (fasting blood glucose, glycated hemoglobin), left ventricular function (left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular end-systolic diameter), N-terminal pro-B-type natriuretic peptide, and 6-minute walk test (Table 1, Figure 1).

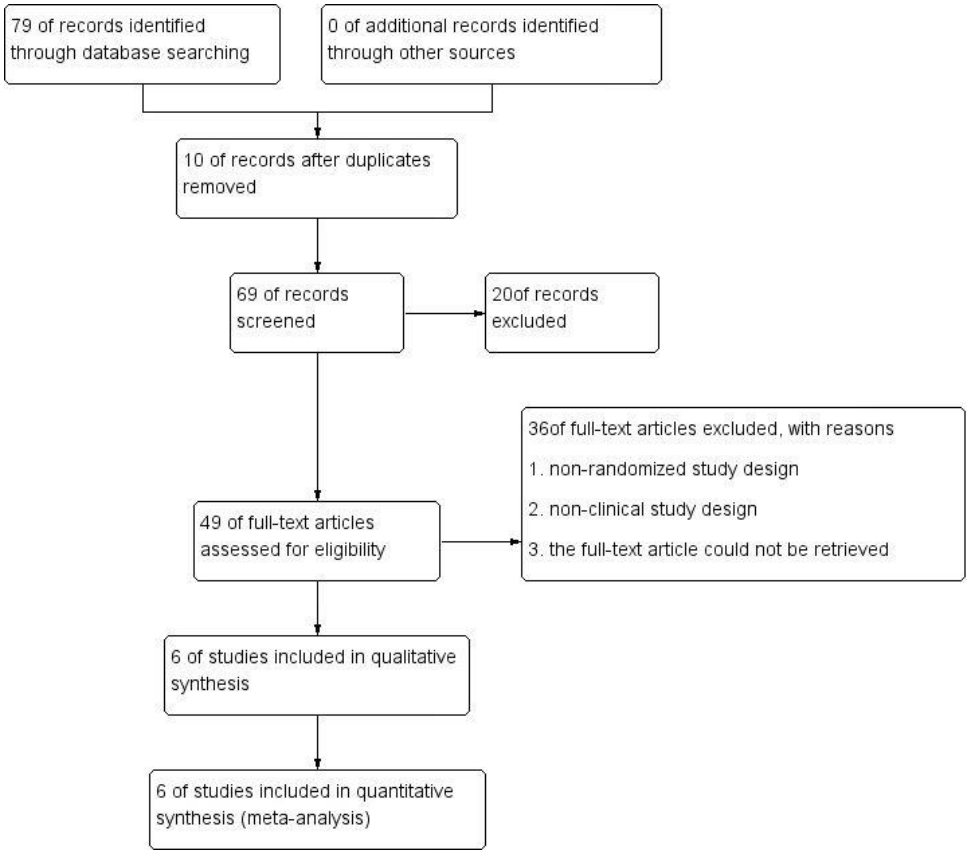
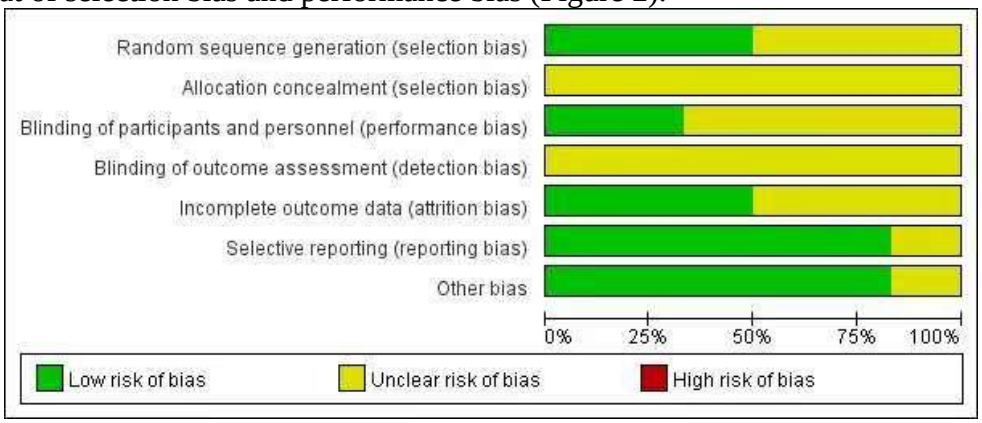


Figure 1 Literature flow diagram

3.2 Quality assessment results

Evaluation was conducted using the Cochrane Risk of Bias tool. Each of the included studies was an RCT, and most of the randomization techniques that were used were clearly stated. Nevertheless, allocation concealment and blinding were not completely documented, and other studies had a smaller sample size. The total methodological quality has been rated as moderate with a slight threat of selection bias and performance bias (Figure 2).



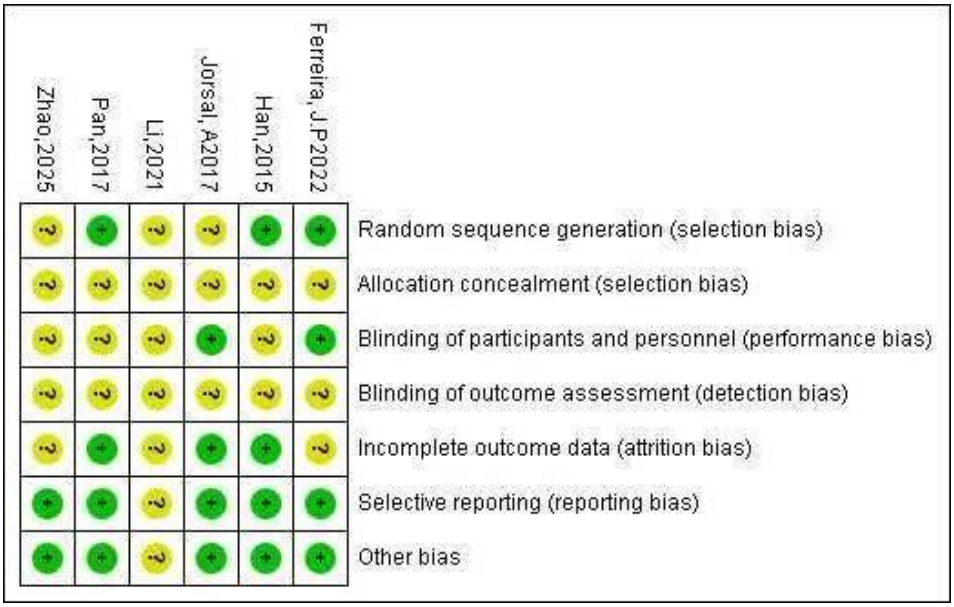


Figure 2 Quality assessment report of the included literature

3.3 Improvement in fasting blood glucose levels

The pooled study of four found that GLP-1 receptor agonist could significantly decrease fasting blood glucose levels (MD = -0.90 mmol/L, 95% CI -1.39 to -0.41, P < 0.001), and this indicated a significant improvement in glycemic control in patients with chronic heart failure and type 2 diabetes mellitus. In general, the outcomes were similar in all the studies, however, heterogeneity was observed to be significant (I2 = 95%), which can be explained by the difference in the initial level of blood glucose, the interventions provided to the groups, and the duration of treatment (Figure 3).The detailed pre- and post-intervention fasting blood glucose values for each included study are shown in Table 2.

Table 1 Characteristics of Included Studies

First Author/ Year	Sample Size (Experimental/ Control)	Study Type	Outcome Measures	Conclusions
Han, 2015	15/16	RCT	BMI, Waist Circumference (WC), Fasting Blood Glucose (FBG), Postprandial Blood Glucose (PBG), Hemoglobin Glycosylated (HbA1c), Fasting Insulin (FIN), 6-Minute Walk Test (6MWT), Left Ventricular Ejection Fraction (LVEF), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), and incidence of adverse reactions	Liraglutide has proven to be effective in treating patients with chronic heart failure who have recently been diagnosed with type 2 diabetes and is as safe as acarbose.
Li, 2021	63/57	RCT	Fasting blood glucose (FBG), 2-hour postprandial glucose (2hPG), N-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9), number of adverse reactions	The drug liraglutide has been shown to be highly effective in improving the condition of patients suffering from chronic heart failure with T2DM, it has shown a significant suppression of inflammatory cytokine release, improvement of glycemic control, and its use is linked to a low rate of adverse effects.

Pan, 2017	64/64	RCT	Cardiac function parameters (LVEDD, LVESD, LVEF, NT-proBNP) and glycemic parameters (fasting blood glucose FBG, 2-hour postprandial glucose PBG, glycated hemoglobin HbA1c)	The use of liraglutide has a significant effect on both glycaemic and cardiac function parameters in chronic heart failure patients who have recently been diagnosed with type 2 diabetes, which shows that it is clinically effective and should be adopted by many.
Zhao, 2025	40/40	RCT	Glucose fasting (FPG), 2-hour postprandial glucose (2hPG), glycated hemoglobin (HbA1c), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), N-terminal pro-B-type natriuretic peptide (NT-proBNP), 6-minute walk test (6MWT), overall clinical response rate	The semaglutide is effective in controlling blood glucose levels and improving cardiac function-related parameters in people with type 2 diabetes and chronic heart failure, and has a positive response in terms of clinical effectiveness.
Ferreira , 2022	4731/4732	RCT	The primary endpoint is a composite of cardiovascular death or heart failure hospitalization; secondary endpoints are cardiovascular death, hospitalization due to heart failure, sudden cardiac death/pump-failure death, all-cause death, and atherosclerotic-related composite endpoints	Albiglutide decreased the incidence of heart failure-related events in people who have never had a history of heart failure, but it does not prevent heart failure in people with a previous history of heart failure. GLP-1RAs decrease atherosclerosis but they do not reduce heart failure results in patients with existing heart failure.
Anders Jorsal, 2016	122/119	RCT	Main result: difference between the left ventricular ejection fraction (LVEF) at baseline and 24 weeks. Secondary results: peak systolic tissue velocity, global longitudinal strain, left ventricular end-systolic/end-diastolic volumes, diastolic function, 6-minute walk test, NT-proBNP, blood pressure, quality of life, and adverse events	When compared to placebo, liraglutide failed to enhance left ventricular systolic function in stable chronic heart failure patients with or without type 2 diabetes. It decreased body weight, enhanced glycemic control, and enhanced exercise capacity, but had a significant increase in heart rate as well as a higher probability of severe cardiac adverse events. The use of liraglutide in this heart failure population needs additional research.

Note: RCT, randomized controlled trial.

Table 2 Information Extraction Table

First author/ Year	Fasting blood glucose level (Experimental/Control)		Left ventricular ejection fraction (Experimental/Control)		Glycated hemoglobin level (Experimental/Control)		NT-proBNP level (Experimental/Control)	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Han, 2015	7.7±0.7/ 7.9±0.4	6.8±0.7/ 7.5±0.8	42.6±4.7/ 41.2±4.4	44.7±5.7/ 41.5±4.1	7.3±0.8/ 7.4±0.7	6.6±0.6/ 6.8±0.5	370.0±55.0/ 373.0±38.0	358.0±56.0/ 374.0±32.0
Li, 2021	9.73±1.23/ 9.74±1.21	6.98±0.36/ 7.58±0.39	41.76±2.09/ 41.74±2.02	44.87±3.19/ 42.87±3.16			373.84±21.57/ 373.58±21.58	350.74±18.62/ 362.57±18.67
Pan, 2017	10.3±2.6/ 10.2±1.7	5.8±0.39/ 7.12±0.3		41.39±5.88/ 48.81±5.29	9.92±0.3/ 9.82±0.6	6.41±0.1/ 7.31±0.8		763.53±93.66/ 362.64±52.42
Zhao, 2025	9.48±1.53/ 9.46±1.49	5.61±1.03/ 6.56±1.36	44.76±5.93/ 44.86±6.09	50.62±6.73/ 47.55±6.66	10.21±1.95/ 10.26±2.04	7.12±2.24/ 8.63±2.43	986.76±101.48/ 982.49±100.61	759.37±46.59/ 854.82±55.96
João Pedro Ferreira, 2022								

Anders Jorsal, 2016		33.7±7.6%/ 35.4±9.4%	34.4±7.6%/ 36.9±9.4%	5.9±0.7%/ 6.0±0.8%	5.6±0.7%/ 6.1±0.8%	413(208-926)pg /mL / 388(153-880)pg /mL	351 (208-926) pg/mL / 466 (153-880) pg/mL

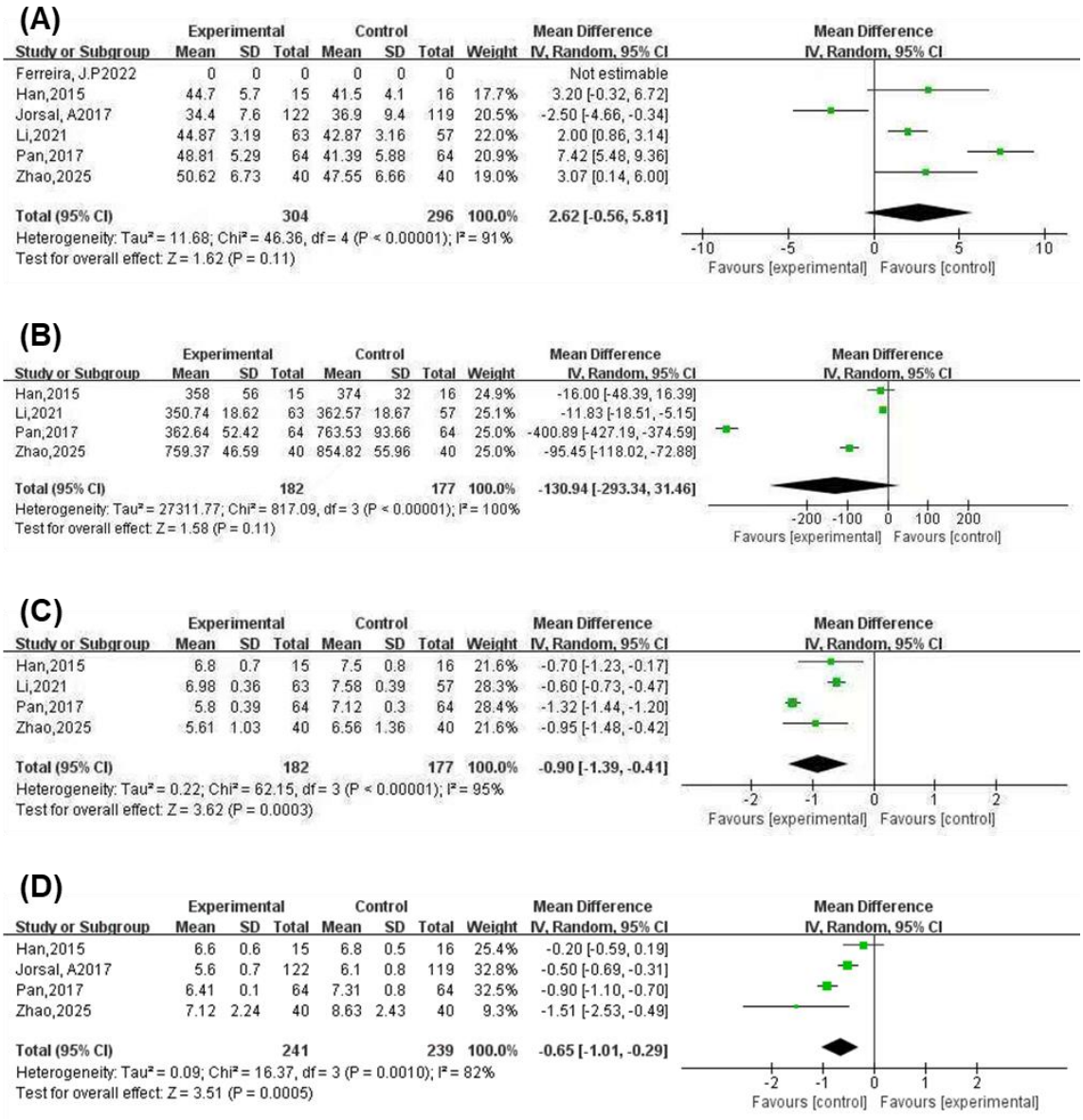


Figure 3 Forest plot: (A) The improvement of left ventricular ejection fraction, (B) The increase of NT-proBNP, (C) Improvement of fasting blood glucose levels (D) The increase of glycated hemoglobin

3.4 Improvement in left ventricular ejection fraction

Six articles presented the results of LVEF, of which five had data that could be included in pooling. In the pooled analysis, there was a tendency that with GLP-1 receptor agonists, LVEF improves, however, the change is not statistically significant (MD = 2.62%, 95% CI -0.56 to 5.81, P = 0.11, I2 = 91%). On the whole, it was suggested that there was a slight enhancement of left ventricular systolic function, but the heterogeneity between the studies was observed (Figure 3).

3.5 Improvement in glycated hemoglobin levels

The pooled analysis of four studies found that GLP-1 receptor agonists resulted in a significant decrease in HbA1c (MD = -0.65, 95% CI -1.01 to -0.29, P < 0.001), indicating that long-term glycemic control in the intervention group is superior to that in the control group. The heterogeneity among the studies was also very high (I 2 = 82%), and this might have been affected by the type of medications used as well as the baseline level of HbA1c in the patients (Figure 3).

3.6 Improvement in NT-proBNP levels

Four studies found that NT-proBNP decreased over time in the intervention group, however the combined effect was not statistically significant (MD = -130.94 pg/mL, 95% CI -293.34 to 31.46, P = 0.11, I 2 = 100%). These findings indicate that GLP-1 receptor agonists can be associated with some advantage in decreasing the burden of heart failure but are very heterogeneous (Figure 3).

4. Discussion

The research consisted of six randomized controlled trials and the systematic assessment of the effectiveness and safety of GLP-1RAs in people suffering from chronic heart failure and type 2 diabetes mellitus [19,24-28]. The findings of the meta-analysis demonstrated that the use of GLP-1RAs resulted in significant decreases in fasting blood glucose and HbA1c levels, which implied a high level of glycemic control in patients with CHF and T2DM. At the same time, the post-treatment trend of LVEF was an increase, and the trend of NT-proBNP levels was a decrease, which implies that there are some beneficial effects of GLP-1RAs on cardiac performance and ventricular loading in CHF patients besides enhancing glucose metabolism.

Considering the outcome measures considered in this research, the enhancement of metabolic parameters through GLP-1RAs was rather consistent. The lowering of fasting blood glucose and HbA1c means that these agents have effects on both short-term and long-term glycemic control. Glycemic control is an important aspect of therapy in the treatment of chronic heart failure and diabetes, as well as a prerequisite in the mitigation of myocardial metabolic disorders, inflammation, and ventricular remodeling among patients with chronic heart failure and diabetes [2]. Hence, GLP-1RAs can be used to alleviate myocardial injury caused by diabetes indirectly by improving the metabolism of glucose.

The results on the cardiac function were also clinically significant. The pooled LVEF result in the current study indicated an increased tendency of the treatment group in comparison with the control group, and the trend of effects in various individual studies confirmed the positive effect of GLP-1RAs on the left ventricular systolic function [24-27]. NT-proBNP is also a key indicator of ventricular wall stress and heart failure burden. According to most of the studies included in this review, NT-proBNP levels decreased after treatment and it indicates that GLP-1RAs can be helpful in decreasing cardiac load and improving the condition of heart failure [24,25,27]. Despite such heterogeneity among the studies, all these observations suggested the possible advantages of GLP-1RAs in cardiovascular performance in individuals with chronic heart failure and diabetes.

In general, the meta-analysis findings of this research indicated that GLP-1RAs were associated with a significant decrease in fasting blood glucose and glycated hemoglobin levels among patients with chronic heart failure and type 2 diabetes and confirmed the steady efficacy of GLP-1RAs to improve glucose metabolism. Also more crucially, the study has also noted the rising trend of left ventricular ejection fraction, and the declining trend of NT-proBNP levels. The findings implied that GLP-1RAs can be not only agents that lower glucose but also have the potential benefits on the cardiac function of patients with chronic heart failure and diabetes by improving the metabolic state,

reducing the ventricular load, and modulating the myocardial function.

4.1 Mechanisms of the GLP-1 receptor agonist as a therapeutic agent in patients with chronic heart failure and diabetes

The pathological process of chronic heart failure associated with type 2 diabetes is multifactorial, including insulin resistance, glucotoxicity, lipotoxicity, chronic inflammation, oxidative stress, endothelial dysfunction, neuroendocrine activation, and myocardial energy metabolism abnormalities [2]. GLP-1RAs can improve these pathological processes by exerting synergistic effects on various pathways and thus have a therapeutic effect in patients with chronic heart failure and diabetes.

To start with, GLP-1RAs can help relieve diabetes-associated myocardial injury by improving glucose metabolism. It is a major peptide hormone of the incretin system that can stimulate insulin secretion in a glucose-dependent fashion as well as suppress glucagon release, slow down gastric emptying, and decrease appetite [7]. Such a way of functioning serves to decrease glycemic variability and mitigate the harmful impact of glucotoxicity on cardiomyocytes, endothelium, and the microvascular system. Patients with chronic heart failure and diabetes frequently are insulin resistant and have dysfunctional myocardial energy use. GLP-1RAs could offer a more stable energy metabolic milieu to the myocardium by enhancing insulin sensitivity and glucose metabolism [29].

Thirdly, GLP-1RAs could also lead to a better heart failure condition by reducing weight and improving metabolic burden. Heart failure and type 2 diabetes are common diseases associated with obesity and visceral adiposity that can worsen volume overload, inflammation, and myocardial remodeling [2]. Liraglutide and semaglutide are examples of GLP-1RAs that have shown beneficial weight-loss effects in clinical trials [30]. The loss of weight has the potential to lower cardiac preload and afterload, increase exercise capacity, and possibly help ease the symptoms of heart failure and enhance their quality of life.

Moreover, GLP-1RAs might have a positive effect on heart performance due to anti-inflammatory and anti-myocardial remodeling. Low-grade inflammation is chronic in diabetes and can cause myocardial fibrosis, extracellular matrix deposition, and ventricular remodeling [8]. Some of the analysis reported indicated a reduction of inflammatory and matrix remodeling-related markers, IL-6 and MMP-9, following treatment with liraglutide, indicating that GLP-1RAs are able to improve myocardial structure and function by reducing inflammatory responses and reducing abnormal extracellular matrix remodeling [24]. Such a mechanism could be partially responsible for the improvement of the LVEF and the decline in the levels of NT-proBNP found in the present study.

According to some studies, GLP-1RAs could have cardiovascular protective mechanisms by enhancing vascular endothelial behavior and microcirculation status. Earlier research has shown that GLP-1 receptor signaling has been implicated as a regulator of vasodilation, endothelial function, coronary blood flow, and myocardial protection following ischemia-reperfusion injury [31]. Chronic heart failure and diabetes patients may suffer from microvascular disease and endothelial dysfunction, which aggravates myocardial ischemia and energy supply shortage. The enhancement of vascular function using GLP-1RAs could also assist to enhance myocardial perfusion and metabolic status.

Equally so, GLP-1RAs could be used directly or indirectly to control the energy metabolism of the myocardium and thus provide a therapeutic effect. The utilization of myocardial energy substrates is abnormal in heart failure conditions where there is a mismatch between fatty acid oxidation and glucose utilization, resulting in reduced myocardial contractility efficiency [8].

GLP-1-related signaling can enhance glucose uptake and energy utilization efficiency, allowing the myocardium to use a more favorable energy source in the face of the diabetic metabolic environment. Early clinical trials also have indicated that GLP-1 infusion may help increase cardiac function among patients with left ventricular dysfunction, offering preliminary evidence of the cardioprotective impact of GLP-1-based treatments [32].

Thus, the therapeutic effect of GLP-1RAs on chronic heart failure with diabetes does not rely on the glucose-lowering effect exclusively, but can also be exerted by several mechanisms, such as, glucose lowering, weight loss, anti-inflammation, endothelial function enhancement, myocardial energy metabolism regulation, and ventricular load decrease. It is this multi-target nature that is exactly why the GLP-1RAs have a potential therapeutic value in patients with chronic heart failure and diabetes.

4.2 The research progress of GLP-1 receptor agonists in the treatment of chronic heart failure complicated by diabetes

GLP-1RAs have been used originally as a treatment of type 2 diabetes to gain glycemic control, but since then there has been a broadening of their clinical use to include weight management, cardiovascular risk control, and renal protection [12]. Following the conclusion of several large cardiovascular outcome studies, the clinical utility of GLP-1RAs has not been restricted to decreasing HbA1c, but has been shown over time to have benefits to overall cardiorenal metabolic health [14].

A number of large cardiovascular outcome trials have established the good cardiovascular safety profile of GLP-1RAs and their usefulness to lower the risk of major adverse cardiovascular events in high-risk groups with type 2 diabetes. The LEADER trial has shown that liraglutide lowers the risk of serious cardiovascular events in high-risk individuals with type 2 diabetes [16]. In the SUSTAIN-6 trial, there were signals of cardiovascular benefit of semaglutide in people with type 2 diabetes [33]. REWIND, Harmony Outcomes, and AMPLITUDE-O studies also added to the benefits of dulaglutide, albiglutide, and efpeglenatide in diabetic subjects with a high cardiovascular risk [34-36]. Such lines of evidence have formed a significant basis of the application of GLP-1RAS to patients with chronic heart failure and diabetes.

Over the last few years, scientists have started to explore more deeply the consequences of GLP-1RAs on cardiac function factors and the burden of heart failure in individuals with heart failure. Initial investigations indicated that GLP-1 infusion enhanced left ventricular ejection fraction and functional levels in patients with chronic heart failure, which implied that GLP-1-related pathways could be involved in the control of myocardial function during heart failure [18]. Several randomized controlled trials conducted on Chinese patients with chronic heart failure and diabetes included in this research also demonstrated improvement of the parameters such as LVEF, NT-proBNP, fasting blood glucose, and HbA1c by different extents after treatment with liraglutide or semaglutide [24-27]. The results of the study are similar to the pharmacological effects of GLP-1RAs on glucose metabolism, body weight reduction, and inflammation burden mitigation.

In terms of guidelines and consensus statements, diabetes treatment plans have been evolving over time in such a way that they are no longer focused on glucose-lowering only but instead on comprehensive management through cardiovascular and renal perspectives. The ADA/EASD consensus states that the use of glucose-lowering agents with proven cardiorenal benefits must be considered in patients with type 2 diabetes when making a decision to use them and depends on whether the patient has atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease [10]. The ESC guidelines on diabetes and cardiovascular diseases also support the use of

GLP-1RAs as a significant treatment choice in people with type 2 diabetes and cardiovascular risk [1]. GLP-1RAs can be used in patients with chronic heart failure and diabetes to simultaneously enhance glycemic control, body weight, and other cardiometabolic variables, and therefore may have promising clinical applications.

In general, the studies on GLP-1RAs in the therapy of chronic heart failure in people with diabetes are slowly expanding to include metabolic-based end points as well as cardiac function-based and clinical outcome-based end points. These findings of this study revealed that the changes in fasting plasma glucose and HbA1c were quite evident, and positive tendencies in LVEF and NT-proBNP were also recorded. It implies that GLP-1RAs can have a double action of improving metabolism and improving cardiac function in patients who have chronic heart failure and diabetes. Additional research in the future to increase the size of samples, lengthen the duration of follow-ups, and perform stratified analyses based on heart failure phenotypes and GLP-1 RA subtypes will be useful in clarifying the clinical advantages.

4.3 Differences in efficacy among GLP-1RA subtypes

GLP-1RAs are a type of drug instead of being a single drug. The subtypes differ in the molecule structure, half-life, dose interval, features of receptor binding, efficacy in lowering glucose levels, efficacy in reducing weight, and cardiovascular reactions [14]. These variations can affect their clinical use in people suffering from chronic heart failure and diabetes.

Liraglutide is a long-acting GLP-1RA that is well established and used early with considerable proof of glucose lowering, weight loss, and cardiovascular effects. In the LEADER trial, it was shown that liraglutide decreased the risk of major adverse cardiovascular events in high-risk patients with type 2 diabetes [37]. Some of the studies involved in this analysis also utilized liraglutide as the intervention and found that there were decreases in fasting blood glucose and HbA1c, and some studies reported improvements in LVEF and NT-proBNP levels [24-26]. It indicates that liraglutide may provide holistic benefits to individuals suffering from chronic heart failure and diabetes by enhancing glucose metabolism, decreasing inflammation, and preventing myocardial remodeling.

Semaglutide is a GLP-1RA that has gained popularity over the last few years due to its strong glucose-lowering and weight loss properties. It was proposed that semaglutide had better cardiovascular results in people with type 2 diabetes during SUSTAIN-6 trial [33]. Head-to-head research has demonstrated that semaglutide is more effective than other GLP-1RAs in lowering the levels of HbA1c and body weight [38]. The paper by Zhao (2025) of this analysis indicated that fasting blood glucose, HbA1c, LVEF, and NT-proBNP were found to be lower after semaglutide treatment than the control group [27]. This suggests that semaglutide may be especially applicable in patients with chronic heart failure and diabetes with poor glycemic control, obesity, or high cardiometabolic risk.

Albiglutide is a prolonged-acting GLP-1RA which has also proven useful in cardiovascular outcome trials. Harmony Outcomes trial indicated that albiglutide lowers the risk of severe cardiovascular complications in people with diabetes type 2 and cardiovascular disease [36]. The paper by Ferreira et al. examined the impact of GLP-1RAs on heart failure-related outcomes in patients with a variety of heart failure histories, which adds valuable additional information to the use of this drug group in the heart failure population [28]. Even though the endpoints were different between the studies, there is still evidence of cardiovascular risk reduction using albiglutide, which suggests its possible clinical usefulness.

The difference in the efficacy of GLP-1RAs can also be associated with the length of action. Short-acting GLP-1RAs are more effective at delaying gastric emptying and have a much higher

advantage in postprandial glycemic control compared to long-acting GLP-1RAs which offer a steadier improvement of fasting blood glucose and HbA1c [14]. When it comes to chronic heart failure and diabetes therapy, longer-acting formulations and weekly doses might be more effective in improving adherence to treatment, decreasing fluctuations in glycemia, and achieving more stable metabolic benefits. The introduction of orally active drugs like semaglutide has seen the clinical availability and patient acceptance of GLP-1RAs increase even more.

Hence, there can be disparities between GLP-1RAs efficacy in people with chronic heart failure and diabetes. More early data have been collected on liraglutide, and semaglutide has shown significant findings in reducing blood sugar and body weight, and albiglutide has been researched related to cardiovascular results. The future research ought to also compare various GLP-1RAs on the basis of LVEF, NT-proBNP, 6-minute walk test, hospitalization due to heart failure, and quality of life to determine the most appropriate patient groups of each subgroup.

Moreover, this research has some drawbacks. Firstly, there were a few studies involved, and several of them were small in size, which can have an impact on the stability of the results. Secondly, the diversity of baseline cardiac functions, diabetic conditions, medications, duration of treatment, and the comparator regimen in different studies led to significant heterogeneity of some of the outcome measures. Thirdly, some of the studies focused mostly on reporting surrogate endpoints like LVEF, NT-proBNP, FBG, and HbA1c, and the data on long-term clinical endpoints (hospitalization due to heart failure, cardiovascular death, all-cause mortality, and quality of life) needs to be added. However, the findings of the current study also indicate the possibility of treating patients with CHF and T2DM using GLP-1RAs positively.

To sum up, GLP-1RAs have been proven effective in improving glycemic control among patients with CHF and T2DM, and demonstrate positive tendencies in LVEF increase and NT-proBNP decrease. Its therapeutic value could also be based on the synergistic effect via various mechanisms such as blood glucose level lowering, weight loss, anti-inflammatory effects, enhancement of the endothelial function, modulation of the myocardial energy metabolism, and ventricular load reduction. Further validation of the benefits of cardiac function, clinical outcome, and long-term safety of different GLP-1RAs in patients with CHF and T2DM will require additional large-scale, multicenter, long-term follow-up RCTs.

5. Conclusion

As a result of this systematic review and meta-analysis, GLP-1 receptor agonists produced a great increase in glycemic control among patients with chronic heart failure and type 2 diabetes, as indicated by decreased levels of fasting blood glucose and glycated hemoglobin. At the same time, following the administration of GLP-1 receptor agonists, an upward trend in left ventricular ejection fraction was observed, and a downward trend in NT-proBNP levels could be seen, indicating possible positive impacts on cardiac function enhancement and a decrease in the load of heart failure. In general, GLP-1 receptor agonists have good clinical application perspectives in patients with chronic heart failure and type 2 diabetes. Nonetheless, the existing literature is constrained by the low number of studies and large discrepancies in the size of samples, and additional large-scale, multicenter, high-quality randomized controlled trials are needed to confirm the efficacy and safety of these drugs.

References

[1] Marx, N., Federici, M., Schütt, K., et al. (2023). 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. European Heart Journal, 44 (39), 4043–4140. https://doi.org/10.1093/eurheartj/ehad192.

[2] Dunlay, S. M., Givertz, M. M., Aguilar, D., et al. (2019). Type 2 diabetes mellitus and heart failure: A scientific statement from the American Heart Association and the Heart Failure Society of America. Circulation, 140 (7), 294–324. https://doi.org/10.1161/CIR.0000000000000691.
[3] Nichols, G. A., Gullion, C. M., Koro, C. E., et al. (2004). The incidence of congestive heart failure in type 2 diabetes: An update. Diabetes Care, 27 (8), 1879–1884. https://doi.org/10.2337/diacare.27.8.1879.
[4] Dauriz, M., Targher, G., Laroche, C., et al. (2017). Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: Results from the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care, 40 (5), 671–678. https://doi.org/10.2337/dc16-2016.
[5] Seferović, P. M., Petrie, M. C., Filippatos, G. S., et al. (2018). Type 2 diabetes mellitus and heart failure: A position statement from the Heart Failure Association of the European Society of Cardiology. European Journal of Heart Failure, 20 (5), 853–872. https://doi.org/10.1002/ejhf.1170.
[6] Heidenreich, P. A., Bozkurt, B., Aguilar, D., et al. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation, 145 (18), 895–1032. https://doi.org/10.1161/CIR.0000000000001063.
[7] Holst, J. J. (2007). The physiology of glucagon-like peptide 1. Physiological Reviews, 87 (4), 1409–1439. https://doi.org/10.1152/physrev.00034.2006.
[8] Drucker, D. J. (2016). The cardiovascular biology of glucagon-like peptide-1. Cell Metabolism, 24 (1), 15–30. https://doi.org/10.1016/j.cmet.2016.06.009.
[9] American Diabetes Association Professional Practice Committee. (2024). Cardiovascular disease and risk management: Standards of care in diabetes—2024. Diabetes Care, 47 (1), 179–218. https://doi.org/10.2337/dc24-S010.
[10] Davies, M. J., Aroda, V. R., Collins, B. S., et al. (2022). Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care, 45 (11), 2753–2786. https://doi.org/10.2337/dci22-0034.
[11] Baggio, L. L., & Drucker, D. J. (2007). Biology of incretins: GLP-1 and GIP. Gastroenterology, 132 (6), 2131–2157. https://doi.org/10.1053/j.gastro.2007.03.054.
[12] Drucker, D. J., & Nauck, M. A. (2006). The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet, 368(9548), 1696–1705. https://doi.org/10.1016/S0140-6736(06)69705-5
[13] Knudsen, L. B., & Lau, J. (2019). The discovery and development of liraglutide and semaglutide. Frontiers in Endocrinology, 10, 155. https://doi.org/10.3389/fendo.2019.00155.
[14] Nauck, M. A., Quast, D. R., Wefers, J., & Meier, J. J. (2021). GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art. Molecular Metabolism, (46), 101-102. https://doi.org/10.1016/j.molmet.2020.101102.
[15] Trujillo, J. M., Nuffer, W., & Smith, B. A. (2021). GLP-1 receptor agonists: An updated review of head-to-head clinical studies. Therapeutic Advances in Endocrinology and Metabolism, (12), 1-15. https://doi.org/10.1177/2042018821997320.
[16] Marso, S. P., Daniels, G. H., Brown-Frandsen, K., et al. (2016). Liraglutide and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine, 375 (4), 311–322. https://doi.org/10.1056/NEJMoa1603827.
[17] Kristensen, S. L., Rørth, R., Jhund, P. S., et al. (2019). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. The Lancet Diabetes & Endocrinology, 7 (10), 776–785. https://doi.org/10.1016/S2213-8587(19)30249-9.
[18] Sokos, G. G., Nikolaidis, L. A., Mankad, S., Elahi, D., & Shannon, R. P. (2006). Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. Journal of Cardiac Failure, 12 (9), 694–699. https://doi.org/10.1016/j.cardfail.2006.08.211.
[19] Jorsal, A., Kistorp, C., Holmager, P., et al. (2017). Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)—A multicentre, double-blind, randomised, placebo-controlled trial. European Journal of Heart Failure, 19 (1), 69–77. https://doi.org/10.1002/ejhf.657.
[20] Margulies, K. B., Hernandez, A. F., Redfield, M. M.,et al. (2016). Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: A randomized clinical trial. JAMA, 316 (5), 500–508. https://doi.org/10.1001/jama.2016.10260.
[21] Lepore, J. J., Olson, E., Demopoulos, L., et al. (2016). Effects of the novel long-acting GLP-1 agonist, albiglutide, on cardiac function, cardiac metabolism, and exercise capacity in patients with chronic heart failure and reduced ejection fraction. JACC: Heart Failure, 4 (7), 559–566. https://doi.org/10.1016/j.jchf.2016.01.008.
[22] Sattar, N., Lee, M. M. Y., Kristensen, S. L., et al. (2021). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of randomised trials. The Lancet Diabetes & Endocrinology, 9 (10), 653–662. https://doi.org/10.1016/S2213-8587(21)00203-5.
[23] Zelniker, T. A., Wiviott, S. D., Raz, I., et al. (2019). Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal

outcomes in type 2 diabetes mellitus. Circulation, 139 (17), 2022–2031. https://doi.org/10.1161/CIRCULATIONAHA.118.038868.
[24] Li, L. (2021). Effects of liraglutide on NT-proBNP and LVEF in patients with chronic heart failure and T2DM. China Prescription Drug, (7), 122–124.
[25] Pan, Y. (2017). Application of liraglutide in the treatment of patients with chronic heart failure and newly diagnosed type 2 diabetes. Chinese Community Doctors, (18), 28–30.
[26] Han, L. (2015). Application of liraglutide in the treatment of chronic heart failure with newly diagnosed type 2 diabetes. Shandong Medical Journal, 46, 54–55.
[27] Zhao, Y., Jin, Y., & Gu, J. J. (2025). Effects of semaglutide on glycemic parameters and cardiac function in patients with type 2 diabetes mellitus complicated with CHF. Diabetes New World, (7), 48–51.
[28] Ferreira, J. P., Sharma, A., Butler, J., Packer, M., Zannad, F., & Janmohamed, S. (2022). Albiglutide in patients with type 2 diabetes and heart failure: A post-hoc analysis from Harmony Outcomes. European Journal of Heart Failure, 24 (10), 1792–1801. https://doi.org/10.1002/ejhf.2660.
[29] Campbell, J. E., & Drucker, D. J. (2013). Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metabolism, 17 (6), 819–837. https://doi.org/10.1016/j.cmet.2013.04.008.
[30] Davies, M. J., Bergenstal, R., Bode, B.,et al. (2015). Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE Diabetes randomized clinical trial. JAMA, 314 (7), 687–699. https://doi.org/10.1001/jama.2015.9676.
[31] Ussher, J. R., & Drucker, D. J. (2012). Cardiovascular biology of the incretin system. Endocrine Reviews, 33 (2), 187–215. https://doi.org/10.1210/er.2011-1052.
[32] Nikolaidis, L. A., Mankad, S., Sokos, G. G., et al. (2004). Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation, 109 (8), 962–965. https://doi.org/10.1161/01.CIR.0000120505.91348.58.
[33] Marso, S. P., Bain, S. C., Consoli, A., et al. (2016). Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. New England Journal of Medicine, 375 (19), 1834–1844. https://doi.org/10.1056/NEJMoa1607141.
[34] Gerstein, H. C., Sattar, N., Rosenstock, J., et al. (2021). Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. New England Journal of Medicine, 385 (10), 896–907. https://doi.org/10.1056/NEJMoa2108269.
[35] Gerstein, H. C., Colhoun, H. M., Dagenais, G. R., et al. (2019). Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. Lancet, 394 (10193), 121–130. https://doi.org/10.1016/S0140-6736(19)31149-3.
[36] Hernandez, A. F., Green, J. B., Janmohamed, S., et al. (2018). Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): A double-blind, randomised placebo-controlled trial. Lancet, 392 (10157), 1519–1529. https://doi.org/10.1016/S0140-6736(18)32261-X.
[37] Mann, J. F. E., Ørsted, D. D., Brown-Frandsen, K., et al. (2017). Liraglutide and renal outcomes in type 2 diabetes. New England Journal of Medicine, 377 (9), 839–848. https://doi.org/10.1056/NEJMoa1616011.
[38] Pratley, R. E., Aroda, V. R., Lingvay, I., et al. (2018). Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): A randomised, open-label, phase 3b trial. The Lancet Diabetes & Endocrinology, 6 (4), 275–286. https://doi.org/10.1016/S2213-8587(18)30024-X.