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The Effects of GLP-1 Agonists on Cardiac Structure and Function: A Systematic Review

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Abstract

Introduction: Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as a promising therapeutic class for addressing the metabolic and cardiovascular complications of obesity and type 2 diabetes mellitus (T2DM). Given the elevated risk of cardiovascular disease in these populations, our review systematically evaluates the long-term effects (>6 months) of GLP-1 receptor agonists on the cardiac structure, function, and major adverse cardiac events (MACE).

Methods: A literature search was conducted via PubMed for English-language human studies published in the past five years that investigated GLP-1 receptor agonist treatment on cardiac structure and/or function. From the 131 initial results, 15 studies met the inclusion criteria for full-text review. The reviewed studies encompassed diverse populations, including patients with T2DM, heart failure with a preserved ejection fraction, coronary artery disease, and obesity.

Results: Results on cardiac structure varied; some studies reported reductions in left ventricular mass and left atrial volume with GLP-1 receptor agonists treatment, while others showed no significant structural changes. Cardiac function outcomes, such as left ventricular ejection fraction and myocardial strain metrics, were largely unchanged, particularly in patients with T2DM. GLP-1 receptor agonists were associated with increased myocardial perfusion and decreased NT-proBNP and C-reactive protein (CRP), suggesting cardioprotective effects. However, heart rate elevation and potential arrhythmic risks were observed in some studies. Importantly, many studies demonstrated reductions in MACE and all-cause mortality with semaglutide, while results for liraglutide were more variable.

Discussion: GLP-agonists demonstrate a myriad of effects on cardiac function and cardiac structure, some have significant effects while others had none. Significantly, MACE was reduced in most of the semaglutide treatments leading to less cardiac dysfunction. Liraglutide did lead to some reduction in MACE but not consistently.

Conclusion: Semaglutide does demonstrate a promising approach especially in the reduction of MACE while liraglutide did not have the uniform benefits. Studies with different forms of GLP-1 agonists distributed to diverse populations are needed to evaluate individualized effects on metabolic disorders.

Keywords: GLP-1 receptor agonist; type 2 diabetes mellitus; obesity; cardiovascular disease; cardiac function; cardiac structure; major adverse cardiovascular events

Introduction

Obesity and Type 2 Diabetes Mellitus (T2DM) have been leading agents in health issues worldwide [1]. The prevalence of diabetes is estimated to be 6.1% worldwide with 521 million affected individuals [2]. T2DM is characterized by insulin resistance, whereby the body fails to respond to insulin effectively, preventing proper glycemic control after feeding. Obesity is a major risk factor for T2DM – 80% of patients with T2DM have comorbid obese [3]. These conditions significantly increase the risk of cardiovascular diseases, including hypertension, heart failure (HF), and atherosclerosis; therefore, people afflicted are at higher risk of suffering from major cardiac events such as myocardial infarction (MI) and stroke. The cardiovascular risks associated with T2DM and obesity occur mainly due to the constant metabolic stress exerted on the heart, which degrades myocardial structure and function [4].

One promising approach to addressing these interconnected maladies is the use of Glucagon-like peptide-1 receptor agonists (GLP-1RAs), a growing class of medications that treat metabolic diseases, including T2DM and obesity [1]. These drugs have revolutionized weight management, making it possible for patients to lose a substantial amounts without major lifestyle interventions or bariatric surgery [5]. In addition to their utility for

managing glucose levels and weight loss, GLP-1RAs have also been shown to reduce cardiovascular risk by improving factors such as hyperglycemia, hypertension, and dyslipidemia. This leads to lower risks of myocardial infarction (MI) and the chance of cardiovascular death [1]. GLP-1 is a naturally occurring hormone released in the intestine after consuming a meal leading to [7]. GLP-1 is initially processed through a gene called proglucagon and causes to insulin secretion and delayed gastric emptying. In addition to stimulating insulin secretion, GLP-1 also inhibits glucagon secretion to prohibit postprandial hyperglycemia. Furthermore, GLP-1 plays a role physiologically in appetite and food intake by acting on the central nervous system [7]. Common GLP-1RAs include Exenatide, Liraglutide, Dulaglutide, and Semaglutide [6]. GLP-1 agonists can be prescribed in combination with regularly prescribed medications or in patients who have developed an intolerance for medications, such as Metformin [6].

Since insulin is known to increase muscle microvascular perfusion, T2DM patients exhibit impaired muscle capillarization [8]. The use of GLP-1RAs restores this function by improving cardiac muscle capillarization [9]. This demonstrates how it helps with the transport of nutrients, oxygen, and hormones, including insulin, to the myocytes [9]. In recent years, numerous studies have assessed the role of GLP-1RAs in cardiac muscle function and structure. While research suggests benefits and potential improvements in myocardium metabolism and cardiovascular risk [10], a summary of these effects is lacking. Herein, we aim to review the direct impact of GLP-1RAs on myocardial structure, function, and contractility. Primarily focusing on cardiovascular outcomes as GLP-1RAs were administered to patients with or without underlying metabolic conditions.

Methods

Search History

A literature review was conducted to evaluate the effects of GLP-1RAs on cardiac muscle structure and function. A PubMed search was conducted using the following terms: *((GLP-1 receptor agonist) OR (semaglutide) OR (dulaglutide) OR (liraglutide) OR (lixisenatide)) AND ((cardiac muscle) OR (myocardi*) OR (cardiomyocyte) OR (cardiac function) OR (cardiac structure) OR (cardiomyopathy)) AND ((y_5[Filter]) AND (casereports[Filter] OR clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (humans[Filter]) AND (english[Filter]))*. Studies were included or excluded based on specific criteria. A total of 141 articles were identified through the initial search.

Data Extraction

Using Covidence, three independent authors screened the titles and abstracts for relevance; conflicts were resolved through discussion and consensus. After the initial screening, 15 articles were selected for full-text review and detailed analysis. Data was extracted including study design, population, authors, publication year, type of GLP-1 agonist used, follow-up duration, cardiac structure findings, cardiac function findings, and major adverse cardiovascular events (MACE).

Study Selection

Studies were included or excluded based on specific criteria. Inclusion criteria encompassed clinical trials (randomized controlled trials, cohort studies, and case-control studies) published in English, involving adults (18 years and older) with metabolic disorders such as obesity, T2DM, or cardiovascular conditions. The studies had to focus on GLP-1 receptor agonists, specifically semaglutide, dulaglutide, and liraglutide with long-term effects (minimum of six months follow-up). The exclusion criteria included case reports, reviews, meta-analyses, editorials, non-English studies, conference abstracts without full data, pediatric populations, animal studies, and studies focusing solely on skeletal muscle without cardiac muscle analysis. Additionally, studies with short-term interventions (less than six months), other weight-loss drugs not related to GLP-1 receptor agonists, or combination therapies that failed to isolate the effects of GLP-1 receptor agonists were excluded. The outcomes of interest were cardiac muscle structure (e.g., left ventricular mass, myocardial thickness) and cardiac function (e.g., ejection fraction, cardiac output), while studies focusing solely on metabolic outcomes (e.g., glycemic control or lipid profiles) were excluded.

Results

A summary of key characteristics and findings from the studies reviewed is presented in **Table 1**.

Table 1 Legend: Summary of clinical studies evaluating the cardiovascular effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs). Each row in the table represents a clinical study assessing how specific GLP-1RAs impacted cardiac structure, cardiac function, and major cardiac events across different patient populations. The table columns include the author and year of publication, study population, GLP-1RA used, follow-up duration, cardiac structure findings, cardiac function findings, and major adverse cardiovascular event outcomes.

Table 1. Summarized Findings of Studies Including Population, GLP-1RA, Follow-Up Duration, Cardiac Structure Findings, Cardiac Function Findings, and MACE Outcomes.

Study	Population	GLP-1RA	Follow-Up Duration	Cardiac Structure Findings	Cardiac Function Findings	MACE Outcomes
Chowdhary et al. (2024)	T2DM (No CVD)	Liraglutide and Pioglitazone	16 weeks	↑LV Mass	↑ Myocardial Perfusion & Energetics	-
Kumarathurai et al. (2021)	T2DM + CAD	Liraglutide	12 weeks	-	Preserved LVEF and ↑ HR	↓ e' (Diastolic Function)
Paiman et al. (2020)	T2DM (South Asian)	Liraglutide	26 weeks	↓LV Mass No change in aortic stiffness, myocardial triglyceride content, or diffuse fibrosis.	No change in LVEF. ↓LVEDV and LVES ↑ HR ↓ Stroke volume	No change in Diastolic Function (No Prevention of HFpEF)
Krychtiuk et al. (2024)	T2DM + Atherosclerotic CD	Albiglutide	1.6 years	-	-	↓MI Risk, STEMI, and NSTEMI
Ikonomidis et al. (2020)	T2DM + CD risk	Liraglutide	12 months	-	No change in LVEF	↑Global Work Index, ↑GLS, ↑Global Constructive Work
Akyay et al. (2022)	T2DM	Exenatide	6 months	No change in LVEF	↑ LVGLS + RVGLS	↓ Cardiac dysfunction
Verma et al. (2024)	HF + obesity +T2DM (only in one trial)	Semaglutide	1 year	-	↓CRP ↓NT-proBNP levels	↓In SAE and serious cardiac disorders (regardless of CRP levels)
Neves et al. (2022)	HFrEF	Liraglutide	6 months	-	↑Arrhythmic events	-
Lingvay et al. (2024)	Overweight/obesity + CVD	Semaglutide	20 weeks	-	-	↓ MACE (across all HbA1c subgroups)

Study	Population	GLP-1RA	Follow-Up Duration	Cardiac Structure Findings	Cardiac Function Findings	MACE Outcomes
Rasmussen et al. (2021)	T2DM	Liraglutide	26 weeks	↓ Cardiac adipose tissue	-	-
Solomon et al. (2024)	Obesity and HFpE (another trial + T2DM)	Semaglutide	52 week	↓ RV end-diastolic area from the baseline right ventricular enlargement LV mass was elevated Patients with T2DM had: higher LV volumes and LV mass, more impaired LV mechanics, worse LV diastolic function Participants with atrial fibrillation had: worse LV remodeling, more impaired LV mechanics and diastolic function, higher LA volumes, lower RV systolic function, and higher RV volumes compared with those without atrial fibrillation	Mild diastolic dysfunction	-
Lincoff et al. (2023)	Obesity (No diabetes)	Semaglutide	Follow up varied from 39.8±9.4 months	-	-	↓ Incidence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke

Study	Population	GLP-1RA	Follow-Up Duration	Cardiac Structure Findings	Cardiac Function Findings	MACE Outcomes
Tougaard et al. (2020)	CHF (LVEF <45%)	Liraglutide	24 weeks	-	↑ HR by 8 ± 9 bpm (pulse), 9 ± 9 bpm (ECG), and 9 ± 6 bpm (device readouts) versus placebo in pts with SR HR remained unchanged in patients without SR	No association between HR increase and adverse events The long-term clinical significance of increased HR in liraglutide treated CHF patients needs to be determined.
Katogiannis et al. (2024)	T2DM with high/very high cardiovascular risk	Liraglutide	6 months	Improved LA reservoir strain compared to insulin treatment	LA conduit strain increased GLS improved PWV decreased	
Kosiborod et al. (2024)	Obesity-related HFpEF and T2DM	Semaglutide	52 weeks	-	Improved HF symptoms, exercise capacity, reduced NT-proBNP.	Fewer SAE and cardiac disorder events in semaglutide group

Abbreviations: BPM, beats per minute; CAD, coronary artery disease; CD, cardiovascular disease; CHF, chronic heart failure; CRP, C-reactive protein; CVD, cardiovascular disease; ECG, electrocardiogram; e′, early diastolic mitral annular velocity; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GLS, global longitudinal strain; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HbA1c, glycated hemoglobin; LA, left atrium; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVES, left ventricular end-systolic volume; LVGLS, left ventricular global longitudinal strain; MACE, major adverse cardiovascular events; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PWV, pulse wave velocity; RV, right ventricle; RVGLS, right ventricular global longitudinal strain; SAE, serious adverse events; SR, sinus rhythm; STEMI, ST-elevation myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; and T2DM, type 2 diabetes mellitus.

Cardiac Structure Results

Cardiac structure was a primary outcome in many of the studies reviewed, as changes in structure have been linked to MACE outcomes [11]. Specific structural outcomes included left ventricular (LV) mass, LV volume, stroke volume, left atrial (LA) volume, right ventricular (RV) volume, cardiac adiposity, early diastolic mitral annular velocity (e'), and peak early mitral inflow velocity (E). Among these, LV mass and LV volume have been consistently studied as indicators of cardiac structural health, particularly in patients with T2DM and other metabolic conditions [12-14].

Chowdhary et al., demonstrated that 16-weeks of pioglitazone treatment significantly increased mean LV mass, whereas liraglutide treatment for did not lead to a similar significant change in LV mass in patients with T2DM without CVD [12]. In contrast, Paiman et al. discovered a trending reduction in LV mass in response to 26-weeks of liraglutide treatment in T2DM patients with or without preexisting coronary artery disease (CAD) [13].
With respect to LV volume, Chowdhary et al. report a trending increase (9.9 mLs) and decrease (8.8 mLs) in the left ventricular end-diastolic volume (LVEDV) with pioglitazone and liraglutide treatment, respectively [12]; the mean difference in LVEDV between liraglutide and pioglitazone was not significant. In line with these findings, Paiman and colleagues [13] demonstrated a significant decrease in LVEDV (19 mL) after 26-weeks of liraglutide treatment, as well as decreased stroke volume and LV end-systolic volume (LVESV). However, since the authors found no differences in any other functional outcomes, they attribute LV volume changes to the significantly increased HR exhibited by the liraglutide group. Building on these investigations, Kumarathurai et al., [14] demonstrated a lack of improvement in diastolic dysfunction after 12-weeks of liraglutide therapy in patients with T2DM and CAD. Most participants had diastolic dysfunction present, and liraglutide treatment did not recover measured parameters, with any changes found attributed to the increased HR observed in the liraglutide group.

Shifting toward structural findings in the atria, results from the Semaglutide Treatment Effect in People with Obesity and Heart Failure with preserved Ejection Fraction (STEP-HFpEF) program reveal a weight loss-dependent effect [15]. Semaglutide treatment blunted the increased LA volume seen in the placebo group, with greater weight loss associated with greater improvements in LA volume after the 52-week treatment. This improvement was associated with functional outcomes like the Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS), 6-minute walk distance (6MWD), and N-terminal pro-brain natriuretic peptide levels (NT-proBNP). STEP-HFpEF participants who also had T2DM or atrial fibrillation saw similar improvements with semaglutide treatment despite higher baseline LA volumes and participants with CAD had the most substantial reduction in LA volume.

Another structural variable with implications for cardiovascular health, cardiac adipose tissue, has been examined in the context of GLP-1RA treatment. Rasmussen et al. [16] assessed the effects of demonstrated a significant reduction (11.5 mL) in cardiac adipose tissue volume compared to placebo after 24-weeks liraglutide therapy. However, significance was lost after adjusting for changes in body mass index (BMI).

It is of note that GLP-1 agonist treatment did not always lead to significant structural changes in the myocardium [12, 14, 15].

Cardiac Function Results

Cardiac function was another primary outcome in many of the studies reviewed. Functional measurements include: LV ejection fraction (LVEF), myocardial perfusion and energetics, global longitudinal strain (GLS), RV global longitudinal strain (RVGLS), LVGLS, LA strain, NT-proBNP, C-reactive protein (CRP), arrhythmic events, heart rate (HR), and pulse wave velocity (PWV).

In particular, LVEF has been evaluated by numerous groups and largely remains unchanged in response to GLP-1RA treatment despite differing GLP-1RA used, intervention duration, study population, and concomitant therapy with standard of care [14, 17, 18]. In patients with T2DM and CAD, LVEF remained unchanged from its baseline of 58.9% after 12-week liraglutide treatment [14]. Similarly, both 4 months and 12 months liraglutide treatment did not alter LVEF in patients with T2DM [17]. This was also the case for the LVEF of T2DM patients receiving exenatide or insulin glargine for six months [18]. In the STEP-HFpEF trial, semaglutide had opposing effects

on LVEF of obese STEP-HFpEF participants and T2DM STEP-HFpEF particpants, causing a slight increase (1.32%) and decrease (−1.55%), respectively [15].

Myocardial perfusion and energetics were also measured after 16-weeks of liraglutide administration in T2DM patients, demonstrating a significant increase in the stress myocardial blood flow and myocardial perfusion reserve [12]. However, there was no significant change in perfusion when pioglitazone was administered in this population.

With regard to myocardial strain parameters, GLS, LVGLS, and RVGLS were measured through echocardiography and revealed modulation by GLP-1RA intervention [17, 18, 19]. T2DM exhibited improved GLS, global circumferential strain, and global radial strain after 4 or 12 months of liraglutide treatment [17]. T2DM patients treated with exenatide for 6 months showed a significant improvement in LVGLS and RVGLS, particularly when receiving insulin [18]. Patients with T2DM with high risk of cardiovascular complications exhibited significantly improved in GLS following 6 months of liraglutide therapy, while GLS of the insulin treatment group was unchanged [19]. They also found that liraglutide treatment resulted in increased LA reservoir strain and LA conduit strain [19].

Clinical markers related to cardiac function also include CRP and NT-proBNP [20]. In the STEP-HfpEF population, higher CRP levels were associated with lower KCCQ-CSS and 6MWD [20]. Semaglutide treatment improved KCCQ-CSS regardless of baseline CRP values and decreased CRP levels in all patients. NT-proBNP was studied by Verma et al., in obesity-related HFpEF patients semaglutide reduced NT-proBNP levels with after 52 weeks, with a greater reduction in NT-proBNP associated with a greater reduction in CRP [20]. Kosiborod et al. treated patients with HFpEF, obesity, and T2DM demonstrating reduction in NT-proBNP after a 12-month semaglutide intervention [21].

Heart rate (HR) was another major factor was influenced by GLP-1RAs. Much of the literature reviewed herein report increased HR with GLP-1RA therapy [12, 14, 17, 22]. T2DM patients receiving liraglutide for 16 weeks had an increased resting HR by 5.9 beats per min (bpm) [12]. Kumarathurai et al., also report increased HR of 6.16 bpm in T2DM patients with CAD receiving liraglutide, despite a shorter treatment duration [14]. Ikonomidis et al., report a 5 bpm and 4 bpm increase in HR after 4 or 12 months of liraglutide treatment, respectively, in patients with T2DM [17]. HF patients with an LVEF $\leq$ 45% had significantly increased sinus rhythm and resting HR (8 bpm) after receiving liraglutide for 24 weeks [22]. Increases in HR correlated with liraglutide dose but were not associated with serious cardiac events. Additionally, liraglutide was found to decrease QT intervals versus placebo.

Pulse wave velocity (PWV), a measure of arterial stiffness, was also investigated. Liraglutide significantly decreased PWV in patients with T2DM at high cardiovascular risk [19].

MACE Results

In addition to extensive investigations of cardiac structure and function, the studies reviewed also assessed how GLP-1RAs impact rates of MACE. HF with reduced ejection fraction (HFrEF) patients treated with liraglutide for 12 weeks reported increased total HF hospitalizations or all cause deaths, and total HF hospitalizations in their 6-month follow up period [23]. The risk for HF hospitalization was higher for T2DM patients and in patients in New York Heart Association (NYHA) Class III or IV versus Class I or II. Conversely, the STEP-HFpEF population receiving semaglutide displayed fewer serious adverse events such as HF, CAD, and arrythmia and cardiac disorders, regardless of CRP levels [20, 21].

Overweight or obese patients without T2DM receiving semaglutide showed reduced MACE, expanded MACE, MACE with all-cause mortality, individual components of MACE, coronary revascularizations, HF composite, HF hospitalizations, and urgent care visits for HF [24]. While the relative risk reduction remained stable, the absolute benefit was greater in participants with higher baseline HbA1c [24]. Patients with T2DM and atherosclerotic CVD demonstrated an overall 25 % risk reduction for MI with albiglutide treatment during a mean follow-up of 1.6 years [25]. After 12 months of liraglutide treatment, T2DM patients had increased myocardial work index and reduced myocardial wasted work; Ikonomidis and colleagues concluded that the liraglutide was one approach of a promising second-line option with individuals with high cardiovascular risk [17]. In obese non-diabetic patients, 16-week semaglutide treatment resulted in MACE was significantly lower in the semaglutide group compared to the placebo group and the incidence of cardiovascular death was numerically lower in the semaglutide group [26].

Discussion

This review thoroughly assessed the reported effects of GLP-1RAs on cardiac structure and function over the past 5 years. A variety of parameters were reported assessing both cardiac structure and cardiac function. MACE was also included to provide a broad perspective on patient health and outcomes. The included patient populations exhibited notable heterogeneity with 10 studies involving patients with T2DM, 4 with HFpEF, 1 with HFrEF, 1 with CAD, and 1 with CHF. The inclusion of a variety of patient populations was essential as it revealed how patient-specific factors and disease processes influenced the therapeutic response.

Cardiac Structure

The studies reviewed did not always reach consensus with regard to GLP-1RA's effects on cardiac structure. While multiple groups report GLP-1RA treatment did not

result in changes in LV mass or LV volumes [12, 15], Paiman et al. found that liraglutide significantly decreased LV mass and volume [13]. As well, reduction in LVEF were reported in multiple [12, 13], but not all [15] studies reviewed. After 26 weeks of liraglutide therapy, LVESV, and stroke volume were also decreased, possibly indicating that the cardiac output was negatively affected [13]. Therefore, this provides some evidence that GLP-1RAs might be more effective in managing diastolic rather than systolic function. This would be particularly relevant in the context of HFpEF, which is characterized by diastolic dysfunction (impaired relaxation and filling of the left ventricle) [13].

The reviewed findings also suggest that liraglutide may have more of a beneficial effect on cardiac structure than semaglutide. However, semaglutide still offers some benefit, as demonstrated by Solomon et al. [15], with patients in the STEP-HFpEF program. Overall, all the studied groups with semaglutide treatment had evidence of improvement in LA volume and those with increased weight loss saw the greatest improvement in LA volume. Therefore, even if LA volumes are higher compared to normal, the controlled increase with GLP-1RA treatment suggests that semaglutide can play a role in mitigating diastolic function and decrease cardiovascular events. Rasmussen and colleagues further demonstrated liraglutide's positive outcomes on cardiovascular health with a significant reduction in cardiac adipose tissue volume [16], leading to a reduced risk of coronary atherosclerosis.

Cardiac Function

One of the most widely assessed indicators of cardiac function, LVEF, was largely maintained in studies despite different GLP-1RA and treatment duration [14, 15, 17, 18]. However, Solomon et al. [15] observed a non-significant decrease and increase in the LVEF of participants from the STEP-HFpEF trial with and without comorbid T2DM, respectively [15]. This contrasting trend may reflect underlying differences in myocardial adaptation in patients with obesity alone versus obesity and T2DM. In people with T2DM, metabolic dysfunction, insulin resistance, and vascular complications can inhibit or counteract the potential cardioprotective effects of GLP-1 RAs, whereas obese patients may be more responsive to treatment as their cardiovascular health is less impaired by chronic hyperglycemia. These findings highlight the complexity of cardiovascular and cardiometabolic health, indicating that GLP-1RAs may provide differential effects on the heart depending on the extent and mechanism of a disease.

Strain parameters like GLS are known to detect subtle changes in cardiac tissue earlier than LVEF and may serve as a predictor of adverse outcomes [27]. GLS was improved in patients with T2DM in multiple studies [17, 18, 19, 27]. Exenatide treatment significantly improved both the LVGLS and RVGLS after six months of treatment [18]. Similarly, liraglutide therapy offered significant improvement in GLS, whereas insulin alone did not [19]. Ikonomidis and colleagues reported significant improvements in GLS, global circumferential strain, and global radial strain following 4 and 12 months of liraglutide treatment [17]. These findings suggest that GLP-1RAs may offer cardioprotective effects against heart failure or the progression of heart failure, through improved heart contractility and mechanics. However, in patients with obesity-related HFpEF receiving semaglutide Solomon and colleagues reported no change in LVGLS, e′, or LA strain [15]. Despite Soloman's report [15], Katogiannis and colleagues demonstrated increased LA reservoir strain and LA conduit strain in T2DM patients after liraglutide treatment [19], demonstrating functional improvement. These improvements reflect the compliance of contractile function of the LA during diastole, which is typically impaired in patients with HFpEF [19]. By increasing LA strain, GLP-1RAs may improve LA function and reduce LV filling pressures, addressing a large problem that patients with HFpEF face [19].

Myocardial perfusion and energetics play a critical role in cardiovascular health, especially those at risk for microvascular dysfunction [12]. It is of note that MBF and MPR were significantly increased after the administration of liraglutide [12]. MPR is a key predictor of cardiovascular outcomes, as a reduced MPR is associated with microvascular dysfunction and HPpEF [12]. The fact that liraglutide was able to increase MPR and MBF suggests that it can be beneficial in increasing blood flow under periods of stress. Additionally, liraglutide treatment caused a significant improvement in PWV in patients with T2DM or risk of cardiovascular complications [19]. This further suggested the positive benefits of liraglutide through improved cardiac contractions and reduced arterial stiffness. This decrease in PWV will likely reduce cardiovascular risk in these patients, as the reduced cardiac workload causes less strain on the heart [19].

Biomarker data, such as NT-proBNP supported physiological findings. NT-proBNP, a key marker of cardiac stress and heart failure and CRP levels were significantly reduced with semaglutide treatment [20, 21].

Although not statistically significant, some functional outcomes reported were not positive [23]. Increased arrhythmic risk was found as a potential concern in patients with HFrEF. Liraglutide treatment was associated with increased total investigator reported arrhythmias and increased new use of anti-arrhythmic drugs [23]. These observations may suggest that GLP-1 RAs impact myocardial excitability in a way that can cause rhythm disturbances in susceptible individuals. Along with increased arrhythmic risk, many investigators observed an increased HR with GLP-1RA therapy [12, 14, 17, 22]. Further, Tougaard and colleagues tied this HR increase to liraglutide doses in patients with CHF [22]. Elevated resting

HR is a risk factor for cardiovascular disease and can increase the risk of cardiac death [28]. This may raise questions about the safety of patients with pre-existing arrhythmia taking GLP-1RA medication, warranting further investigation into the long-term cardiovascular implications of increased HR.

MACE

While the studies reviewed have demonstrated significant effects of GLP-1RAs on cardiac structure and function, ultimately their impact (MACE) was a primary outcome. The findings from the various analyzed studies suggest a complex relationship between GLP-1RAs and cardiovascular outcome, suggesting even differences between liraglutide and semaglutide.

Treatment with liraglutide was associated with a pattern of increased hospitalizations and all cause deaths, especially among patients with T2DM [23], suggesting that while liraglutide was found to have many benefits on cardiac structure or function, its impact on cardiovascular health and life expectancy still remains uncertain. Further studies suggest that liraglutide may not provide meaningful improvements in cardiac function. Multiple studies reviewed found no improvement in diastolic function after liraglutide administration [13, 14], contradicting prior findings that suggested improvements in structure may lead to improved function [13, 15, 16]. This raises the question about whether liraglutide can play a role in preventing HF in T2DM patients. However, liraglutide still offers promising benefits in specific populations. It was concluded that liraglutide treatment improved myocardial work index and reduced myocardial wasted work in T2DM patients with high cardiovascular risk [17], suggesting that GLP-1RAs may be a beneficial for these patients. Additionally, improvements in global stain parameters indicate liraglutide may be beneficial for patients at high risk for cardiac dysfunction [18].

Contrarily, semaglutide was associated with fewer serious adverse events and cardiac disorders [20, 21, 24, 26]. MACE and related cardiovascular endpoints were reduced, including all-cause mortality, with semaglutide treatment [24]. Although reduction in cardiovascular death did not reach statistical significance in all studies, the overall trend towards improvements suggests there is a beneficial potential of semaglutide [26]. While relative risk reduction remained stable when evaluating HbA1c levels, a greater benefit was seen in patients with higher baseline HbA1c levels [24], demonstrating that baseline glycemic status of the patient influences the magnitude of cardiovascular benefit with GLP-1RA treatment. Thus, patients with less controlled diabetes may benefit more from treatment compared to those with more controlled hyperglycemia or with normal glycemic status.

Beyond liraglutide and semaglutide, albiglutide has also demonstrated promising cardiovascular benefits [25]. Albiglutide treatment was associated with a significant reduction in MI risk, with a 25% decrease in overall MI incidence [25]. Albiglutide also lowered the rates of first and recurrent cardiovascular events, suggesting that albiglutide may provide more consistent and clinically meaningful cardioprotective effects.

Taking these findings together, although GLP-1 receptor agonists did not show clear and uniform cardiovascular benefits, there is still strong potential in treatments reducing adverse cardiovascular outcomes.

Limitations and Future Directions

This review found that GLP-1RAs demonstrate long term benefits differently that vary based on the duration and drug types, ultimately result in distinct outcomes on cardiac structure, function, and MACE. However, this review is limited by the heterogeneity of the included study populations, variations in treatment durations, and inconsistencies in outcome measures, all of which complicate interpretation and cross-study comparisons. Additionally, many studies featured small sample sizes or short follow-up periods, restricting our ability to assess long-term cardiovascular outcomes. Because our review encompassed a range of GLP-1 receptor agonists rather than focusing on a specific subtype, definitive conclusions about the cardiac effects of any single agent cannot be made. Future research should aim to evaluate the cardiac impact of individual GLP-1 agonists more precisely. Long-term, large-scale randomized controlled trials are also needed to standardize outcome metrics and improve comparability. These studies should include more stratified populations, taking into account factors such as age, ethnicity, pre-existing conditions, and concurrent medications to better understand which patient groups derive the most benefit.

Conclusions

GLP-1RAs are widely used for the management of obesity and T2DM and may offer cardioprotective effects [1]. It can be concluded that GLP-1RAs demonstrate long-term benefits to a varying degree on cardiac structure and function, ultimately impacting MACE in patients with metabolic disorders. Differences in patient outcomes relate to the type of GLP-1RA prescribed, duration of treatment, and patient characteristics. This review highlights these differences and how ultimately there may be structural or functional improvement, even if it is minimal in preventing cardiovascular events. Further studies should continue to investigate how patient characteristics relate to differences in cardiovascular benefit with GLP1-RA treatment. This will provide further confirmation as to whether GLP-1RAs, and which kind specifically, can have long-term effects on patient myocardial structure, function, and MACE.

List of Abbreviations

bpm: beats per minute
CAD: coronary artery disease

CHF: congestive heart failure
CRP: C-reactive protein
CVD: cardiovascular disease
e': early diastolic mitral annular velocity (a measure of diastolic function)
GLP-1: glucagon-like peptide-1
GLS: global longitudinal strain
HF: heart failure
HR: heart rate
KCCQ-CSS: Kansas City cardiomyopathy questionnaire clinical summary score
LA: left atrium
LV: left ventricle
LVEDV: left ventricular end-diastolic volume
LVEF: left ventricular ejection fraction
LVESV: left ventricular end-systolic volume
LVGLS: left ventricular global longitudinal strain
MACE: major adverse cardiovascular events
MI: myocardial infarction
NT-proBNP: N-terminal pro-brain natriuretic peptide
PWV: pulse wave velocity
RVGLS: right ventricular global longitudinal strain
STEP-HFpEF: semaglutide treatment effect in people with heart failure with preserved ejection fraction
STEP-HFpEF-DM: semaglutide treatment effect in people with heart failure with preserved ejection fraction and diabetes mellitus
T2DM: type 2 diabetes mellitus

Conflicts of Interest
The author(s) declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
This study did not require an ethics approval and/or participants consent as it was a systemic literature review where only an online search engine was utilized to conduct the research.

Authors' Contributions
SS: Made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.
AM: Made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.
JK: Made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.

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