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Cardioprotective properties of glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus patients: A systematic review

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ABSTRACT

Background and aims: Cardiovascular disease is one of the main contributors for the mortality in type 2 diabetes mellitus (T2DM) patients. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) had shown cardiovascular benefits which may be advantageous to reduce mortality in T2DM patients. This systematic review focused on analyzing the effects of GLP-1 RAs on cardiovascular outcomes.

Methods: We conducted an extensive search through JSTOR, PubMed, Scopus, EBSCOhost, and CENTRAL. All related studies assessing the use of GLP-1 RAs in T2DM patients from inception up to October 2020 were screened. Any cardioprotective properties as the outcomes were obtained.

Results: A total of six studies (4 randomized, 2 observational) with a total of 182,205 patients were included in this review. The GLP-1 RAs used were either liraglutide or exenatide in combination with antihypertensive or antilipidemic drugs. All studies showed that GLP-1 RA significantly caused weight loss and improved cardiac functional capacity by increasing left ventricular ejection fraction and reducing end-systolic and end-diastolic left ventricle volume. GLP-1 RA also improved myocardial blood flow without affecting myocardial glucose uptake. However, GLP-1 RA failed to show its effect in reducing blood pressure and improving lipid profiles.

Conclusions: Despite the limited number of studies, consistent data showed that GLP-1 RA has several cardioprotective properties.

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1. Introduction

The worldwide prevalence of diabetes mellitus is estimated to reach 4.4% in 2030 for all age-groups. This “diabetes epidemic” will continue to develop, especially in developing countries [1]. Based on WHO Multinational Study of Vascular Disease in Diabetes, 52% of deaths in type 2 diabetes mellitus (T2DM) were caused by cardiovascular disease, with coronary arterial disease as the leading cause [2,3]. T2DM patients also have increased risk of developing cardiovascular disease and will have worse prognosis after developing acute coronary syndrome [3]. Therefore, cardiovascular disease must be prevented in T2DM patients, before progressing and causing mortality.

Recently, several anti-diabetic drugs gained attention through showing cardiovascular mortality reduction, including Glucagon-like peptide-1 receptor agonist (GLP-1 RA) [4]. In 2019, American Diabetes Association (ADA) decided to incorporate GLP-1 RA into their guideline treatment, as a combination with metformin in T2DM patients with established atherosclerotic cardiovascular disease (ASCVD) [5]. GLP-1 RA is a class of T2DM medication in adults, that mimics GLP-1, with various effects including enhances insulin production, induces satiety, and inhibits gastric acid & glucagon production [6]. In 2005, US Food and Drug Administration (FDA) approved the first GLP-1 RA for T2DM treatment, which was exenatide [7]. According to ADA Standard of Medical Care 2020, GLP-1 RA is proven to exhibit cardiovascular benefit. Compared to insulin, it has a lower risk of developing hypoglycemia and is also beneficial for weight loss [7]. Several clinical trials show various results on the cardiovascular benefit of GLP-1 RA therapy. However, to the best of our knowledge, there is no systematic review that comprehensively assess the cardioprotective properties regarding

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GLP1-RA treatment in comparison with other oral antidiabetic drugs (OADs). Thus, this study aimed to evaluate and thoroughly assess the cardioprotective properties of GLP-1 RA in T2DM patients with PICO of participants (T2DM patients), intervention (GLP-1 RA), comparison (other oral antidiabetic drugs), and outcomes (cardiovascular risks and events).

2. Methods

2.1. Data searching strategy

This systematic review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and Cochrane Handbook for Systematic Review of Interventions (S1 Table) [8,9]. Several databases including JSTOR, PubMed, Scopus, EBSCOhost, and CENTRAL. We reviewed all relevant studies from inception to October 2020 with the following keywords: (“GLP 1 receptor agonist[MeSH Terms] OR (glucagon like peptide 1[MeSH Terms])” AND “cardioprotective agents[MeSH Terms]”) AND (type 2 diabetes mellitus[MeSH Terms]).

2.2. Eligibility criteria

The participants of this review are T2DM patients, the intervention is GLP-1 RA, while the comparison is other oral antidiabetic drugs, and we analyzed the cardiovascular outcomes of each study. The search was limited to human participants with language restriction to English and Bahasa Indonesia. The inclusion criteria were as follows: 1) observational and interventional study either randomized or non-randomized; 2) population with adult samples (>18 years old) and diagnosed with T2DM with GLP-1 RA therapy; and 3) metformin or other standard oral antidiabetic drugs were used as the comparison. Any measured outcomes majorly including but not limited to cardiovascular events. The exclusion criteria were as follows: 1) irrelevant title; 2) irretrievable full-text articles; and 3) wrong PICO settings.

2.3. Data extraction and quality assessment

Two investigators (WW and AC) conducted the data screening and extraction from eligible studies including: author and year of publication, study design and setting, sample size, mean or range of sample age, duration of therapy, type of GLP1-RA, and outcomes. To minimize the risk of bias, quality assessment of the eligible studies was performed through Newcastle-Ottawa Scale (NOS) for observational study and JADAD scale for interventional study [10,11]. The quality assessment was conducted by two independent investigators (WW and AC). Disagreements between investigators were adjudicated by third investigators (DN and FFA).

3. Results

3.1. Literature search

Searches retrieved 102 items, 94 were unique, and 86 titles and abstracts were eliminated, leaving 8 studies for full-text articles assessment. Of those, two studies did not focus on the cardiovascular outcomes of GLP-1 RA. In the end, we included six studies (one retrospective study [12], one multi center cohort study [13], and four randomized control studies [14–17]) ranging from 2012 to 2020 involving 182,205 participants (Fig. 1). Based on the quality assessment using NOS and JADAD scale, all included studies are with low risk of bias (S2 and S3 Tables).

3.2. Characteristic of study

3.2.1. Type of GLP-1 RA

Three studies used Liraglutide for their studies, while the other two used Exenatide, and the last study by Raparelli et al. (2020) did not state the drugs used in their study [13]. Study by Varanasi et al. (2012) uptitrated the Liraglutide from 0.6 mg/day, 1.2 mg/day, and 1.8mg/day every two weeks [12]. Study by Arturi et al. (2016) and Bizino et al. (2019) also uptitrated the Liraglutide in the same dose but for every one week [15,16]. Study by Gejl et al. (2012) used intravenous Exenatide 0.066 pmol/kg.min [14] and study by Bethel et al. (2020) used Exenatide 2 mg for once per week [17] (see Table 1).

3.2.2. Medical history

All of the studies included obese patient with body mass index (BMI) above 25 kg/m². Study by Gejl et al. (2012) included only non-smoker patients and excluded those with coronary artery diseases or other significant diseases [14]. Study by Arturi et al. (2016) stated a more specific criteria for their study. They included patients with history of previous acute myocardial infarction and NYHA class II/III and/or LVEF ≤45%. In addition, they excluded patients with CHF due to or associated with uncorrected thyroid disease, clinically active cardiovascular disease, conventional myocardial revascularization procedure, hospitalization for acute heart failure, uncontrolled hypertension, history of malignancy, history of alcohol or drug abuse, liver or kidney failure, and any drug use that may disturb the glucose metabolism and known or suspected hypersensitivity to trial or related products [15]. Study by Bizino et al. (2014) had the criteria of stable BP < 150/85 mmHg for at least 1 month prior to the experiment and excluded those with history of renal, hepatic, or cardiovascular disease; history of gastric bypass surgery; pancreatitis; and pregnant or lactating women [16]. Different from Gejl et al. (2012), study by Bethel et al. (2020) included patients with any degree of prior cardiovascular risk and also prior coronary, cerebrovascular, or peripheral artery events. Other than that, Bethel et al. (2020) also excluded patients with history of two or more episodes of severe hypoglycemia in the last 12 months, end stage kidney diseases, personal or familial history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, and a baseline calcitonin level >40 ng/L [17]. Finally, study by Raparelli et al. (2020) excluded patients with gestational diabetes, type 1 diabetes mellitus, and cystic fibrosis [13].

3.2.3. Previous diabetes treatment

In the study of Varanasi et al. (2012), in total of 110 patients, 65 patients received combined therapy with insulin, 102 combined with metformin, 54 combined with sulfonylurea, 38 combined with thiazolidinediones, and 18 patients combined with DPP-4 inhibitor (sitagliptin) [12]. On the contrary, all patients in the study by Gejl et al. (2012) were insulin-naïve but received metformin therapy. Six out of eight patients received sulfonylurea, but all of these OAD medications were discontinued 48 h prior the study day and other remaining medications were stopped 12 h before treatment [14]. Study by Arturi et al. (2016) only included patients with previous treatment of metformin and/or sulfonylurea [15]. Additionally, study by Bizino et al. (2019) had 6 patients with combined therapy with sulfonylurea and 15 patients combined with insulin [16]. Both studies by Arturi et al. (2016) and Bethel et al. (2020) excluded patients who had a history of GLP-1 RA medications [15,17]. The last study by Raparelli et al. (2020) selected patients with ongoing use of metformin with criteria at least one prescription in 90 days before cohort entry [13].

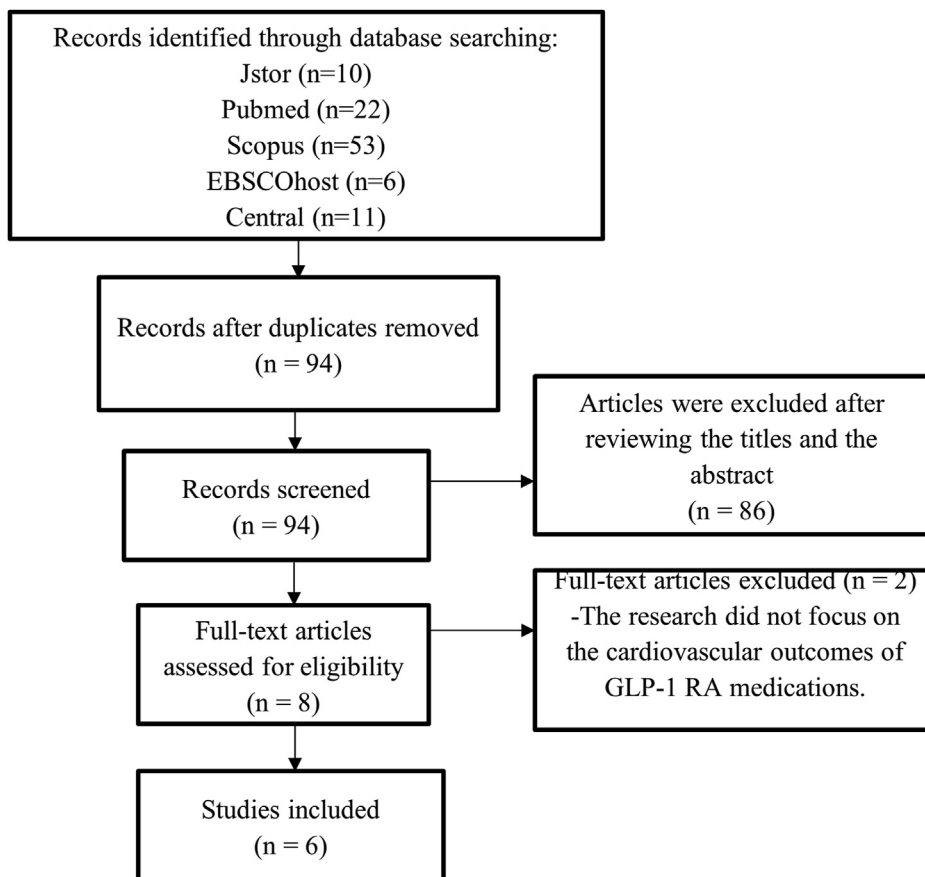


Fig. 1. PRISMA flow diagram.

Table 1
Summary of included study characteristic in this systematic review.

Study (risk of bias assessment)	Study Design	Country	Sample Size	Duration of Therapy (months)	Age (year old)	Analyzed Variable	Type of GLP-1 RA
Varanasi et al. (2012) [12] (NOS score: 9/9)	Retrospective cross-sectional study	New York	110	7.5 (mean)	n/a	BMI, HbA1c, SBP, CRP, fasting lipid concentrations	Liraglutide (titrated from 0,6 mg/day, 1,2 mg/day, 1,8 mg/day every 2 weeks)
Gejl et al. (2012) [14] (JADAD score: 3/5)	Randomized, double-blinded, placebo-controlled crossover study	Denmark	8	n/a	58,3 (mean)	Myocardial Blood Flow (MBF), Myocardial Glucose Uptake (MGU)	Exenatide IV 0,066 pmol/kg.min
Arturi et al. (2016) [15] (JADAD score: 3/5)	Single center, randomized, parallel-group, pilot study	New York	32	12	59,5 (mean)	Gender, age, BMI, SBP, DBP, HR, FPG, HbA1c, serum creatinine, ProBNP, total cholesterol, HDL, LDL, amylase, lipase, calcitonin	Liraglutide (uptitrated from 0,6 mg, 1,2 mg, 1,8 mg every week)
Bizino et al. (2019) [16] (JADAD score: 5/5)	Randomized, double-blind, assessor-blinded, placebo-controlled, single-center clinical trial	Netherlands	49	6.5	Mean liraglutide group: 60; Mean placebo group: 59	LV diastolic and systolic function, BP, body weight, HbA1c, LVEDV, LVESV, LVM, LVMI, LVMI/LVEDVI, creatinine, NTproBNP.	Liraglutide (uptitrated from 0.6 mg, 1.2 mg, and 1.8 mg in each week).
Bethel et al. (2020) [17] (JADAD score: 3/5)	Randomized, double-blind, placebo-controlled	United Kingdom	14752	38.4 (median)	60 (mean)	MACE, ACM	Exenatide 2 mg once per week
Raparelli et al. (2020) [13] (NOS score: 9/9)	Multiple center cohort study	Rome	167254	12	59 (median)	Major cardiovascular events: AMI, unstable angina, heart failure, stroke.	n/a

3.2.4. Consumption of other drugs

All of the studies disclosed their samples' additional drug consumption beside antidiabetic drugs. Most patients consumed antihypertensive and antilipidemic agents including angiotensin II antagonist, ACE inhibitor, calcium channel blocker, ARBs, beta blocker, aldosterone agonist, diuretic, digoxin, aspirin, fibrate, niacin and statins. Study of Varanasi et al. (2012) included 102 patients with antihypertensive; 92 patients with statin; 34 patients with fibrate; 22 patients with niacin; 76 patients with ACE inhibitor; 56 patients with hydrochlorothiazide; 47 patients with beta blocker; and 28 patients with calcium channel blocker [12]. On the other hand, Bizino et al. (2019), included 21 patients with antilipidemic agents and 18 patients with antihypertensive agents [16]. Study by Gejl et al. (2012) stated that their sample included 3 patients with angiotensin II antagonist, 6 patients with ACE inhibitor, and 5 patients with calcium channel blocker [14]. Study of Bethel et al. (2020) included 393 patients with antihypertensive, 300 patients with aspirin, 57 patients with thienopyridines, 333 patients with antiplatelets; 336 with ACE inhibitor or ARB, 236 patients with beta blocker, 123 patients with calcium channel blocker, 336 patients with statin and 355 patients with any lipid lowering agents [17]. Raparelli et al. (2020) stated that their samples consumed additional drugs to prevent cardiovascular adverse effects [13].

3.3. Research focus

Varanasi et al. (2012) focused on observing the effect of liraglutide on BMI, HbA1c, systolic blood pressure (SBP), C-reactive protein (CRP), and fasting lipid concentrations. This study uptitrated the dosage of liraglutide every two weeks, from 0,6 to 1,8 mg/day [12]. Moreover, Bizino et al. (2019) also uptitrated liraglutide every week from 0,6 to 1,8 mg/day. They specifically observed cardiac function, blood pressure, body weight, serum creatinine, and N-terminal pro-brain natriuretic peptide (NT-proBNP) [16].

The study of Arturi et al. (2016) focused on the cardiac functional capacity of T2DM patients with a history of post-ischemic chronic heart failure. Similar to the other studies, they observed gender, age, BMI, blood pressure, heart rate, fasting plasma glucose, serum creatinine, proBNP, lipid profile, pancreas enzyme, and calcitonin [15]. Study by Bethel et al. (2020) observed EXSCEL (EXenatide Study of Cardiovascular Event Lowering) in patients with type 2 diabetes. Patients in this study are allowed to consume up to three oral glucose-lowering agents either alone or in combination with insulin [17]. Raparelli et al. (2020) focused on differentiating the major cardiovascular events between male and female in GLP-1 RA medication [13].

3.4. Cardiovascular outcomes

From these studies, we listed several parameters that related to cardiovascular disease and its risk factors including BMI, HbA1c, blood pressure, lipid profile, CRP, myocardial blood flow (MBF), myocardial glucose uptake (MGU), left ventricular function, proBNP, heart rate, and cardiovascular event-free survival (see Table 2).

Varanasi et al. (2012) found that liraglutide caused significant reduction in body weight; 120 ± 5 kg to 115 ± 3 kg, CRP; 4,7 to 3,2, and HbA1C. Additionally, CRP reduction was dose dependent. Moreover, they also found decreased TG level and mean SBP in the population that received liraglutide therapy [12]. On the other hand, Gejl et al. (2012) examined MBF and MGU. They revealed that exenatide significantly increased MBF by 24% (0,69 ml/g.min to 0,86 ml/g.min), without altering MGU level. Exenatide also stabilized GLUT transport in patients with low insulin sensitivity [14].

Moreover, study of Arturi et al. (2016) found that liraglutide induced significant increase of LVEF and decrease of end-systolic & end-diastolic LV volume. Decrease of end-diastolic LV volume affected significant improvement in anterograde stroke volume [15].

Study by Bizino et al. (2019) found that liraglutide reduced early LV diastolic filling and LV filling pressure, thus postponing the onset of HFpEF and concomitant morbidity and mortality. The use of sulfonyleurea derivatives (SUD) was decreased from 26% at baseline to 18% at 26 weeks and the use of insulin also decreased from 70 ± 46 to 54 ± 43 IU/day in the liraglutide group. It is also found that liraglutide reduces weight and NT-proBNP level significantly, while there is no significant difference between HbA1c level in liraglutide group and placebo. None of the patients experienced symptoms of heart failure during their study, but one participant in the liraglutide group who started calcium channel blocker medication developed edema [16].

Study by Bethel et al. (2020) demonstrated that MACE (major adverse cardiovascular events) and ACM (all-cause mortality) remained potent after right censoring or application of literature-derived risk reductions, but exenatide versus placebo MACE effect size and statistical significance were increased by IPTW (inverse probability for treatment weighting) [17].

Finally, a study by Raparelli et al. (2020) found that women experienced less major cardiovascular events than men and the risk reduction was found stronger in women. Other than that, the use of antihypertensive and statins medication also found less frequent among women than men. Unfortunately, women experienced higher adverse events than men, such as urosepsis and genital yeast infection [13].

4. Discussion

The results are varied between each study and all studies have distinct findings related to cardiovascular outcomes (cardiovascular risks and events). Generally, all studies showed positive outcomes toward GLP-1 RA therapy in T2DM patients. All studies used different types of GLP-1 RA including liraglutide and exenatide, with various therapy duration, between 6 months up to 3,2 years. However, a study by Gejl et al. (2012) did not reveal their therapy duration [14]. Two studies by Arturi et al. (2016) and Bethel et al. (2020) excluded patients with previous history of GLP-1 RA therapy [15,17]. Besides, most patients received GLP-1 RA therapy in combination with other oral antidiabetics, except Gejl et al. (2012) that stopped all oral antidiabetic and remaining medications before giving exenatide therapy to their patients [14].

Previous diabetes treatment plays an important role, because poor glycemic control will lead to worse cardiovascular treatments. Currently, it is emphasized to closely monitor and control the glycemic levels of T2DM patients, in order to improve cardiac outcomes [18]. In this systematic review, Arturi et al. (2016) and Bethel et al. (2020) excluded patients with previous history of GLP-1 RA treatment [15,17]. Possibly, the authors used this method to evaluate the effect of initial GLP-1 RA therapy on their samples.

From the current recommendation, GLP-1 RA used as a combination with metformin in T2DM patients with established ASCVD [7]. Most patients in these studies previously received either metformin or insulin therapy and would be combined with GLP-1 RA throughout the research period. This condition created an ideal therapy regiment that corresponded with the current guideline. When combined with insulin, GLP-1 RA therapy improved glycemic control without increasing the risk of hypoglycemia. Moreover, this combination therapy did not cause any major adverse event besides gastrointestinal events, which was also found in GLP-1 RA monotherapy [19]. Hypoglycemia effect from GLP-1 RA only emerged

Table 2
Summary of included study outcomes in this systematic review.

Study	Evaluated Characteristic				
	BMI (kg/m ²)	Previous Diabetes Treatment	Medical History	Consumption of Other Drugs	Cardiovascular Outcomes
Varanasi et al. (2012) [12]	38.2	insulin/metformin/sulfonylurea/thiazolidinediones/sitagliptine.	Obese, uncontrolled hyperglycemia,	antihypertensive and antilipidemic drugs	Reduction in mean body weight, mean HbA1C, CRP, TG concentration, and SBP. Significant relationship between the reduction of TG & HbA1C and the reduction of CRP & HbA1c.
Gejl et al. (2012) [14]	31.9 ± 1.0	Insulin-naïve, combined with metformin or sulfonylurea.	Non-smoker and without coronary arteries disease	Statins, sulfonylurea, angiotensin II antagonists, ACE inhibitors, and CaCB.	Exenatide stabilized GLUT transport in patients with low insulin sensitivity. Exenatide significantly increased MBF and did not alter MGU.
Arturi et al. (2016) [15]	≤45	metformin and/or sulfonylurea.	Acute myocardial infarction and NYHA class II/III and/or LVEF ≤45%	ACE inhibitors and/or ARB, beta blocker, aldosterone agonists, diuretics and/or digoxin.	Liraglutide increase LVEF, anterograde stroke volume, and cardiac output. Liraglutide reduce indexed end-systolic & end-diastolic LV volume, mitral regurgitation and was associated with a significant reduction of ProBNP levels.
Bizino et al. (2019) [16]	≥25	insulin or metformin.	Stable BP < 150/85 mmHg for at least 1 month.	antilipidemic agent or antihypertensive drugs.	Liraglutide cause reduced early LV diastolic filling and LV filling pressure, indicating its potential ability to postpone the onset HFpEF and concomitant morbidity & mortality.
Bethel et al. (2020) [17]	35	Excluded patient with previous treatment of GLP-1 RA.	Included patient with any prior CV risk and coronary, cerebrovascular, or peripheral artery event.	aspirin, thienopyridines, antiplatelets, antihypertensive, and antilipidemic agents	EXSCEL-observed HRs for MACE and ACM remained robust after right censoring or application of literature-derived risk reductions, but exenatide versus placebo MACE effect size and statistical significance were increased by IPTW.
Raparelli et al. (2020) [13]	n/a	Ongoing use of metformin.	Excluded patient with diagnosis of T1DM, gestational diabetes mellitus, and cystic fibrosis.	antihypertensive, statins, and aspirin.	Women experienced less major cardiovascular event and stronger risk reductions than men who currently treated with GLP-1RA than those treated with sulfonylurea.

when it is combined with other agents that triggers hypoglycemia [20]. In combination with metformin, GLP-1 RA also demonstrated positive outcomes, including more dominant weight loss effect [21] and additive glucose-lowering control [22].

Moreover, study by Varanasi et al. (2012) found that liraglutide significantly caused weight loss on their samples [12]. Bizino et al. (2019) also found similar results on their study [16]. This weight loss effect from GLP-1 RA also demonstrated by other studies [23–25]. Better results were found in exenatide therapy, that significantly reduced body weight, waist circumference, and total body and fat truncal fat mass [26]. This effect will be helpful for T2DM patients in reducing the risk of cardiovascular disease, because excess fat accumulation triggered cardiovascular disease through supporting premature atherosclerosis formation in large arteries and causing abnormality in coronary microvasculature. From these studies, we can see that the samples' BMI varied from 31.9–45 kg/m², that can be categorized as obese. Thus, the weight loss effect from GLP-1 RA would be beneficial in reducing the risk of developing cardiovascular disease and as well as heart failure in T2DM patients [27].

Antihypertensive drugs are known to reduce cardiovascular events risks in patients with T2DM and those with SBP above 140 mmHg. Almost all participants in studies reviewed in this article also consumed antihypertensive drugs in combination with their antidiabetic drugs. Recent systematic review concluded that the treatment reduced all-cause mortality (including myocardial infarction, stroke, and heart failure) if the baseline SBP before treatment was more than 140 mmHg or if SBP with treatment was 130–140 mmHg. However, the treatment was not beneficial for those with SBP below 140 mmHg which increased the cardiovascular events risks. This may reinforce the medication for T2DM if those antihypertensive agents are combined with GLP-1RA which have proven to have cardioprotective effects [28].

Several studies also included patients with antilipidemic agents. Lipid profile control in T2DM patients is very important because elevated total cholesterol level, especially triglyceride, can independently become a risk factor for CHD in T2DM patients [29,30]. Moreover, in T2DM patients, LDL cholesterol are adjusted into

small, dense LDL (sdLDL), which tends to be more atherogenic [31]. Studies in this systematic review did not report any drug interaction between anti lipidemic agents and GLP-1 RA. Therefore, GLP-1 RA therapy will be beneficial for T2DM patients in controlling their lipid profile and reducing the risk of developing cardiovascular.

Generally, diabetes mellitus is independently associated with abnormal left ventricular (LV) relaxation [32]. This thing happened because advanced-glycation-end products (AGEs) accumulated in the interstitial. This condition contributes to the occurrence of congestive heart failure (CHF). From these studies, Arturi et al. (2016) demonstrated that liraglutide therapy results in improved LVEF, and reduced end-systolic and end-diastolic LV volume, without affecting LV mass [15]. Similar results also demonstrated by Bizino et al. (2019) [16]. Therefore, these effects are beneficial to preserve diastolic function, especially in preventing CHF and HFpEF, which are frequently developed in T2DM patients. Latest results from LEADER study concludes that liraglutide is considered to be suitable treatment option for T2DM patients with or without HF [33]. However, it is advised to be careful in treating patients with severe heart failure that have high E/Ea ratio using liraglutide, because liraglutide may exacerbate heart failure symptoms and decompensation [16]. The exacerbation can be caused by the effect of liraglutide in increasing the heart rate [34,35].

Based on the study of Gejl et al. (2012), Exenatide significantly increased MBF by 24% from 0,69 to 0,86 ml/g.min. It also stabilized GLUT transporters in patients with low insulin sensitivity [14]. However, these effects did not appear in liraglutide therapy [36]. Moreover, GLP-1 RA did not alter MGU, but it is originally lower in T2DM patients because low insulin infusion produced a similar condition to fasting state and caused high circulating FFA [37]. The MBF boosting effect from GLP-1 RA may be beneficial for ischemic heart disease and coronary arterial disease patients.

Varanasi et al. (2012) demonstrated that liraglutide significantly caused SBP reduction, especially the first three months after treatment initiation [12]. This outcome may be beneficial in improving arterial compliance and reducing arterial stiffness. Similar results also stated by other studies that compared liraglutide to insulin glargine, in addition to glimepiride and metformin

[38]. However, Arturi et al. (2016) found no significant SBP reduction in liraglutide therapy, in addition to sitagliptin [15]. Bizino et al. (2019) also did not find any significant blood pressure changes in liraglutide therapy, in addition to metformin or insulin [16]. Different outcomes from these studies happened because each study has different sample characteristics and methods in giving GLP-1 RA to their samples. Thus, further comprehensive investigation should be conducted.

Based on several studies, GLP-1 RA therapy caused significant changes in lipid profile, with slight reduction of HDL-C [39–41]. Varanasi et al. (2012) demonstrated similar result, that liraglutide caused mean triglyceride concentration reduction from 173 ± 19 mg/dL to 151 ± 15 mg/dL [12], but other studies in this systematic review did not find any significant cholesterol level reduction in GLP-1 RA therapy. This may be because each study's sample has different characteristics, with various doses and types of GLP-1 RA. Therefore, the effect of GLP-1 RA in improving lipid profile needs further investigation.

Studies in this systematic review included patients with various histories and additional risks of cardiovascular disease. However, Gejl et al. (2012) and Bizino et al. (2019) excluded patients with a history of cardiovascular disease [14,16]. This might affect the outcomes of the drugs' benefits if compared with studies that include patients with prior cardiovascular disease. On the other hand, GLP-1 RA, especially liraglutide, has potential mechanisms that can be used to prevent cardiovascular disease. It increased eNOS activity and reduced ICAM-1 expression, which can be protective against endothelial dysfunction [42]. These effects may add more benefits in GLP-1 RA therapy, but further investigation should be done to comprehensively understand its mechanism.

Study by Varanasi et al. (2012) included obese patients with uncontrolled hyperglycemia into their study [12]. Generally, samples in these studies also had high BMI, that categorized as obese. Indeed, GLP-1 RA, specifically liraglutide, will be more beneficial in obese patients because it had been approved as anti-obesity medication [43]. Moreover, Bethel et al. (2020) excluded samples with end-stage kidney diseases or an eGFR at entry <20 ml/min/1.73 m² [17]. Bizino et al. (2019) also excluded samples with history of renal-hepatic disease [16]. This decision is really wise, considering that most GLP-1 RA therapy required dose adjustment in patients with lower eGFR [7].

5. Study strength and limitation

There is still no other review study that focuses on the cardioprotective elements of GLP-1 RA in medication for T2DM patients. Therefore, this review gives the newest update of cardioprotective benefits GLP-1 RA has as the novel strategy in treating T2DM. We reviewed the cardiovascular outcomes of each study which showed the superiority of this drug in the aspect of cardioprotective properties. However, this study also has limitations including baseline characteristics that differ from one study to another. Samples that were included in these studies have different medical history. Thus, further study must take this factor into account to avoid any biases to the study outcomes. Moreover, this review approach is limited to descriptive only because each study had a different objective and methodology, heterogeneous population, and these studies were small, and it is possible to be underpowered.

6. Conclusion

GLP-1 RA has cardioprotective benefits for T2DM patients by enhancing weight loss, improving and preserving cardiac functional capacity and elevating MBF without affecting MGU. Though

these are some promising outcomes regarding the cardioprotective properties of GLP-1 RA, the studies are still limited. These studies failed to demonstrate several effects of GLP-1 RA which are reducing blood pressure and improving lipid profile. Further studies in different populations and ethnicity should be conducted in the future, to explore more about these benefits.

Submission declaration and verification

This manuscript is not under consideration for publication elsewhere and all authors have approved the final version of the manuscript. If this manuscript is accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

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