



The Analysis Study of Effects of Glucagon-Like Peptide-1 Receptor to Reduce Adverse Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: A Comprehensive Systematic Review

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ABSTRACT

Background: The aim of this study to show about effects of glucagon-like peptide-1 receptor to reduce adverse cardiovascular events in patients with type 2 diabetes mellitus. **Methods:** By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. **Result:** Eight publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles. **Conclusion:** GLP-1 receptor agonists represent a relatively new class of drugs used for the treatment of T2DM. They are not only able to improve hyperglycaemia of diabetic patients but also directly influence in addition other significant risk factors for CVD such as high blood pressure, dyslipidaemia or obesity. These properties explain at least in part the positive results of the CV outcome studies for liraglutide, semaglutide, dulaglutide and albiglutide, all of which showed not only CV safety but also an improvement in CV prognosis.

Keyword: Type 2 Diabetes mellitus, cardiovascular, glucagon-like peptide-1 receptor.

INTRODUCTION

In healthy people without diabetes, glycemic homeostasis is regulated by pancreatic hormones such as insulin, amylin, and glucagon, as well as by incretin hormones released from the gastrointestinal cells, eg, GLP-1 and glucose-dependent insulinotropic polypeptide. In response to ingestion of glucose, the L and K intestinal cells release incretin hormones that stimulate pancreatic beta cells, leading to insulin secretion. This mechanism is mainly activated after oral ingestion of glucose rather than intravenous administration, and may be impaired in patients with impaired glucose tolerance or non-insulin-dependent diabetes, leading to hyperglycemia. Incretin's role in reducing hyperglycemia is also mediated by glucagon suppression and delayed gastric emptying.¹⁻³

Cardiovascular disease is the leading cause of death and complications in patients with type 2 diabetes. Recently, trials evaluating a sodium-glucose cotransporter 2

inhibitor (empagliflozin) and a glucagon-like peptide 1 (GLP-1) analogue (liraglutide) have shown improved cardiovascular outcomes in patients with type 2 diabetes who were at high risk for cardiovascular events. Semaglutide, a GLP-1 analogue with an extended half-life of approximately 1 week (which permits once-weekly subcutaneous administration), is currently in development but not yet approved for the treatment of type 2 diabetes. Regulatory guidance specifies the need to establish the cardiovascular safety of new therapies for type 2 diabetes in order to rule out excess cardiovascular risk.^{4,5}

To address this critical issue, the past decade has witnessed a surge in cardiovascular outcome trials (CVOTs) focused on evaluating the cardiovascular safety and efficacy of various antidiabetic drugs. One class of drugs that has gained significant attention in this context is the glucagon-like peptide-1 (GLP-1) receptor agonists. CVOTs evaluating

GLP-1 receptor agonist's (GLP-1 RA) effects on cardiovascular outcomes have consistently shown a reduction in MACE rates, primarily in rates of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. A positive effect on cardiovascular outcomes is achieved through several mechanisms. GLP-1 RAs are associated with blood pressure reduction, lipid levels reduction, weight loss and endothelial function improvement.⁶⁻⁸

GLP-1 is an incretine hormone that has a pivotal role in metabolic processes. Primary site of GLP-1 secretion are L-cells in small intestine and colon, but it is also secreted by the pancreatic α cells and neurons in nucleus tractus solitarius in the brainstem. There are evidence that microglial cells also secrete GLP-1 in mice. GLP-1 secretion itself is stimulated in response to food intake. GLP-1 was discovered in 1981 when it was isolated from the pancreatic islet of anglerfish. Further research identified GLP-1 in L cells of mammalian gut mucosa and later, it was proved that GLP-1 enhances

insulin secretion in response to nutrient ingestion. GLP-1 exerts physiological effects by binding to the GLP-1 receptor (GLP-1R) on target cells. The activation of GLP-1R triggers a complex intracellular signaling cascade, which at the end activates protein kinase A (PKA) pathway via production of cyclic adenosine monophosphate (cAMP). GLP-1R are found, apart from the pancreas, in lungs, kidney, central nervous system, stomach, cardiomyocytes, and vascular endothelial cells.^{6,9,10}

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast effects of glucagon-like peptide-1

receptor to reduce adverse cardiovascular events in patients with type 2 diabetes mellitus. It is possible to accomplish this by researching of the effects of glucagon-like peptide-1 receptor to reduce adverse cardiovascular events in patients with type 2 diabetes mellitus. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the effects of glucagon-like peptide-1 receptor to reduce adverse cardiovascular events in patients with type 2 diabetes mellitus. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials,

submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " effects of glucagon-like peptide-1 receptor to reduce adverse cardiovascular events in patients with type 2 diabetes mellitus." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which

all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which

publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

Table 1. Search Strategy

Database Search Strategy		Hits
Pubmed	((("Diabetes mellitus"[MeSH Subheading] OR "Type 2 diabetes mellitus"[All Fields] OR "Therapy" [All Fields]) AND ("Glucagon-like peptide-1"[All Fields] OR "Glucagon-like peptide-1 receptor"[All Fields]) AND ("Effects"[All Fields] OR ("Outcome" [All Fields])))	4328
Science Direct	((("Diabetes mellitus"[MeSH Subheading] OR "Type 2 diabetes mellitus"[All Fields] OR "Therapy" [All Fields]) AND ("Glucagon-like peptide-1"[All Fields] OR "Glucagon-like peptide-1 receptor"[All Fields]) AND ("Effects"[All Fields] OR ("Outcome" [All Fields])))	734
Sagepub	((("Diabetes mellitus"[MeSH Subheading] OR "Type 2 diabetes mellitus"[All Fields] OR "Therapy" [All Fields]) AND ("Glucagon-like peptide-1"[All Fields] OR "Glucagon-like peptide-1 receptor"[All Fields]) AND ("Effects"[All Fields] OR ("Outcome" [All Fields])))	292

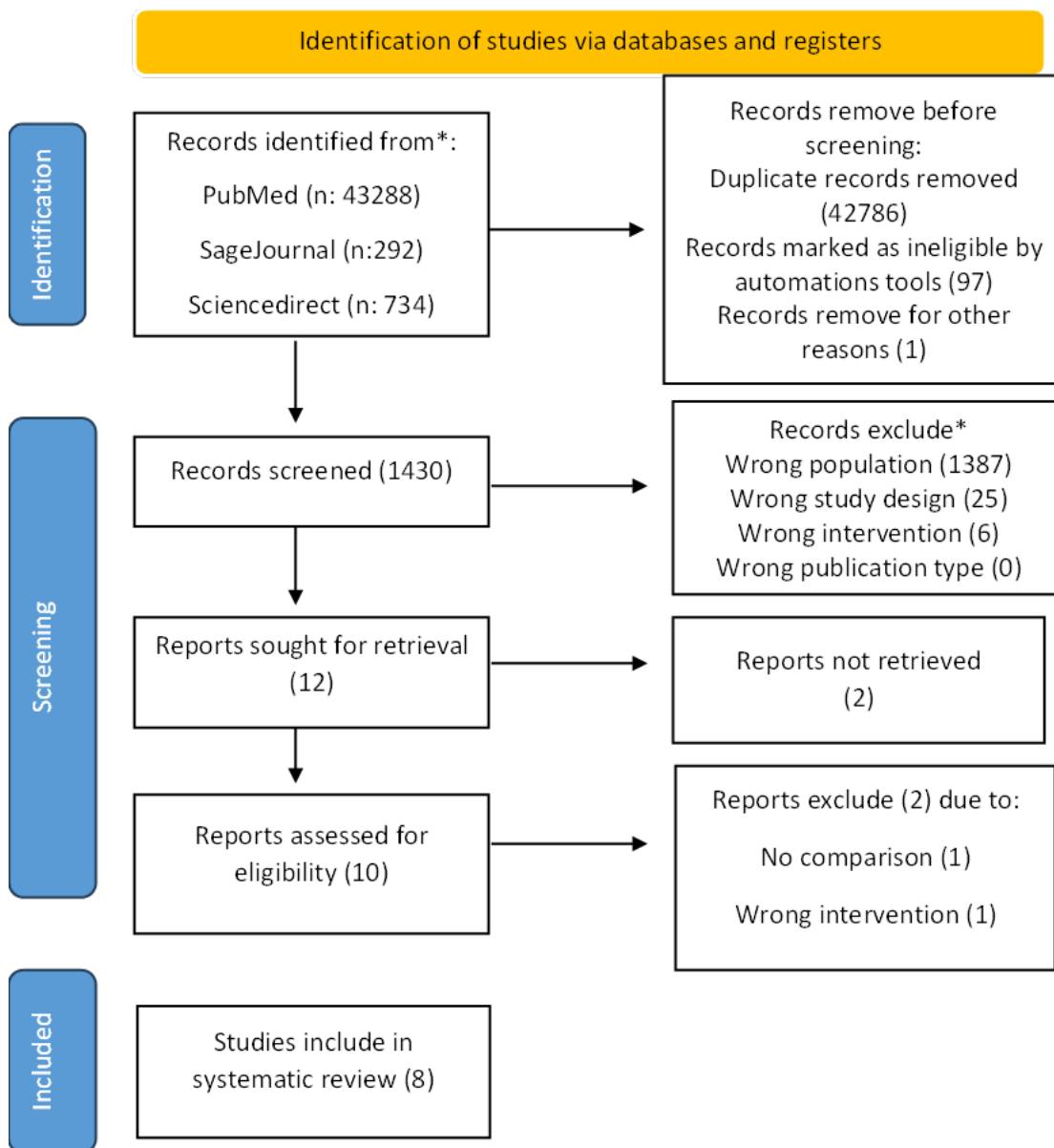


Figure 1. Article search flowchart

Table 2. Critical appraisal of Study

Parameters	(West er, A et al., 2024)	(Mars o, SP et al., 2016)	(Yen, FS et al., 2024)	(Lin, Y et al., 2023)	(Pan, HC et al., 2024)	(Stenbe rg, E & Naslun d, E., 2023)	(Trevi san, M et al., 2021)	(Wang, L et al., 2024)
1. Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation Was there a control group?	No	Yes	Yes	No	No	No	No	No
3. Bias related to confounding factors Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No	No	No	No	No	No	No	No
5. Bias related to assessment, detection, and measurement of the outcome Were there multiple measurements of the outcome, both pre and post the intervention/exposure? Were the outcomes of participants included in any comparisons measured in the same way? Were outcomes measured in a reliable way?	No Yes Yes	No Yes Yes	No Yes Yes	No Yes Yes	No Yes Yes	No Yes Yes	No Yes Yes	No Yes Yes
6. Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Statistical conclusion validity Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 44314 publications. A thorough three-level screening strategy was used to identify only eight papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 3 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 3. The literature include in this study

Author	Origin	Method	Sample	Result
Wester, A et al., 2024 ¹¹	Sweden	We used observational data from Swedish healthcare registers 2010–2020 to emulate a target trial of GLP1 agonists in eligible patients with chronic liver disease and type 2 diabetes. We used an inverse-probability weighted marginal structural model to compare parametric estimates of 10-year MALO risk (decompensated cirrhosis, hepatocellular carcinoma, liver transplantation or MALO-related death) in initiators of GLP1 agonists with non-initiators. We randomly sampled 5% of the	1026	GLP1 agonist initiators had a 10-year risk of MALO at 13.3% (42/1026) vs 14.6% in non-initiators (1079/15 633) in intention-to-treat analysis (risk ratio (RR)=0.91, 95% CI=0.50 to 1.32). The corresponding 10-year per-protocol risk estimates were 7.4% (22/1026) and 14.4% (1079/15 633), respectively (RR=0.51, 95% CI=0.14 to 0.88). The per-protocol risk estimates at 6 years were 5.4% (21/1026) vs 9.0% (933/15 633) (RR=0.60, 95% CI=0.29 to 0.90) and at 8 years 7.2% (22/1026) vs 11.7% (1036/15 633) (RR=0.61, 95% CI=0.21 to 1.01).

		non-initiators to increase computational efficiency.		
Marso, SP et al., 2016⁴	Germany	In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo.	9340	A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the
Yen, FS et al., 2024¹²	Taiwan	From January 1, 2008, to December 31, 2018, we used propensity-score matching to identify 31,183 pairs of GLP-1 RA users and nonusers from Taiwan's National Health	31183	The median (Q1, Q3) follow-up time for GLP-1 RA users and nonusers were 2.19 (1.35, 3.52) and 2.14 (1.19, 3.68) years, respectively. The all-cause mortality incidence rate was 5.67 and 13.06 per 1000 person-years for GLP-1 RA users and nonusers, respectively. Multivariable-adjusted analysis showed that GLP-1 RA use had significantly lower risks of all-

		Insurance Research Database. Multivariable-adjusted Cox proportional hazards models were used to examine the outcomes between the study and control groups.		cause mortality (aHR 0.48, 95%CI 0.43–0.53), cardiovascular events (aHR 0.92, 95%CI 0.86–0.99), cardiovascular death (aHR 0.57, 95%CI 0.45–0.72), and liver-related death (aHR 0.32, 95%CI 0.13–0.75). However, there was no significant difference in the risk of liver cirrhosis development, hepatic failure, and hepatocellular carcinoma compared to GLP-1 RA no-use.
Lin, Y et al., 2023 ¹³	Taiwan	In this cohort study, patients with type 2 diabetes mellitus and eGFR < 30 mL/min per 1.73 m ² with a first prescription for GLP-1RAs or dipeptidyl peptidase 4 inhibitors (DPP-4is) from 2012 to 2021 (n = 125,392) were enrolled. A Cox proportional hazard model was used to assess the cardiorenal protective effects between the GLP-1RA and DPP-4i groups.	8922	A total of 8922 participants [mean (SD) age 68.4 (11.5) years; 4516 (50.6%) males; GLP-1RAs, n = 759; DPP-4is, n = 8163] were eligible for this study. During a mean follow-up of 2.1 years, 78 (13%) and 204 (13.8%) patients developed composite cardiovascular events in the GLP-1RA and DPP-4i groups, respectively [hazard ratio (HR) 0.88, 95% confidence interval CI 0.68–1.13]. Composite kidney events were reported in 134 (38.2%) and 393 (44.2%) patients in the GLP-1RA and DPP-4i groups, respectively (subdistribution HR 0.72, 95% CI 0.56–0.93).
Pan, HC et al., 2024 ¹⁴	Taiwan	We identified 165,860 patients diagnosed with type 2 diabetes and AKD upon admission to the enrolled healthcare facilities during study period	165860	The most common causes of AKI are sepsis (55.2%) and cardiorenal syndrome (34.2%). After a median follow-up of 2.3 years, GLP-1 RAs users exhibit reduced risks of mortality (adjusted hazard ratio [aHR]: 0.57), MACEs (aHR: 0.88), and MAKEs (aHR: 0.73). External validation in a multicenter dataset of 1245 type 2 diabetes patients with AKD supports the favorable

				outcomes. These results emphasize the potential of GLP-1 RAs in individualized treatment for this population.
Stenberg, E & Naslund, E., 2023¹⁵	Sweden	In this propensity score matched cohort study on nationwide data, patients with T2D and severe obesity who underwent MBS in Sweden from 2007 until 2019 were identified from the Scandinavian Obesity Surgery Registry and matched to a non-surgical group with T2D treated with GLP-1 RA (81.7% liraglutide, 9.0% dulaglutide, 6.0% exenatide, 1.6% lixisenatide and 0.8% semaglutide) from the general population using generalized linear model.	2161	In total 2161 patients (obesity class I (10.2%), class II (40.3%), class III (49.5%)) were matched to 2161 non-surgical patients (mean age 51.1 ± 9.29 vs 51.5 ± 8.92 years, 64.8% vs. 64.4% women, with mean number of diabetes drugs of 2.5 ± 0.89 vs 2.6 ± 0.87 , a mean duration of diabetes of 6.0 ± 4.15 vs 6.0 ± 4.51 years with 44.2% vs. 42.8% being treated with insulin at baseline). During the study period, 113 patients (8-year cumulative incidence 9.3%) compared to 130 non-surgical patients (8-year cumulative incidence 11.3%) suffered from MACE or all-cause mortality (HR 0.76, 95%CI 0.59–0.98), and 69 patients (8-year cumulative incidence 5.1%) compared to 92 non-surgical patients (8-year cumulative incidence 7.6%) suffered from a non-fatal MACE (HR 0.68, 95%CI 0.49–0.93).
Trevisan, M et al., 2021¹⁶	Sweden	Prospective observational study including all patients with diabetes surviving an MI and registered in the nationwide SWEDEHEART registry during 2010–17.	17868	In total, 17 868 patients with diabetes were discharged alive after a first event of MI. Their median age was 71 years, 36% were women and their median estimated glomerular filtration rate was 75 mL/min/1.73m ² . Of those, 365 (2%) were using GLP-1 RAs. During median 3 years of follow-up, 7005 patients experienced the primary composite outcome. Compared with standard of diabetes care, use of GLP-1 RAs was associated with a lower event risk [adjusted hazard ratio (HR) 0.72; 95% confidence interval (CI): 0.56–0.92],

				mainly attributed to a lower rate of re-infarction and stroke. Results were similar after propensity score matching or when compared with users of sulfonylurea. There was no suggestion of heterogeneity across subgroups of age, sex, chronic kidney disease, and STEMI.
Wang, L et al., 2024 ¹⁷	USA	This retrospective cohort study was based on a nationwide multicenter database of electronic health records (EHRs) of 113 million US patients. The study population included 1 651 452 patients with T2D who had no prior diagnosis of OACs and were prescribed GLP-1RAs, insulins, or metformin during March 2005 to November 2018. Data analysis was conducted on April 26, 2024.	1 651 452	. Although not statistically significant, the HR for stomach cancer was less than 1 among patients who took GLP-1RAs compared with those who took insulin (HR, 0.73; 95% CI, 0.51-1.03). GLP-1RAs were not associated with a reduced risk of postmenopausal breast cancer or thyroid cancer. Of those cancers that showed a decreased risk among patients taking GLP-1RAs compared with those taking insulin, HRs for patients taking GLP-1RAs vs those taking metformin for colorectal and gallbladder cancer were less than 1,

DISCUSSION

Management of type 2 diabetes mellitus (T2DM) has evolved from a glucocentric to a cardiometabolic approach. Consequently, choosing anti-hyperglycemic therapies with proven cardiovascular and renal benefits is now a cornerstone of T2DM management. Both glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) have individually been shown to reduce cardiovascular and kidney outcomes in patients with T2DM, with a low hypoglycemia risk. Cardiovascular risk reduction seems however to be more pronounced in individuals with T2DM and established atherosclerotic cardiovascular disease (ASCVD) as compared to those without established ASCVD.^{18–20}

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of medications that have shown efficacy in lowering blood glucose levels and are commonly used in the treatment of type 2 diabetes. GLP-1 RAs directly stimulate the GLP-1

receptors, leading to a strong antihyperglycemic effect by enhancing insulin secretion. In the past few years, these drugs have shown promise in many areas, including their role in the reduction of cardiovascular events. In 2008, the United States Food and Drug Administration issued a mandate requiring novel antihyperglycemic medications to demonstrate cardiovascular safety and efficacy through large cardiovascular outcome trials (CVOTs). Improvement in HbA1c is anticipated to reduce cardiovascular risk in diabetic patients. The cardiovascular benefits of GLP-1 RAs demonstrated in CVOTs could be partly due to better glycemic control in patients with type 2 diabetes. Although previous studies have shown the superiority of GLP-1 RAs compared with placebo in terms of major adverse cardiovascular events (MACEs), mortality, and stroke, there is a paucity of data on cardiovascular efficacy of GLP-1 RAs in patients without diabetes.^{21–23}

A recent meta-analysis of GLP1-RA cardiovascular outcomes trials, which did not include the

HARMONY Outcomes trial (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus), showed a 10% reduction in MACE, but differences in the treatment effect of GLP1-RA on MACE between patients with and without ASCVD have not been confirmed, because primary prevention patients represent only a relatively small proportion of the patient population in each of the trials, yielding much fewer events and thereby resulting in underpowered analyses.^{24,25}

CONCLUSION

In conclusion, GLP-1 receptor agonists represent a relatively new class of drugs used for the treatment of T2DM. They are not only able to improve hyperglycaemia of diabetic patients but also directly influence in addition other significant risk factors for CVD such as high blood pressure, dyslipidaemia or obesity. These properties explain at least in part the positive results of the CV outcome studies for liraglutide, semaglutide,

dulaglutide and albiglutide, all of which showed not only CV safety but also an improvement in CV prognosis.

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

REFERENCES

1. Nachawi N, Rao PP, Makin V. The role of GLP-1 receptor agonists in managing type 2 diabetes. Cleve Clin J Med. 2022;89(8):457–64.
2. Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectr [Internet]. 2017 Aug 1;30(3):202–10. Available from: <https://diabetesjournals.org/spectrum/article/30/3/202/32399/Glucagon-Like-Peptide-1-Receptor-Agonists-for-Type>
3. Collins L, Costello RA. Glucagon-Like Peptide-1 Receptor Agonists [Internet]. StatPearls. 2024. Available from:

- <http://www.ncbi.nlm.nih.gov/pubmed/31641522>
4. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834–44.
 5. Rivera FB, Cruz LLA, Magalong JV, Ruyeras JMMJ, Aparece JP, Bantayan NRB, et al. Cardiovascular and renal outcomes of glucagon-like peptide 1 receptor agonists among patients with and without type 2 diabetes mellitus: A meta-analysis of randomized placebo-controlled trials. *Am J Prev Cardiol* [Internet]. 2024;18(March):100679. Available from: <https://doi.org/10.1016/j.ajpc.2024.100679>
 6. Ferhatbegović L, Mršić D, Macić-Džanković A. The benefits of GLP1 receptors in cardiovascular diseases. *Front Clin Diabetes Healthc*. 2023;4(December):1–8.
 7. Qiu M, Ding L, Wei X, Wei W, Zhou H. Effects of glucagon-like peptide 1 receptor agonists and sodium glucose cotransporter 2 inhibitors on major adverse cardiovascular events in type 2 diabetes by race, ethnicity, and region: A meta-analysis. *Med (United States)*. 2020;99(49):1–9.
 8. Simms-Williams N, Treves N, Yin H, Lu S, Yu O, Pradhan R, et al. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: Population based cohort study. *Bmj*. 2024;
 9. Guo X, Sang C, Tang R, Jiang C, Li S, Liu N, et al. Effects of glucagon-like peptide-1 receptor agonists on major coronary events in patients with type 2 diabetes. *Diabetes, Obes Metab*. 2023;25(S1):53–63.
 10. Kim GS, Park JH, Won JC. The role of glucagon-like peptide 1 receptor agonists and

- sodium-glucose cotransporter 2 inhibitors in reducing cardiovascular events in patients with type 2 diabetes. *Endocrinol Metab.* 2019;34(2):106–16.
11. Wester A, Shang Y, Toresson Grip E, Matthews AA, Hagström H. Glucagon-like peptide-1 receptor agonists and risk of major adverse liver outcomes in patients with chronic liver disease and type 2 diabetes. *Gut.* 2024;73(5):835–43.
12. Yen FS, Hou MC, Wei JCC, Shih YH, Hwu CM, Hsu CC. Effects of glucagon-like peptide-1 receptor agonists on liver-related and cardiovascular mortality in patients with type 2 diabetes. *BMC Med* [Internet]. 2024;22(1):1–9. Available from: <https://doi.org/10.1186/s12916-023-03228-4>
13. Lin Y, Wang TH, Tsai ML, Wu VCC, Tseng CJ, Lin MS, et al. The cardiovascular and renal effects of glucagon-like peptide 1 receptor agonists in patients with advanced diabetic kidney disease. *Cardiovasc Diabetol* [Internet]. 2023;22(1):1–11. Available from: <https://doi.org/10.1186/s12933-023-01793-9>
14. Pan HC, Chen JY, Chen HY, Yeh FY, Sun CY, Huang TTM, et al. GLP-1 receptor agonists' impact on cardio-renal outcomes and mortality in T2D with acute kidney disease. *Nat Commun* [Internet]. 2024;15(1). Available from: <http://dx.doi.org/10.1038/s41467-024-50199-y>
15. Stenberg E, Näslund E. Major adverse cardiovascular events among patients with type-2 diabetes, a nationwide cohort study comparing primary metabolic and bariatric surgery to GLP-1 receptor agonist treatment. *Int J Obes.* 2023;47(4):251–6.
16. Trevisan M, Fu EL, Szummer K, Norhammar A, Lundman P, Wanner C, et al. Glucagon-like peptide-1 receptor agonists and

- the risk of cardiovascular events in diabetes patients surviving an acute myocardial infarction. *Eur Hear J - Cardiovasc Pharmacother.* 2021;7(2):104–11.
17. Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients with Type 2 Diabetes. *JAMA Netw Open.* 2024;7(7):e2421305.
18. Gourdy P, Darmon P, Dievart F, Halimi JM, Guerci B. Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM). *Cardiovasc Diabetol* [Internet]. 2023;22(1):1–14. Available from: <https://doi.org/10.1186/s12933-023-01798-4>
19. Marsico F, Paolillo S, Gargiulo P, Bruzzese D, Dell'Aversana S, Esposito I, et al. Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with Type 2 diabetes mellitus with or without established cardiovascular disease: A meta-analysis of randomized controlled trials. *Eur Heart J.* 2020;41(35):3346–58.
20. Parab P, Chaudhary P, Mukhtar S, Moradi A, Kodali A, Okoye C, et al. Role of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in Cardiovascular Risk Management in Patients With Type 2 Diabetes Mellitus: A Systematic Review. *Cureus.* 2023;1(December 2008):1–11.
21. Hosseinpour A, Sood A, Kamalpour J, Zandi E, Pakmehr SA, Hosseinpour H, et al. Glucagon-Like Peptide-1 Receptor Agonists and Major Adverse Cardiovascular Events in Patients With and Without Diabetes: A Meta-Analysis of Randomized-Controlled Trials. *Clin Cardiol.* 2024;47(7).
22. Macisaac RJ. Glucagon-like

- peptide-1 receptor agonists and the cardiorenal axis in Type 2 diabetes: a focus on dulaglutide. *Future Cardiol.* 2021;17(3):459–73.
23. Qin J, Song L. Glucagon-like peptide-1 (GLP-1) receptor agonists and cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of double-blind, randomized, placebo-controlled clinical trials. *BMC Endocr Disord* [Internet]. 2022;22(1):1–7. Available from: <https://doi.org/10.1186/s12902-022-01036-0>
24. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. 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: Systematic review and meta-analysis of cardiovascular outcomes trials. *Circulation.* 2019;139(17):2022–31.
25. Helmstädter J, Keppeler K, Küster L, Münzel T, Daiber A, Steven S. Glucagon-like peptide-1 (GLP-1) receptor agonists and their cardiovascular benefits—The role of the GLP-1 receptor. *Br J Pharmacol.* 2022;179(4):659–76.