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The Role of GLP-1RA(glucagon-like peptide-1receptor agonist) drugs on cardiovascular disease in diabetes

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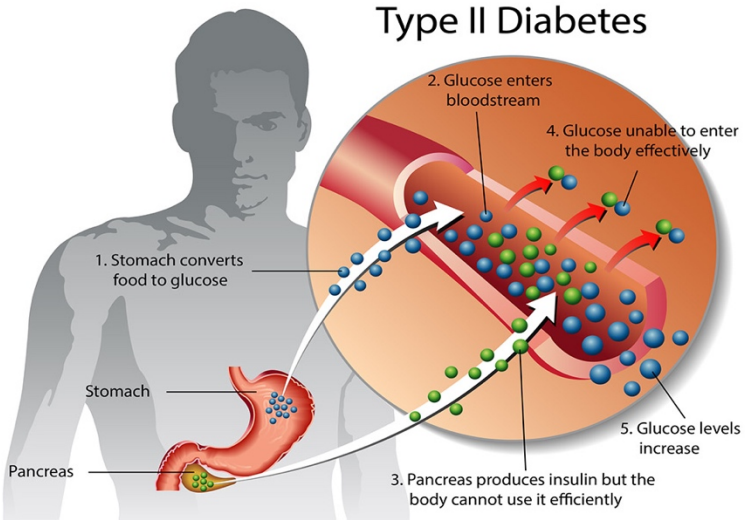
Abstracts:
The prevalence of type 2 diabetes mellitus (T2DM) constantly increasing worldwide that's led to the emergence of several anti diabetic drugs with different mechanisms of action. The incretin hormones and their effect on glucose metabolism and the pathogenesis of T2DM have become a landmark discovery in the treatment of this increasingly common metabolic disorder. Glucagon-like peptide-1 receptor agonists is one of main classes of incretin-based therapies that regulate glucose uptake in various ways while reducing body weight (GLP receptor agonists -1) In addition, the data indicate its possible therapeutic potential in the treatment of other clinical conditions such as obesity, cardiovascular disease and other diseases. This review examines the current GLP-1 receptor agonists and itsuse in possible treatment strategies for T2DM, as well as its future in the context of diabetes and other diseaseincluding the impact of ventricular loading conditions, direct effects on cardiac structure and function, myocardial energetics and modulation of endothelial function for Glucagon-like peptide-1

Aim and Objective: -is to review the role of GLP-1 receptor agonists on cardiovascular disease in type 2 diabetes mellitus patients

Keywords: Diabetes mellitus, Heart failure,Hypoglycemic agents, Myocardial ischemia; Cardiovascular mechanisms; Cardiovascular outcomes; GLP-1 agonists Cardiovascular outcomes.

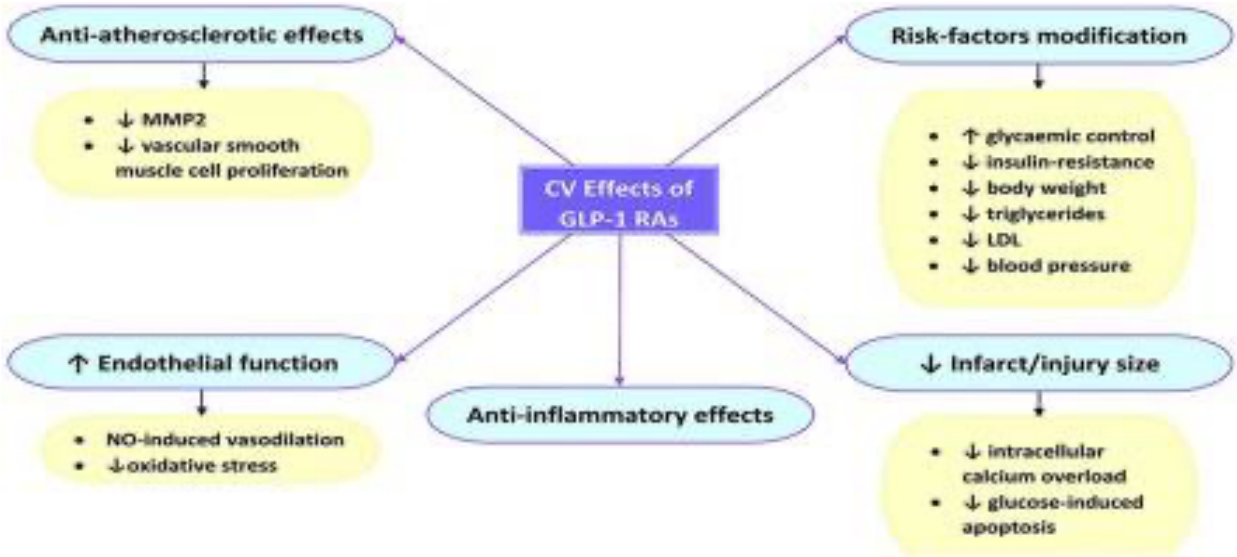


INTRODUCTION:

Type 2 diabetes mellitus (T2DM) prevalence is increasing wordwide. Though type 2 diabetes mellitus prognosis has improved, the associated cardiovascular mortality and morbidity pose a challenge considerable for healthcare systems. cardiovascular disease (CVD) risk is two to four times higher in patients with diabetes than in their non diabetic patients .preventing CVD in these patients is essential in addition to glucose control. Though the intensive glucose control has been shown to reduce microvascular complications controversy remains as to whether it reduces macrovascular complications.Glucose-lowering agents negative effects in patients with an increased risk of heart failure (HF) became evident after rosiglitazone, was withdrawn from the European Union market due to evidence of increased risk of CVD, including MI.The United state Food and Drug Administration and the European Medicines Agency in response began requiring hypoglycemic therapies to demonstrate an acceptable cardiovascular risk . Newly several drug classes have demonstrated a significant reduction in major adverse cardiovascular events (MACE), death, and hospitalizations for heart failure These drugs include incretin-based therapies,such as glucagon-like peptide 1 (GLP-1) receptor agonists Based on these findings, the recently published guidelines of the American Diabetes Association and the European Association for the Study of Diabetes recommend GLP-1 receptor agonist in patients with T2DM who cannot achieve their target level of glycemic control with metformin We review the most recent cardiovascular outcome trials (CVOTs) of GLP-1 receptor agonists andr discuss their implications for treating patients with T2DM in terms of cardioprotective Effects . Cardiovascular morbidity and mortality are higher among patients with type 2 diabetes mellitus (T2DM) In type 2 diabetes mellitus patient's intensive glucose lowering reduces microvascular disease but it has a smaller and debated effect on CV events or mortality In this setting the US Food and Drug Administration (FDA) in 2008 required that all new agents for the treatment of T2DM should be evaluated in terms of cardiovascular safety . multiple clinical trials since then have been designed to assess cardiovascular outcomes of GLP-1 RA therapy.trials assessed endpoints for major adverse cardiac events (MACE), mainly 3-point outcomes including CV death, non-fatal myocardial infarction and non-fatal stroke Some of the studies have also included hospitalisation for unstable angina or heart failure .Trials were randomised double blind and placebo controlled and enrolled patients with established cardiovascular disease and/or high risk for CV events. The trials we're all designed and powered to demonstrate CV safety (non-inferiority) and some of them to demonstrate both superiority and non-inferiority of anti_ diabetics

Incretins:Glucagon -like peptide-1 (Glp-1):

Incretins are gut hormones that potentiate insulin secretion after meal ingestion in a glucose-dependent manner[1]. The two best-studied incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), exert their insulinotropic actions through distinct G-protein-coupled receptors highly expressed on islet β cells. The GLP-1 and GIP receptors are also widely expressed in nonislet cells(figure 1) and also exert indirect metabolic actions (figure 2) hence, there is considerable interest in identifying extrapancreatic actions of incretin hormones. Two strategies encompassing potentiation of incretin receptor signaling have been pursued for the treatment of type 2 diabetes. Inhibition of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for N-terminal cleavage and inactivation of GIP and GLP-1, has been achieved through the use of orally available medications with high selectivity for the catalytic subunit of DPP-4. A second class of incretin-based therapies is comprised of injectable GLP-1R agonists that exhibit structural differences homology to human GLP-1 or to nonmammalian GLP-1R agonists[2] more than 25 years ago The insulinotropic properties of GIP and GLP-1 were identified however, new actions of incretin hormones continue to be identified. We now discuss recent advances in our understanding of incretin hormone action since the last review in this journal wherever possible, we contrast mechanisms and actions deduced from pharmacological (figure 1 and 2) and physiological (figure 3)preclinical experiments, with comparable data from humans research . As incretin action in the cardiovascular system has recently been reviewed elsewhere we focus our review on noncardiovascular actions of GLP-1 and GrIp.



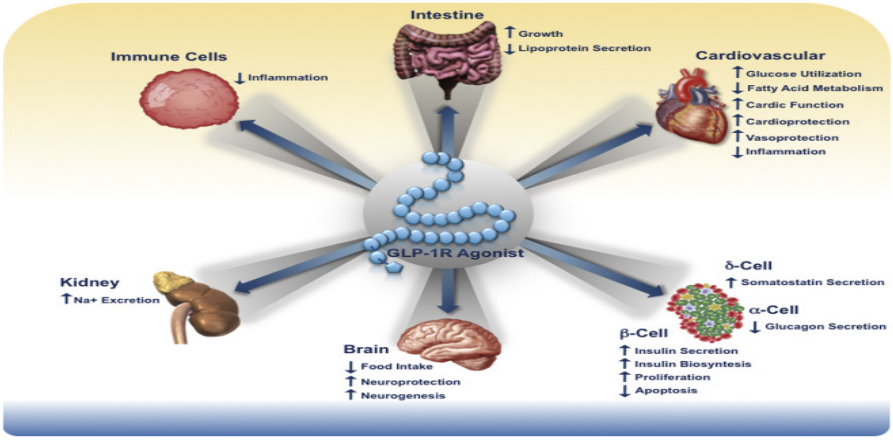


Figure 1.Direct Pharmacological Actions of GLP-1R Agonist

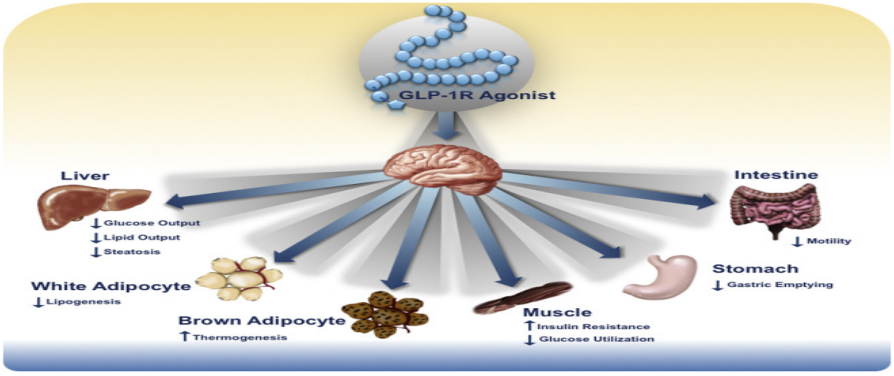
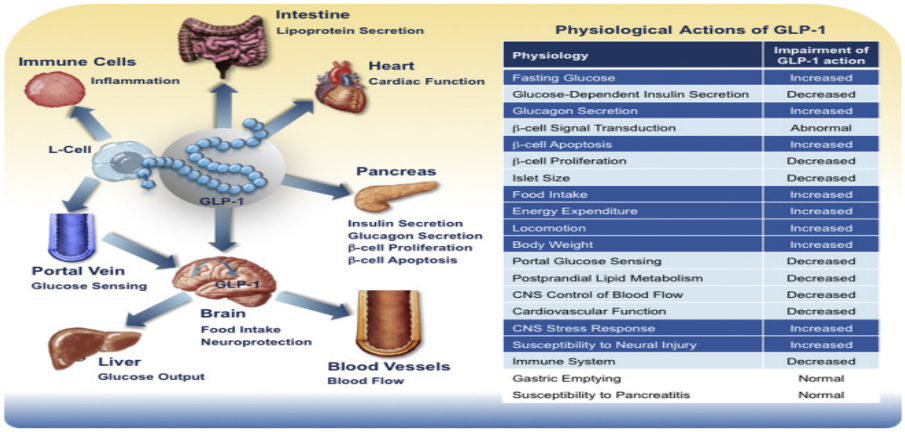


Figure 2.Indirect Pharmacological Effects of GLP-1R Agonising



Physiological Actions of GLP-1

Physiology	Impairment of GLP-1 action
Fasting Glucose	Increased
Glucose-Dependent Insulin Secretion	Decreased
Glucagon Secretion	Increased
β-cell Signal Transduction	Abnormal
β-cell Apoptosis	Increased
β-cell Proliferation	Decreased
Islet Size	Decreased
Food Intake	Increased
Energy Expenditure	Increased
Locomotion	Increased
Body Weight	Increased
Portal Glucose Sensing	Decreased
Postprandial Lipid Metabolism	Decreased
CNS Control of Blood Flow	Decreased
Cardiovascular Function	Decreased
CNS Stress Response	Increased
Susceptibility to Neural Injury	Increased
Immune System	Decreased
Gastric Emptying	Normal
Susceptibility to Pancreatitis	Normal

Figure 3. Physiological Roles of Endogenous GLP-1

Without a previous history of myocardial infarction Diabetic patients have the same level of risk for acute coronary syndromes as nondiabetic patients with previous myocardial infarctions. In diabetic patients the 5-year mortality rate after myocardial infarction is twice that of nondiabetic individuals and can be as high as 50% .In addition, the risk of coronary artery disease increases in diabetic patients by 11% for each 1% increment in hemoglobin A1c greater than 6.5%. In adults with diabetes, but without baseline cardiovascular disease, a HbA1c of 9% is associated with an increased risk of myocardial infarction/acute coronary syndrome odds ratio = stroke and heart failure .Additional risk factors for coronary artery disease in patients with diabetes are increased concentrations of Low density lipoprotein cholesterol, decreased concentrations of high density lipoprotein cholesterol, hypertension, smoking and physical inactivity. Diabetic inactive adults with have a 2.81 increased risk of cardiovascular mortality as compared with inactive adults without diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation {ADVANCE} trial .Adjusted risk of macrovascular events,every 5-year increase including cardiovascular death, nonfatal stroke or nonfatal myocardial infarction , by 49% when adjusted for age at diagnosis.in the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects study, 1123 patients with T2D, aged 50–75 years, with no known or suspected coronary artery disease, were randomly assigned to either stress testing with myocardial perfusion imaging and 5-year clinical follow-up or to only clinical follow-up .One hundred and thirteen patients had silent ischemia of the myocard, including 83 patients with regional myocardial perfusion abnormalities and 30 patients with adenosine-induced electrocardiographic ST-segment depression, ventricular dilation or rest ventricular dysfunction indicative of myocardial ischemia. Markedly abnormal perfusion images with moderate or large stress myocardial perfusion defects occurred in 33 patients . The strongest predictors for abnormal stress tests with myocardial ischemia were patient autonomic nervous system dysfunction with abnormal Valsalva maneuver , male sex and diabetes duration .

Atherosclerosis: the epidemiology and pathogenesis of disease:

Atherosclerosis is one of the most common fatal complications in type 2 dm patients. coronary artery disease prevalence (10.3%) and stroke (6.7%) is three times higher in patients with cardiovascular disease. In patients with T2DM, chronic hyperglycemia, elevated levels of low-density lipoprotein cholesterol and triglycerides, and increased inflammatory response are associated with atherosclerosis. Additionally, people with diabetes may have other risk factors for developing cardiovascular disease, such as high blood pressure, dyslipidemia, obesity, lack of physical activity, chronic kidney disease (CKD), and smoking. Previous studies indicated that concomitant control of other cardiovascular risk factors is important for controlling glucose, as well as for reducing CVD events and death. Although strict glycemic control is associated with a lower incidence of microvascular complications, the effect of glucose control on large vascular complications is not well understood. Modern drugs have advantages in treating cardiovascular disease risk factors and thus can reduce the rate of cardiovascular disease events .

Table 1. CV outcome trials using GLP-1 Receptor agonist

Trial	No. of patients	Study population	Agent	Follow-up	Outcomes
ELIXA[3]	6,068	T2DM with acute coronary event 180 days before randomisation	lixisenatide once-daily vs placebo	2.1 years	4-point MACE: 13.4% in the lixisenatide group vs 13.2% in the placebo group HR: 1.02, 95% CI: 0.89-1.17 $p < 0.001$ for non-inferiority $p = 0.81$ for superiority
LEADER [4]	9,340	T2DM, ≥50 years with known CVD, or age ≥60 years with multiple CV risk factors.	liraglutide once-daily vs placebo	3.8 years	↓ 3-point MACE: 13.0% in the liraglutide group vs 14.9% in the placebo group HR: 0.87, 95% CI: 0.78-0.97 $p < 0.001$ for non-inferiority $p = 0.01$ for superiority ↓ all-cause mortality: 8.2% in the liraglutide group vs 9.6% in the placebo group HR: 0.85, 95% CI: 0.74-0.97 $p = 0.02$ for superiority ↓ CV death: 4.7% in the liraglutide group vs 6.0% in the placebo group $p = 0.007$ for superiority
Sustained [5]	3,297	T2DM, ≥50 years with established CVD, or CKD ≥ stage 3, or age ≥60 years with multiple CV risk factors	semaglutide once-weekly vs placebo	2.1 years	↓ 3-point MACE: 6.6% in the semaglutide group vs 8.9% in the placebo group HR: 0.74, 95% CI: 0.58-0.95 $p < 0.001$ for non-inferiority ↓ non-fatal stroke: 1.6% in the semaglutide group vs 2.7% in the placebo group HR: 0.61, 95% CI:

Trial	No. of patients	Study population	Agent	Follow-up	Outcomes
					0.38-0.99 p = 0.04 for superiority
EXSCEL[6]	14,752	T2DM, 70% with previous CV events	exenatide extended-release once-weekly vs placebo	3.2 years	3-point MACE: 11.4% in the exenatide group vs 12.2% in the placebo group HR: 0.91, 95% CI: 0.83-1.00 p < 0.001 for non-inferiority p = 0.06 for superiority
HARMONY[7] OUTCOMES	9,463	T2DM, age ≥40 years with CVD	albiglutide once-weekly vs placebo	1.6 years	↓ 3-point MACE: 7.0% in the albiglutide group vs 9.0% in the placebo group HR: 0.78, 95% CI: 0.68-0.90 p < 0.0001 for non-inferiority p = 0.0006 for superiority ↓ MI: 4.0% in the albiglutide group vs 5.0% in the placebo group HR: 0.75, 95% CI: 0.61-0.90 p = 0.003 for superiority

MACE points : (3 points means major adverse cardiac events including cardiovascular death, non~fatal myocardial infarction and non~fatal stroke) (4 points means major adverse cardiac events including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalisation for unstable angina ;chronic kidney disease ;cardiovascular;cardiovascular disease; myocardial infarction; type 2 diabetes mellitus).

2. Cardiovascular trials outcomes with GLP-1 RAs: main results:

The Liraglutide Action and effects in Diabetes: Evaluation of Cardiovascular Outcome Results trial [8] investigated cardiovascular outcomes in 9340 patients with T2DM treated after a median follow-up of 8 years with liraglutide or placebo once a day. Patients investigated were aged 50 years with known cardiovascular disease or aged 60 years with multiple cardiovascular risk factors. Liraglutide decrease both all-cause mortality and the 3 points MACE .In pre-specified non-inferiority and superiority analyses this was significant . However, even though the reduction in primary end point was mostly driven by the reduction in CV death . Liraglutide arm had non~significant lower rates of nonfatal myocardial infarction and nonfatal stroke. No difference between the groups in rates of hospitalization for heart failure. Potential increased benefit with liraglutide in patients with a reduced estimated glomerular filtration rate and established cardiovascular disease this was demonstrated by subgroup analysis.The Evaluation of Lixisenatide in Acute coronary syndrome trial [9] included 6068 patients with type 2 diabetes milletus who had sustained an acute coronary event within 180 days before randomization. Results showed a neutral effect of lixisenatide compared with placebo on the occurrence of the primary composite outcome and non-significant differences between groups when components of the primary outcome were assessed independently . Differences between groups regarding hospitalization for HF were also non-significant .The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with semaglutide [10] in Subjects with Type 2 Diabetes was a non-inferiority trial that compared once-weekly semaglutide with placebo in reducing major CV events in 3297 patients with T2DM who are at high CV risk , after a median of 2.1 years. Although the study was not specifically designed to test superiority, semaglutide reduced the rate of 3-point MACE by 26% . This reduction was mostly driven by a significant decrease in the rate of nonfatal stroke and a non-significant decrease in nonfatal MI , with a lack of effect on CV mortality .More recently, the exenatide [11] Study of Cardiovascular Event Lowering was conducted in 14752 patients with T2DM who had a wide range of CV risk . The findings for secondary outcomes did not differ significantly between groups .In 2018, the trial on albiglutide and CV outcomes in patients with T2DM and CV disease was completed, and it showed that the long-acting GLP-1 RA albiglutide, when added to standard care in patients with T2DM and established CVD, reduced the risk of the primary composite outcome by 22% compared with placebo[12] . The results indicated that albiglutide was both non-inferior to placebo for CV safety and superior for efficacy , and this was conducted for a relatively short period of follow-up . The point estimate for the secondary outcome of hospital admission because of HF did not show significant difference between the albiglutide and placebo groups . However, of all three components of the primary outcome, only MI showed a significant point estimate that indicated a beneficial effect . The reductions in each of the other components of the composite and all-cause mortality were not statistically significant .

3.CV outcome trials with GLP-1 RAs: discussion

The results of the EXSCEL trial mostly contrast with those of the LEADER trial because EXSCEL resembles LEADER more than the other GLP-1 RA trials .Beyond this, considering as a whole the results of the recent trials comparing the effect of GLP-1 RAs and placebo on CV outcomes, the lack of CV efficacy in EXSCEL and ELIXA and the differences in the results of the trials are partly attributed to differences and variations in trial design and population[
] . HARMONY Outcome had the shortest duration of follow-up and ELIXA and SUSTAIN-6 had 2.1 years of follow-up period and the duration of exposure to study drug was 1.9 and 2.1 years, respectively, whereas the follow-up period for LEADER was 3.8 years and the therapeutic exposure was 3.5 years . The EXSCEL trial [12] also had a long follow-up period of 3.2 years, but one of its limitations was the shorter time of therapeutic exposure ,mainly because of a higher study drug discontinuation rate , attributed to the complexity of the first-generation device used to deliver exenatide . Different patient selection criteria,notably percentage of subjects with CVD, baseline glycated haemoglobin ,as well as different study design and therapeutic exposure duration, could affect trial results, thereby obscuring the possibility that GLP-1 RAs as a whole reduce CV outcomes . As mentioned above, the findings of the CV outcome trials suggest a potential beneficial CV class-effect of GLP-1 RAs.Indeed, the results of a recent meta-analysis of the first four CV outcome trials with GLP-1 RAs indicate that this class of agents, particularly long-acting ones, has CV protective properties. All studies have shown improved glycaemic control compared with placebo. In both LEADER and SUSTAIN-6, the differences in CV outcomes were apparent by 6 months, thus suggesting that possibly it was not the glycaemic control that affected the CV outcomes .Insulin resistance is promoted by obesity, a common finding in T2DM, and is also connected to arterial hypertension and dyslipidemia, considered to be important CV risk factors . Even subjects with metabolic syndrome and insulin resistance without T2DM are at increased CV risk . Accordingly, it seems that CV outcomes are affected mainly by insulin resistance and less by hyperglycaemia . The potential cardioprotective effect of incretin-based therapies is attributed to their multiple non-glycaemic actions in the CV system . Previous clinical trials have demonstrated that the potential CV benefits of GLP-1 RAs are mediated through effects on CV risk factors including weight loss, reduction in blood pressure and improved lipid profile, along with direct effects on the heart and vascular and endothelial
The results of all trials support a modest reduction in body weight.

However, patients receiving semaglutide and liraglutide had more substantial weight loss than those treated with placebo,lixisenatide, exenatide or albiglutide. Of note, these differences across GLP-1 RAs are not confirmed as clinically meaningful because they do not result from a comparison analysis. The small but significant weight loss was −0.7 kg compared to placebo in the ELIXA trial, −0.83 kg in HARMONY Outcomes, −1.27 kg in EXSCEL, −2.3 kg in LEADER and −2.9 kg in the group receiving 0.5 mg of semaglutide and −4.3 kg in the group receiving 1.0 mg of semaglutide in SUSTAIN .Similarly, there was a modest reduction in systolic blood pressure (SBP) with GLP-1 RA therapy. SBP was reduced by 1.57 mmHg compared to that in placebo in the EXSCEL trial, by 1.2 mmHg in LEADER, by 0.8 mmHg in ELIXA, by 1.3 to 2.6 mmHg in SUSTAIN and by 0.67 mmHg in HARMONY Outcomes . This BP-lowering effect could be attributed to weight loss, but it occurred early during the trials and was independent of it . Nonetheless, according to a meta-analysis, GLP-1 RAs did not affect incident hypertension .The results of the randomised controlled trials also support the beneficial effect of GLP-1 RAs on lipid metabolism , namely, decrease in triglycerides and low density lipoprotein , while GLP-1 RAs seem to increase adiponetin levels . Additionally,renal protection , which adds to the CV benefits of GLP-1 RAs, was observed. Indeed, there was a significant improvement in the urine albumin/creatinine ratio with lixisenatide in the ELIXA trial , while LEADER and SUSTAIN-6 also showed lower rates of nephropathy events with GLP-1 RAs than those with placebo . One of the limitations of the HARMONY Outcomes trial was the absence of the measurement of lipids and urinary albumin excretion .

4. CV outcome trials with GLP-1 RAs: potential underlying mechanisms:

The mechanisms underlying the cardioprotective effect of GLP-1RAs are uncertain and cannot be explained only by traditional risk factor modification . Therefore, it seems that other direct effects on the CV system are also important [13]. There are studies with mechanisms underlying the anti-atherosclerotic effects of these agents through reduction in matrix metalloproteinase -2 (MMP2) levels[14] or inhibition of vascular smooth muscles cell proliferation , their anti inflammatory effects[15] and their effects on endothelial function through nitric oxide-induced vasodilation and reduced oxidative stress[16] . Animal and clinical studies have demonstrated reduction in infarct size and reperfusion injury by GLP-1 RAs, through the reduction of intracellular calcium overload and of high glucose-induced apoptosis from another point of view, there is heterogeneity across the results of GLP-1 RA trials, thus raising the question whether the agents of the same class exert different biological effects.

LEADER, SUSTAIN-6 and HARMONY
Outcomes showed reduction in the risk of MACE, whereas ELIXA and EXSCEL were neutral .In LEADER, all-cause mortality was also decreased; in SUSTAIN-6, the risk of stroke was decreased and in HARMONY Outcomes, the risk of fatal or non-fatal MI also decreased, while none of the trials resulted in the reduction of HF . Regarding the discrepancies in the secondary outcomes, we should consider that it was the primary outcome (the composite of MACE) that determined the sample size. Beyond this, the agents have different molecular structures, which affect their pharmacodynamics properties. As liraglutide, semaglutide and albiglutide (GLP-1 derivatives) are analogues of the human GLP-1, they could activate more effectively the GLP-1 receptor than exenatide and lixisenatide, which are exendin-4-based compounds . Moreover, exenatide and lixisenatide are more immunogenic and could promote an antibody response that could reduce their beneficial CV actions . The different pharmacokinetics properties seem to play an equally significant role. Lixisenatide is a short acting drugs , while liraglutide, semaglutide, albiglutide and exenatide extended-release are long-acting drugs. The latter are known to ensure more increased drug concentrations and more steady actions although this cannot explain the neutral CV effects of exenatide in the EXSCEL trial.

5.Conclusions:

The major CV outcome trials with GLP-1 RAs have proven the CV safety of these anti diabetic agents[17,18,19,20] . Considering the differences in trial design and study population, as well as the results of recent meta-analyses, the class of GLP-1 RAs as a whole seems to have cardioprotective effects. However, it is conceivable that there are different drug-specific properties across GLP-1 RA agents, and hence, head-to-head comparison trials are welcome to shed more light on this issue. At the ends it is fortunate that new antidiabetic agents contribute to a reduced risk for CVD . Lixisenatide and extended- release exenatide were neutral, that is, they are safe from a cardiovascular point of view, but for the moment they have not demonstrated to provide any benefit.Although many of the mechanisms by which liraglutide and semaglutide produce a cardiovascular benefit are still unknown , it would be desirable for these benefits to be incorpo- rated into the therapeutic algorithms routinely used in clinical practice.Since cardiovascular disease continues to be the leading cause of death in patients with T2DM, the prevention of cvs complications and the cardiovascular safety of the treatment in individuals who have already developed a cardiovascular episode should be a primary objective when selecting treatment for our patients.

Researcher opinion:
Glp-1 RAs appear to have a number of direct and indirect effects that may reduce cardiovascular risk .benefits on blood pressure, weight reduction,the vascular endothelium, atherosclerosis progression and inflammation, myocardial ischaemia, heart failure .Liraglutide and semaglutide showed highest cardiovascular benefit compared with placebo, both in the presence of standard treatment. Lixisenatide and extended-release exenatide were neutral, they are safe from a cardiovascular point of view, but for the moment they have not demonstrated to provide any benefit.

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