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RESEARCH ARTICLE

GLP-1 RECEPTOR AGONISTS AND CARDIOVASCULAR OUTCOMES AND MORTALITY IN TYPE 2 DIABETES. A NEW APPRAISAL

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Abstract

Diabetes mellitus is a chronic disease prevalence of which is high and continually growing. Cardiovascular disease continues to be the leading cause of death in patients with T2DM. The prevention of cardiovascular complications and the cardiovascular safety of treatments should be a primary objective when selecting treatment. Among all the drugs available, the compounds known as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) appear to be not just innocuous in terms of CVD but indeed to be beneficial. GLP-1 RA actions not only translate on an improvement of well-known cardiovascular risk factors such as glycaemic control, dyslipidaemia, weight, or arterial hypertension but also might show benefits on endothelial function, coronary ischaemia, and heart failure. On the other hand, recent clinical trials aimed at studying cardiovascular episodes have been conducted with GLP-1 RAs. Only liraglutide and semaglutide have shown superiority in cardiovascular benefit compared with placebo. 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 incorporated into the therapeutic algorithms routinely used in clinical practice. The purpose of this review is to explore GLP-1 RA actions not only in cardiovascular risk factors (glucose, weight, and hypertension) but also the possible effects on established cardiovascular disease.

Introduction:-

Diabetes mellitus (DM) is a chronic disease, the worldwide prevalence of which is high and continually growing. It is associated with high morbidity and mortality and is one of the diseases with the greatest impact on public health. Between 1990 and 2010, the number of adults diagnosed with diabetes in the United States tripled, from 6.5 million to 20.7 million, while the total population increased by only 27% (from 178 million to 226 million). The International DiabetesFederation calculated that, in 2015, one in every 11 adults had diabetes (415 million

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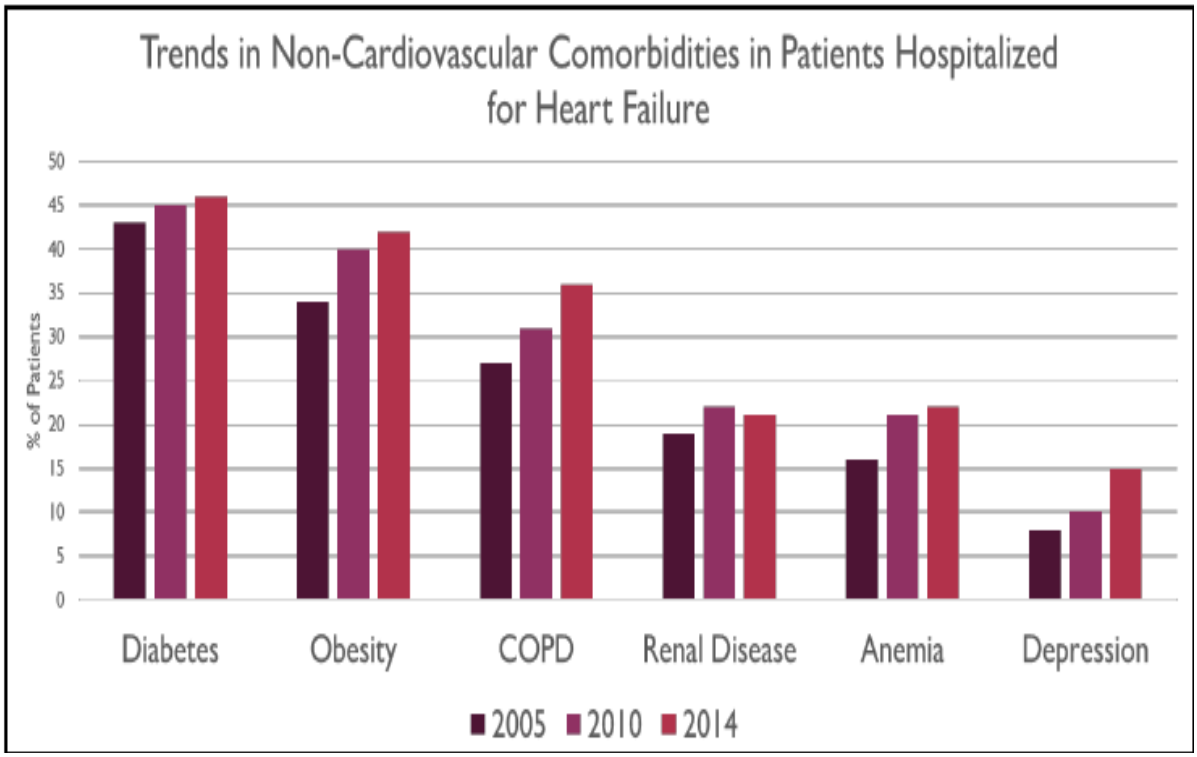
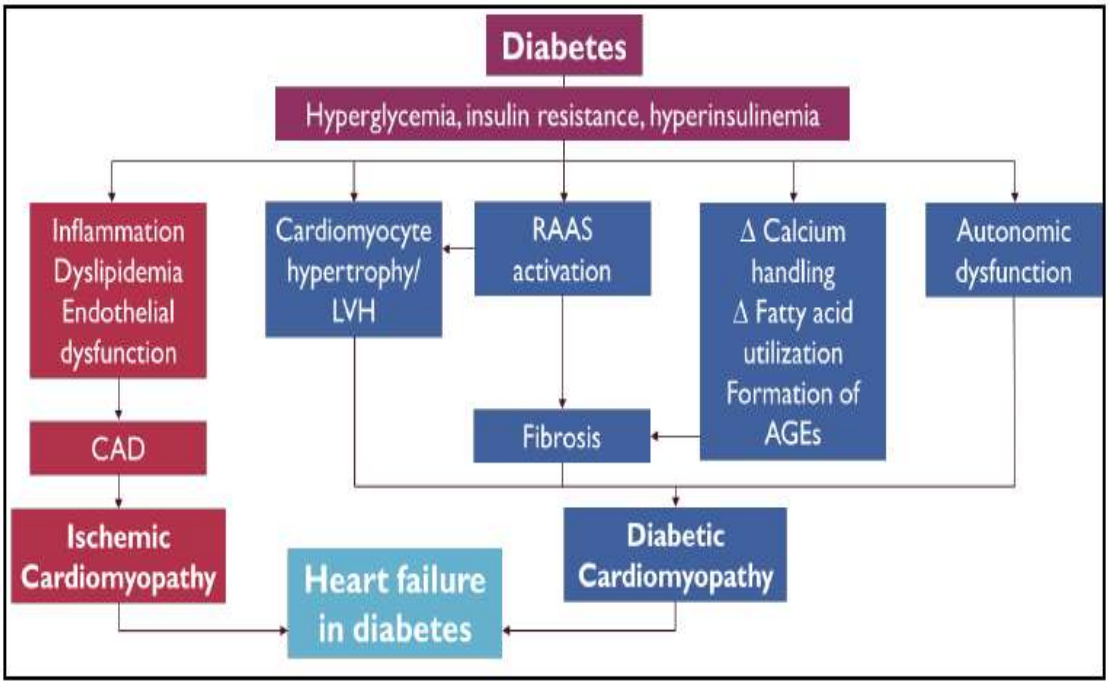
individuals) and estimated that by 2040, the prevalence would be one every 10 (642 million individuals). The American Diabetes Association (ADA) reports that if the current epidemiological trend continues, by 2050 one in three American adults could have DM. In kingdom of Saudi Arabia, the results of the largest epidemiological study ever conducted in the country were published in 2012. Of these, almost one million had been diagnosed, but 2.3 million—43% of the total—were unaware that they had the disease. DM is not only prevalent; it is a complex chronic disease. It is very closely related to the presence of comorbidities and chronic complications that can be micro-vascular, or mixed. Macro-vascular complications include cerebral and peripheral vascular disease and cardiovascular disease. Micro-vascular complications include diabetic retinopathy, neuropathy, and nephropathy. Mixed complications are also common such as diabetic foot and erectile dysfunction.

Descriptive studies have noted a gradual decline in complications these recent years. This probably reflects the advances in acute clinical care and improvement in national health services and health education in individuals with diabetes. Nevertheless, cardiovascular disease continues to be the main complication and cause of death in the diabetic patient. Heart failure, with an estimated prevalence of 5%, is also considered a health problem of first order in Spain, despite a lack of proper studies to correctly estimate its impact. It is the main cause of hospitalization in adults over 65 years and accounts for 3% of hospital admissions and 3.5% of healthcare costs. In 2010, heart failure was responsible for 3% of all deaths in men and in 10% in women.[19]

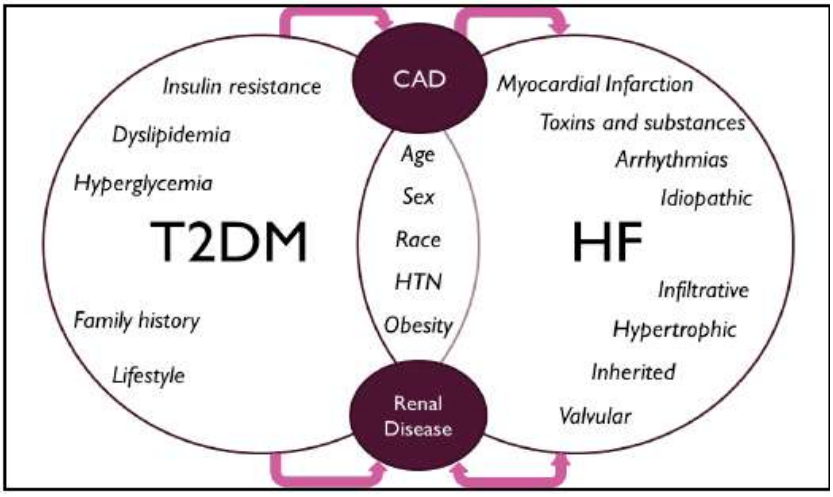


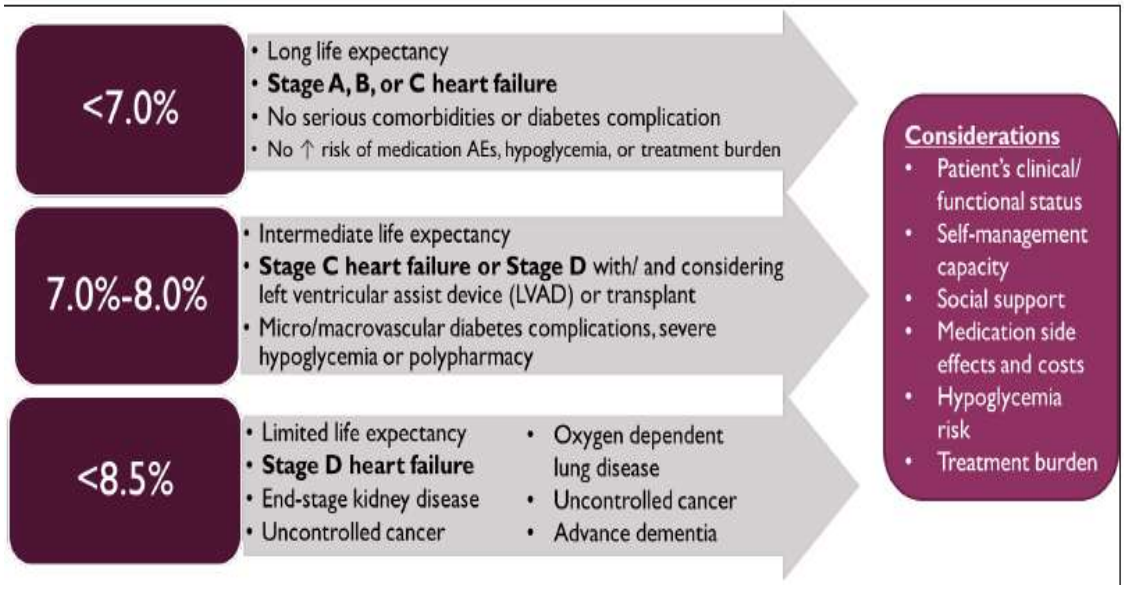
Cardiovascular Disease and Diabetes

The increase in cardiovascular disease (CVD) in patients with DM was already apparent in the Jeddah (1979) and Riyadh (1993) clinical trials, which suggested that diabetic patients have a two- to fourfold risk of CVD compared to nondiabetic patients. Moreover, CVD in patients with DM is three times more likely to have a fatal outcome compared to the normal population. Now that the false concept of equivalence of diabetes and CVD has been overcome, it is important to bear in mind the concept of vascular continuum introduced by Dzau et al. in 1991. The concept of vascular continuum describes the inexorable progression of CVD from the presence of risk factors to the development of myocardial infarction, left ventricular hypertrophy, and cardiovascular death. This concept has been changing over the years, especially as a result of acceptance of the effects of the renin-angiotensin aldosterone system (RAAS), introducing the notion of the cardiorenal continuum.



Furthermore, the boundary between macroandmicrovascular complications is becoming blurred due to a better understanding of the molecular pathogenic mechanisms of DM. A diabetic patient can be found on very different parts of the CVD spectrum. He may be newly diagnosed or present more advanced disease and have suspected silent CVD or may be progressing towards the terminal stages of a cardiovascular disease. In all these cases with the accompanying constellation of other cardiovascular risk factors (CVRF) (hypertension [HT], smoking, obesity, dyslipidaemia, and so on). The choice of treatment in a patient with T2DM is complex, not only because of the large therapeutic arsenal currently available but also the multitude of circumstances that must be assessed when selecting the right treatment (efficacy, weight loss, risk status or CVD, side effects, costs, hypoglycaemias, etc.). In addition, CVD and the safety of treatments for T2DM have achieved special prominence in recent years. On 21 May 2007, cardiologist Steve Nissen published a meta-analysis suggesting that, compared to a control group, rosiglitazone treatment showed a statistically significantly higher risk of myocardial infarction and an increase in mortality close to statistical significance. Since rosiglitazone was withdrawn in 2010 due to this potentially harmful cardiovascular effect, studies must now demonstrate cardiovascular safety in all new drugs for the treatment of T2DM. Among all the drugs available, the compounds known as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) appear to be not just innocuous in terms of CVD but indeed to be beneficial.[1,15]





Incretins: Glucagon-Like Peptide-1 (Glp-1)

The concept of the incretin hormone system and its relationship with DM dates from the 1970s. The incretins are hormones secreted by cells in the midgut that potentiate glucose-dependent insulin secretion. GLP-1 (GLP-1 7-36) is secreted continuously in both interprandial and prandial periods. Primary biological actions described for intact GLP-1 are mediated by the GLP-1 receptor (GLP-1R). GLP-1 (9-36) metabolite which appears after dipeptidyl-peptidase 4 (DPP-4) action also exhibits its own biological actions. The biological action of native GLP-1 and its metabolites GLP-1 and GLP-1 is under study, as it seems that these metabolites could exhibit their own biological actions independent of those mediated via GLP-1R. The actions exerted by GLP-1 through GLP-1R are the best known and are affected in numerous areas as a result of the wide distribution of GLP-1R in the body. These actions include GLP-1 increases glucose-dependent insulin synthesis and secretion in the pancreatic islets. In animal studies, they show an increase or maintenance of the beta cell mass. It also decreases glucagon secretion by acting on the alpha cells. GLP-1 acts as a neurotransmitter and can act on both the CNS (satiety and loss appetite) and peripheral nervous system (PNS). GLP 1 delays gastric emptying and inhibits penta gastrin and acid secretion stimulated by food ingestion.

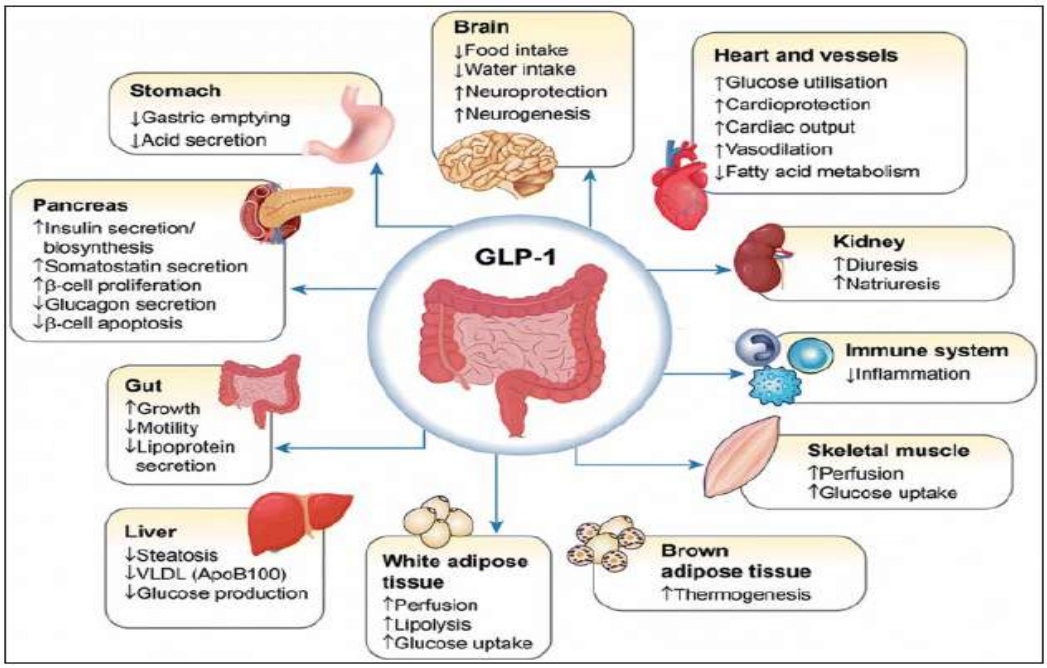
GLP-1 has cardiovascular benefits on blood pressure, the vascular endothelium, atherosclerosis progression and inflammation, myocardial ischaemia, heart failure, and so on, which will be discussed in detail below.[19.2]

Beneficial Effects of Glp-1 Analogues on Cardiovascular Risk Factors in Patients with Type 2 Diabetes

Glycaemic Control. Although glycaemic control is associated with reductions in the risk of microvascular complications, the benefits of strict glucose control on macrovascular complications are more questionable. It seems reasonable to think after the VADT, ACCORD, and ADVANCE studies that intensive treatments in patients with established cardiovascular disease failed to show a reduction in cardiovascular episodes. Nevertheless, it should be taken into account that the patients selected in these trials were high cardiovascular risk. In contrast, the UKPDS study showed that patients whose treatment began intensively at diagnosis presented a lower incidence of cardiovascular episodes, even at 10 years, when the HbA1c levels for both groups were similar. This arose the concept of "glycaemic legacy," which was expanded to the concept of "metabolic legacy" following the STENO 2 trial. [19]

It therefore seems clear that the intensive treatment of glycaemia along with other metabolic abnormalities in the early stages of the disease produces a benefit on macrovascular complications that is maintained in the long term.All GLP-1 RAs currently approved for the treatment of T2DM are administered subcutaneously. Depending on their pharmacokinetic properties, they will be administered daily or weekly. Short-acting GLP-1 RAs (daily exenatide and lixisenatide) are administered in relation to meals. These exhibit large fluctuations in their plasma concentrations, resulting in intermittent activation of GLP-1 RAs, producing a modest effect on both glucose levels

between doses and fasting plasma glucose and HbA1c control. Exenatide 10 μg twice daily experiences a drop in HbA1c. Exenatide 10 μg experiences a drop in HbA1c of −0.78% and the 5 μg a drop of −0.4%, both significant against placebo. On the other hand, lixisenatide decreases A1c in about −0.32%. However, they show a higher capacity for delaying gastric emptyingand, therefore, greater efficacy in reducing postprandial glucoselevels. Lixisenatide showed a better reduction in postprandial blood glucose compared to liraglutide which had a better reduction in fasting blood glucose, which is not surprising considering their half-lives. Long-acting agonists were developed to prolong their action on the GLP-1R and consequently their pharmacodynamics action. They are administered daily (liraglutide) or weekly (exenatide-LAR, albiglutide, and dulaglutide). [1,13,17]



In head-to-head studies, they show better efficacy in reducing fasting plasma glucose and HbA1c control compared to short-acting drugs. The DURATION-1 study compared the efficacy of exenatide twice daily with a weekly dose. At the end of the study, both treatment arms showed a clear improvement in HbA1c values: 1.9% for the long-acting compared to −1.5% of the short-acting agonist (p = 0 0023). The LEAD-6 study compared treatment with liraglutide(1.8 mg/day with dose escalation) versus exenatide(10 μg/12 hours with dose titration). After a 26-week follow- up, liraglutide showed a reduction of −1.2%, compared to −0.79%. In the AWARD-1 study, dulaglutide was superior to twice-daily exenatide (−1.51% for dulaglutide 1.5 mg/ week, −1.30% for dulaglutide 0.75 mg/week, and −0.99 for twice-daily exenatide) [20]. But, due to tachyphylaxis, they do not exert as much effect on the gastric emptying that affects postprandial glycaemic control. In summary, with respect to glycaemic control, long acting agonists are more effective in reducing A1c than short-acting. Within long-acting agonists and glycaemic control, liraglutide 1.8mg has not been statistically significantly surpassed by any GLP-1 RA in head-to-head comparisons carried out to date. It is important to note that, in addition to glycaemic control, glycaemic variability is a factor that has sometimes been related with a higher risk of CVD due to increased oxidative stress. [8,9,13]

Studies with GLP-1 RAs to date have not included this measurement. However, in the 52-week extension trial dual action of liraglutide and insulin degludec in type 2 diabetes (DUAL I), the authors studied the fluctuations in plasma glucose of the combination of insulin degludecandliraglutide (IDegLira) against each of its components separately. A significantly lower number of fluctuations were observed in the interstitial glucose with IDegLira, compared to insulin degludec alone. Furthermore, the liraglutide treatment arm behaved similarly—as regards variability—to the cohort with insulin degludec alone. Glycaemic variability should undoubtedly be a field to explore in trials with GLP-1 analogues, due to its possible impact on cardiovascular morbidity.

Drug	Dose	Frequency	Half Life	Average A1c Reduction	Weight Loss Effects	Side Effects
Short Acting						
Exenatide BID (Byetta)	5mcg SubQ for 1 month then increase to 10mcg SubQ based on response	Twice daily	2.4 hours	-0.8 to -1.7%	-1.1 to -3.0kg	Nausea (8%) Diarrhea (2%) Injection site reaction (17%)
Lixisenatide (Adlyxin)	10mcg SubQ for 14 days then 20mcg SubQ from day 15	Once daily	~3 hours	-0.6 to -0.9%	+0.3 to -2.7kg	Nausea (25%) Gastrointestinal symptoms (40%) Headache (9%)
Intermediate Acting						
Liraglutide (Victoza)	0.6mg SubQ for 1 week then 1.2mg (maximum dose = 1.8mg/day)	Once daily	~13 hours	-0.8 to -1.5%	-0.2 to 3.6kg	Increased heart rate (>10bpm from baseline: 34%; >20 bpm from baseline: 5%) Nausea (39%) Constipation (19%) Diarrhea (21%) Headache (14%)
Long Acting						
Semaglutide SubQ (Ozempic)	0.25mg SubQ for 4 weeks then 0.5mg escalated to 1mg after 4 weeks if needed	Once weekly	~7 days	-1.1 to -1.4%	-3.6 to 4.9kg	Increased amylase (10-13%) Increased lipase (PO: 30-34%; SubQ: 22%) GI adverse effects (32-41%) Nausea (11-20%)
Semaglutide PO (Rybelsus)	3mg PO for 30 days then 7mg escalated to 14mg after 30 days if needed	Once daily	~7 days	-1.0%	-4.2kg	

Arterial Hypertension.

Arterial hypertension (HT) is a very common complication in patients with T2DM. It affects 79.4% of diabetic adults in SAUDI ARABIA, Excess weight and obesity, insulin resistance, andhyperglycaemia itself are the main factors associated with itsgreaterpresence.The combination of poor blood pressure (BP) control together with poor glycaemic control considerably increases the risk of developing a myocardial infarction, heart failure, or stroke. According to the UKPDS study, a reduction in systolic blood pressure (SBP) of 10mmHg results in a 15% reduction in mortality in patients with T2DM. In the ADVANCE study, a reduction of 5.6mmHg reduced the risk of cardiovascular death by 18%. The HOPE study also showed that a reduction of 2.5 mmHg, with or without a 1mmHg reduction in diastolic blood pressure (DBP), may reduce the risk of myocardial infarction, stroke, or cardiovascular death by 25% .Clinical trial data so far seems to significantly conclude that treatment with GLP-1 analogues reduces BP values. The mechanism by which this reduction occurs has not yet been clearly identified but may be due to complex regulation. In fact, effects occur early—two weeks after the start of treatment—suggesting that it is a decrease independent ofweight loss and that other mechanisms may be involved. One potential mechanism could be direct activation of the GLP-1R in arteries and the renal system, including an improvement in endothelial function, as well as a vasodilator and natriuretic effect by inhibition of the RAAS. However, other mechanisms could be independent of GLP-1R, for example, the activation of nitric oxide by cyclic GMP. None of the trials conducted to date has been specially designed to evaluate the effects of GLP-1 RAs on BP. Nevertheless, several reviews and meta-analyses seem to agree that both exenatide and liraglutide produce a mean decrease of −1 to −5mmHg compared with placebo and other active comparators. In the DURATION trials,weeklyexenatide showed a mean reduction in BP of −3 to −5mmHg. Moreover, in clinical trials with exenatide, twice-daily dosing also resulted in a significant decrease in SBP compared with placebo (−2.8mmHg) or insulin (−0.37 mmHg), with larger decreases in those patients who started with SBP >150mmHg. In the LEAD studies, liraglutide caused a decrease in SBP of between −2.7 and− 6.6mmHg. It is important to remember that GLP-1 RAs do not reduce BP in normotensive subjects. Furthermore, GLP-1 RA treatment is also known to be associated with a slight increase in heart rate, generating a mean increase of +1.86 beats per minute (bpm) compared with placebo and + 1.90bpm with active comparator. These increases are more evident with liraglutide and extended release exenatide. The mechanism for this could be related to vagal depression, insulin-mediated activation of the sympathetic system, and the large increase in insulin after the infusion of GLP-1. Although drugs that reduce heart rate have been shown to

reduce cardiovascular risk, no harmful effect of this increased rate has been observed with GLP-1 agonists to date.[17,18,19]

Dyslipidaemia.

Given the insulin resistance and metabolic disorder in patients with T2DM, dyslipidaemia is an important and common comorbidity. The typical lipid profile of a T2DM patient, known as atherogenicdyslipidaemia, includes a decrease in HDL cholesterol (HDL-C) and an increase in LDL cholesterol (LDL-C), total cholesterol, and triglycerides. The combination of dyslipidaemia and poorglycaemic control plays an essential role in the development of atherosclerosis. According to the Quebec Cardiovascular Study, the combination of diabetes, high LDL-C, and high apolipoprotein B confers a 20-fold risk of developing cardiovascular episodes. It is interesting to note that several clinical trials with GLP-1 RAs have described an improved lipid profile due to as yet unknown mechanisms. No clinical trials have been conducted that evaluate the different doses and impact onlipid profiles of each GLP-1 RA. Additionally, most trials were not specifically designed to look at the effect of GLP-1 RAs on lipid profile. The majority are head-to-head trials in which the GLP-1 agonist is compared to placebo or other treatments, such as an active comparator, mainly exenatide and liraglutide. Exenatide in both twice-daily doses of 5 μg and 10 μg and in the extended-release formulation and liraglutide 1.8mg have shown a reduction in total cholesterol levels. The loweringeffect seems more marked with extended-release exenatideandliraglutide 1.8 mg. In terms of lowering triglyceridevalues, liraglutide (1.2mg and 1.8 mg) has been found to be more effective. In a meta-analysis of the LEAD trials (liraglutide clinical development program), it was observed that, in all of them, treatment with liraglutide reduced LDL-C (−7.73 mg/dL), total cholesterol (−5.03 mg/dL), and triglycerides, compared with standard treatment. The LEAD-6 study found a reductionin triglycerides of −15.7 mg/dL, compared with twicedailyexenatide. Moreover, decreases in HDL-C were observed, except in patients on combined treatment with TZD. In the DURATION studies (with extended-release exenatide), reductions of between 4.64 and 34.8 mg/dL were found in total cholesterol compared with standard treatment. These reductions were much greater than with twice-daily exenatide. No changes were observed in HDL-C levels. In a 3-year follow-up trial that compared twice-daily exenatidewith placebo, the group treated with exenatidewerefound to have reductions of −6% in LDL-C values, −5% in total cholesterol, and− 12% in triglycerides. Another study, the EUREXA trial, also showed reductions in triglycerides and improvement in HDL-C with twice-daily exenatide compared to glimepiride.[1011,14]

Guideline or Statement	Year	SGLT-2i preferred in HF	GLP-1 RA as second line option in HF	Caution use in recently decompensated HF patients
American Diabetes Association (ADA)	2020	+	+	-
	2021	+	+/-	-
American Association of Clinical Endocrinologists (AACE)	2020	+	+	-
American College of Cardiology (ACC)	2020	+	+/-*	-
American Heart Association/ Heart Failure Society of America (AHA/HFSA)	2019	+	+/-^	+

A modest improvement in the lipid profile of a patient with T2DM can produce a significant impact from a clinical point of view; nevertheless, the mechanism has not been clearly identified. One possible explanation could be improved glycaemic control, which would reduce insulin resistance and hepatic triglyceride synthesis. Another possible action could be mediated by GLP-1R in the intestinal mucosa, resulting in reduced secretion of apolipoproteinB48, present in the chylomicrons, with a consequent reduction in plasma triglycerides. The beneficial effects of liraglutidecouldbe related to modulation of the expression of certain genes related to lipid and glucose

metabolism. Furthermore, in studies performed with exenatide, this agent was seen to suppress the production of intestinal lipoproteins by acting directly on their synthesis, independently of changes in weight, satiety, or gastric emptying. It is important that new trials should be carried out that include all GLP-1 agonists and their effect on the lipid profile as the primary objective and that they explore the mechanism by which this improvement occurs.

Weight.
Obesity contributes to the development of both T2DMand CVD. Modest weight losses of 5%–10% have been found to contribute to changes in glycaemic control, number of medications for controlling CVRFs, the patient's functional activity, and their quality of life. GLP-1 RAs have been shown to improve glycaemic control with an added beneficial effect on weight. Mean weight loss has been estimated at between 0.4 and 5.1 kg. However, this improvement in weight varies between GLP-1 RAs and between individuals, although up to 30% of patients do not lose weight.

Current Situation: Cardiovascular Outcome Trials (Cvots) on Glp-1 Receptor Agonists
As mentioned above, as of 2008, specific studies must be conducted in all new drugs for the treatment of T2DM to demonstrate their cardiovascular safety. These are performed in order to prove noninferiority as regards the appearance of MACE (major adverse cardiovascular events) with antidiabeticdrugs. A multitude of studies has been performed aimed at demonstrating this noninferiority: TECOS, SAVOR TIMI 53, EXAMINE, ELIXA, EMPA-REG, LEADER, SUSTAIN-6, CANVAS, and EXSCEL. Next, we will discuss those that were carried out with GLP-1 receptor analogues: ELIXA, LEADER, SUSTAIN-6, and EXSCEL.[11]

The ELIXA study (evaluation of lixisenatidein acute coronary syndrome) was the first safety study
carried out on GLP-1 RAs and was published in December 2015. A total of 6068 patients were included, randomised to treatment with lixisenatide 10 μg daily (which could be increased to 20 μg at the investigator's discretion) or placebo. The aim of the study was to demonstrate the non inferiorityoflixisenatide compared with placebo, both with the standard treatment that they required, on the development of MACE. The primary endpoint was the time to occurrence of any of the following events: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Other secondary endpoints were a composite of the primary endpoint or hospitalization for heart failure and a composite of the primary endpoint and hospitalisation for heart failure or coronary revascularisation procedures. The patients included in this trial were all patients with T2DM who had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 days (secondary prevention). [20]

Mean follow-up was 25 months in each group. With respect to the primary endpoint results, lixisenatideshowednoninferiority to placebo (hazard ratio [HR] = 1.02; 95% confidence interval [CI], 0.89–1.17; p < 0 001) but not superiority (p = 0 81). Analysing the different components separately, the number of deaths from cardiovascular causes (p = 0 85), nonfatal myocardial infarction (p = 0 71), nonfatal stroke (p = 0 54), and hospitalisation for unstable angina (p = 0 81) was also similar in both groups. The same occurred with hospitalization for heart failure (p = 0 75), coronary revascularisation, and death from any cause. Within other CVRFs, a modest but significant between group difference in the change in body weight from baseline was apparent at 12 weeks (−0.6 kg in the lixisenatide group versus −0.0 kg in the placebo group, p < 0 001). This relative weight difference was sustained throughout the follow-up period. A modest relative difference (lixisenatideminus placebo) in systolic blood pressure in the lixisenatidegroup as compared with the placebo group was sustained throughout follow-up, with an average difference across all visits of −0.8mmHg (95% CI, −1.3 to −0.3) infavor of lixisenatide (p = 0 001).Thus, lixisenatide showed a neutral cardiovascular profile in patients with type 2 diabetes and a recent acute coronary syndrome.

LEADER Study.
The LEADER trial, published in July 2016, was conducted to study the cardiovascular effect of
liraglutide when added to standard treatment for T2DM. The study included 9340 patients who were randomised to treatment with liraglutide (up to a maximum dose of 1.8 mg/day) or placebo. The primary composite outcome was the time to occurrence of the first MACE: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included the time to occurrence of the first event: expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, hospitalisation for unstable angina, or hospitalization for heart failure), death from any cause, and each of the individual components of the expanded composite cardiovascular

outcome. Mean follow-up was 3.8 years.

Margulies KB, Hernandez AF, Redfield MM, et al; NHLBI Heart Failure Clinical Research Network. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA*. 2016;316(5):500-508.		
Objective	Determine the effect of liraglutide in patients with advance heart failure who have been recently hospitalized for acute decompensated heart failure.	
Methods		
Study Design	Multicenter, double-blind, randomized, placebo-controlled, Phase 2 trial conducted from 2013 to 2015. • Patients were identified based on hospital admission records and enrolled in last 24 hours of hospitalization or within 2-weeks of discharge.	
Population	**Inclusion Criteria** • Established HF with LVEF less than 40% within prior 3 months • Recent hospitalization within 14 days for acute HF exacerbation while receiving evidence-based medications (including ACE-inhibitor/ARB and beta-blocker) • Receiving at least 40mg of furosemide (or equivalent) prior to admission	**Exclusion Criteria** • Recent acute coronary syndrome or coronary intervention within 4 weeks of randomization • Primary infiltrative or restrictive cardiomyopathy • Ongoing hemodynamically significant arrhythmias • VAD or heart transplant likely within 6 months • Active infection driving HF hospitalization • Severe pulmonary, renal or hepatic disease • History of gastroparesis, pancreatitis, or medullary thyroid cancer
Intervention	**Intervention (n=154)**: liraglutide SubQ daily; initially started at 0.6mg/dL and then increased to 1.2mg/dL after 14 days if tolerated; increased to a maximum of 1.8mg/dL if tolerated after additional 14 days **Control (n=146)**: placebo SubQ daily • Randomized 1:1 to receive liraglutide or placebo. Performed follow up testing at 30-, 90-, and 180-days. Continued concomitant HF therapies and allowed for up titration of neurohormonal agents after hospitalization as tolerated. Continued T2DM drugs with adjustments made to sulfonylurea and insulin doses in combination with at least daily blood glucose monitoring to reduce the risk of hypoglycemia.	
Outcomes	**Primary Outcome**: global rank score (hierarchical arrangement based on 1) time to death, 2) time to HF hospitalization, and 3) time averaged proportional change in N-terminal pro-B-type natriuretic peptide [NT-proBNP] from baseline to 180 days) **Secondary Outcomes (selected)**: death, HF hospitalization, time averaged change in NT-proBNP, change in LVEF%, change in Kansas City Cardiomyopathy Questionnaire scores (KCCQ), and change in 6 min walk distance. **Safety Outcomes**: collected by telephone at 210 days, reported by site investigators, not adjudicated	
Statistical Analysis	Estimated 150 subjects needed in each group to provide a power of 92% assuming a 25% reduction in clinical outcomes (mortality and HF hospitalizations) Intention to treat analysis Utilized Chi-square test and Fisher's exact test for binary outcomes Used general linear models and nonparametric approaches for continuous outcomes Kaplan Meier survival estimates and log-rank tests used for unadjusted time-to-event comparison	

Individuals included were either patients with high cardiovascular risk (>50 years with established CVD) or >60 years with at least one CVRF. With these criteria, approximately 80% of all the patients included had a history of CVD and was, therefore, on secondary prevention, and 20% was on primary prevention. With respect to primary outcomes, the liraglutidegroup had a statistically significant lower risk of MACE compared with placebo (HR = 0.87; 95% CI, 0.78–0.97). With respect to deaths from cardiovascular causes, the risk was also lower in the liraglutide group (HR = 0.78; 95% CI, 0.66–0.93 p = 0 007). The risk of death from any cause was also lower in the liraglutide group (HR = 0.85; 95% CI, 0.74–0.97; p = 0 02), as was the risk of nonfatal myocardial infarction and nonfatal stroke, but the results were not statistically significant. [5,6,7]

Analysis of the secondary composite outcome of microvascularcomplications (nephropathy and retinopathy) showed that the liraglutide group had lower risk (HR = 0.84; 95% CI, 0.73–0.97; p = 0 02). In terms of nephropathy alone, there was also lower risk in the liraglutide group (HR = 0.78; 95% CI, 0.67–0.92; p = 0 003), although the risk of retinopathy (HR = 1.15; 95% CI, 0.87–1.52; p = 0 33) rose slightly but not significantly, in the liraglutide group (probably related to better early glycaemic control). Significant differences were also observed as regards other CVRFs between the group treated with liraglutideand the placebo group. Weight loss was −2.3 kg greater in the liraglutide group, together with a greater decrease in SBP (−1.2mmHg) and DBP (−0.6mmHg). The liraglutidegroup showed a mean increase in heart rate of 3 bpm. In this trial, patients on treatment with liraglutide had a lower risk of presenting the primary outcome and a lower risk of cardiovascular death and death from any cause and microvascular complications, demonstrating superiority in terms of cardiovascular safety. The number of patients needed to treat (NNT) to prevent an episode in 3 years was 66 for the primary outcome and 98 for death from any cause.

Sustain

The SUSTAIN-6 trial (cardiovascular and other long-term outcomes with semaglutide in subjectswith type 2 diabetes) was conducted to determine the cardiovascular safety of semaglutide compared to placebo, both in the presence of standard treatment, and was published in September 2016. Semaglutide is a new GLP-1 RA that has still not been approved for the treatment of T2DM; it has a long half-life (6-7 days), which enables weekly subcutaneous

administration. SUSTAIN-6 was a randomised, double-blind, placebocontrolledtrial. It included 3297 patients who were randomized 1 : 1 : 1 : 1 to treatment with semaglutide 0.5 mg, semaglutide 1 mg, or placebo (two doses similar to those of the semaglutide treatment). The primary composite outcome was the time to occurrence of the first MACE: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondaryoutcomes included the time to occurrence of the first event:expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, hospitalisation for unstable angina, or hospitalisation for heart failure) and death from any cause and each of the individual components of the expanded composite cardiovascular outcome. Retinopathy and follow-up of nephropathy were also assessed. As in the LEADER trial, patients included in SUSTAIN-6 were patients with very high cardiovascular risks who were ≥50 years old with established CVD (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease stage III or greater, or heart failure NYHA class II or III) or ≥60 years old with at least one CVRF. Mean follow-up was 2.1 years. Of the 3297 patients, 2735 (83.0%) had established cardiovascular disease (including chronic kidney disease of stage 3 or higher), 1940 patients (58.8%) had established cardiovascular disease without chronic kidney disease, 353 (10.7%) had chronic kidney disease only, and 442 (13.4%) had both cardiovascular disease and kidney disease; 17% of the patients had cardiovascular risk factors and was 60 years of age or older. With respect to the primary outcome results of the semaglutide group, the first cardiovascular episode presentedon 108 occasions (1648 patients; 6.6% of them with at least one episode) compared to 146 episodes in the placebo group (1649 patients; 8%), which implies a HR= 0.74 (95% CI, 0.58–0.95), p < 0 001 for noninferiorityandp = 0 02 for superiority.

The first episode of nonfatal myocardial infarction occurred on 47 occasions in the semaglutide group and in 64 in the placebo group: HR= 0.74 (95% CI, 0.51–1.08; p = 0 12), a difference that was not significant. With respect to nonfatal stroke, the semaglutide group presented 27 episodes compared with 44 in the placebo group: HR= 0.61 (95% CI, 0.38–0.99; p = 0 04). The risk of cardiovascular death was similar in both groups (p = 0 92), nor were differences observed in death from any other cause (p = 0 79). Significant differences were also observed as regards other CVRFs between the group treated with semaglutideand the placebo group. The semaglutide group presented a reduction in HbA1c of −1.1% in patients who received the 0.5mg dose and− 1.4% in those treated with the 1mg dose, both with significant differences with the placebo group (p < 0 001). During the trial, the use of antidiabeticmedication in the placebo group was much greater than in the semaglutide group, and they tended to take insulin more than twice as frequently. Weight loss was −3.6 kg greater in the semaglutide 0.5mg group and − 4.9 kg in the semaglutide1mg group. In the placebo group, weight losses of −0.7 kg and− 0.5 kg were observed, respectively. Compared to the placebo group, the weight loss in the semaglutide group was 2.9 kg in those who received doses of 0.5mg and 4.3 kg in those who received 1mg (p < 0 001). [2,9,15]

The semaglutidegroup also presented a decrease in SBP of −1.3mmHg (0.5 mg) and− 2.6mmHg (1 mg), compared with placebo (p < 0 001). As with liraglutide, the semaglutide group showed an increase in heart rate with respect to placebo of 2bpm (0.5mg group) and 2.5bpm (1 mg) (p < 0 001).Fifty diabetic retinopathy complications occurred in the semaglutide arm and 29 in the placebo arm (HR = 1.76; 95% CI, 1.11–2.78; p = 0 02). These differences were observed early in the trial. With respect to retinopathy treatments, photocoagulation was required on 38 occasions in thesemaglutidegroup versus 20 in the placebo group and intravitrealagents on 16 occasions with semaglutide versus 13 with placebo. Complications such as vitreous haemorrhageoccurred on 16 occasions (semaglutide) versus 7 (placebo), while 5 (semaglutide) patients versus 1 (placebo) developed diabetes-related blindness. Of the 79 patients with retinopathy complications, 66 (83.5%) had preexisting retinopathy (42 of 50 in the semaglutide group [84%], and 24 of 29 in the placebo group [82.8%]). Worsening of retinopathy was related to the presence of retinopathy at the start of the study, poor baseline metabolic control and with greater reductions in HbA1c in the first 16 weeks of the trial. As regards the appearance of new nephropathy or worsening of existing nephropathy, there were 62 episodes in the semaglutide arm and 100 in the placebo group (HR = 0.64; 95% CI, 0.46–0.88; p = 0 005). In this trial, patients on semaglutide treatment had a 26% lower risk of developing the primary outcome. This lower risk is attributed above all to the significantly lower risk of developing nonfatal stroke (39%) and a nonsignificantreduction in the risk of developing a nonfatal myocardialinfarction (26%), since no differences were observed as regards cardiovascular death. The NNT to avoid this primary event would be 45 for 24 months. Thus, semaglutide shows superiority as regards cardiovascular safety.[5]

EXSCEL

The EXSCEL trial (exenatide study of cardiovascular event lowering), published in September 2017, was conducted to demonstrate the cardiovascular safety of extended-release exenatide versus placebo, both administered with

standard treatment. This study included the largest number of patients with T2DM among the cardiovascular safety studies conducted with GLP-1 RAs (more than 14,752 patients, in 687 centresin 35 countries) with a wide variety of cardiovascular situations. Patients were randomly assigned in a 1 : 1 ratio to receive subcutaneous injections of extended release exenatide at a dose of 2mg or matching placebo once weekly. The primary outcome was defined as the first occurrence of any component of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (three-component MACE outcome), in a time-to-event analysis. Secondary outcomes included death from any cause, death from cardiovascular causes, and the first occurrence of nonfatal or fatal myocardial infarction, nonfatal or fatal stroke, hospitalization for acute coronary syndrome, and hospitalization for heart failure, in time-toevent analyses.

The trial was designed such that approximately 70% of enrolled patients would have had previous cardiovascular events, and 30% would not have had previous cardiovascular events. Of the 14,752 patients (of whom 10,782), 73.1% had previous cardiovascular disease. The median duration of follow-up was 3.2 years. Weekly exenatide did not increase the incidence of the first episode of MACE (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) compared to placebo (HR = 0.91; 95% CI, 0.83–1.00; p < 0 001for noninferiority). Fewer episodes were observed with exenatide (839; 11.4%) than with placebo (905; 12.2%), but statistical significance was not reached to demonstrate superiority (p = 0 061). The rates of the first fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and other secondary outcomes did not differ significantly between the two groups. Additionally, in a prespecifiedsecondary analysis, patients treated with weekly exenatidehad a 14% lower incidence of death from all causes compared to placebo (HR = 0.86; 95% CI, 0.77–0.97). Therefore, the incidence of MACE did not differ between weekly exenatide and placebo. Within other CVRFs, the mean glycated hemoglobin level was 0.7 percentage points lower in the exenatidegroup than in the placebo group (95% confidence interval [CI], −0.7 to −0.6). [2,3]

Overall, least-square mean values were also lower with exenatide than with placebo with respect to body weight (difference of −1.27 kg), systolic blood pressure (−1.57 mmHg), low-density lipoprotein cholesterol (−1.5mg per deciliter [−0.04mmol per liter]), and triglycerides (−1.8mg per deciliter [−0.02 mmol per liter]); values were higher in the exenatide group than in the placebo group with respect to diastolic blood pressure (difference of 0.25 mmHg). To conclude, once-weekly administration of extendedreleaseexenatide in patients with type 2 diabetes at a wide range of cardiovascular risk appeared not to cause an increase in their overall cardiovascular risk. CV safety trials conducted to meet the FDA guidance generally use an efficient trial design that enrolls patients with more advanced atherosclerotic CV risk or established CVD to accrue sufficient events in a timely manner. However, a major limitation of such an approach is that the safety population is not representative of patients in ambulatory diabetes care, thereby raising questions about generalizability. Differences in baseline characteristics of the patient population recruited as well as in trial design and protocol make it difficult to compare results from these trials and inappropriate to reliably assess relative benefits of therapies. Another notable finding is that the favorable CV outcome benefit observed in LEADER and SUSTAIN-6 contrasts with the null results seen with other GLP-1 RA, lixisenatide, and ELIXA trial, which enrolled patients within 180 days of acute coronary syndrome or EXSCEL trial. Although the exact reasons are not clear, thisdiscrepancy might be related to differences in pharmacokinetic and pharmacodynamicproperties. Another explanation for the contrasting results might be the trial differences in the enrollment of lower-risk versus higher-risk patients and between the time of follow-up.

Trial	Population	N	% HF	Median Follow Up, years	Primary Outcome	Impact on Primary CV Outcome	Impact on HF Hospitalization
ELIXA	Recent ACS	6068	22.4	2.1	CVD, MI, UA, stroke	No difference in risk (HR 1.02; 95% CI 0.89-1.17)	No difference in risk (HR 0.96; 95% CI 0.75-1.23)
LEADER	CVD or high risk	9340	17.8	3.8	CVD, MI, stroke	Decreased risk (HR 0.87; 95% CI 0.78-0.97)	No difference in risk (HR 0.87; 95% CI 0.73-1.05)
SUSTAIN-6	CVD or high risk	3297	23.6	2.1	CVD, MI, stroke	Decreased risk (HR 0.74; 95% CI 0.58-0.95)	No difference in risk (HR 1.11; 95% CI 0.77-1.61)
EXSCEL	With or without CVD	14752	16.2	3.2	CVD, MI, stroke	No significant difference (HR 0.74; 95% CI 0.83-1.00)	No difference in risk (HR 0.94; 95% CI 0.78-1.13)
HARMONY	CVD	9463	20.3	1.5	CVD, MI, stroke	Decreased risk (HR 0.78; 95% CI 0.68-0.90)	Decreased risk (HR 0.71; 95% CI 0.53-0.94)
PIONEER-6	CVD or high risk	3183	12.2	1.3	CVD, MI, stroke	No significant difference (HR 0.79; 95% CI 0.57-1.11)	No significant difference (HR 1.11; 95% CI 0.77-1.61)
REWIND	CVD or high risk	9901	8.6	5.4	CVD, MI, stroke	Decreased risk (HR 0.88; 95% CI 0.79-0.99)	No significant difference (HR 0.93; 95% CI 0.77-1.12)
Kristensen, et al.	N/A	56004	N/A	N/A	N/A	Decreased risk (HR 0.88; 95% CI 0.82-0.94)	Decreased risk (HR 0.91; 95% CI 0.83-0.99)

Conclusions:-

Recent clinical trials aimed at studying cardiovascular episodes associated with the use of antidiabetics have increased our understanding of the potential effects of drugs for T2DM on cardiovascular risk. Clinical trials conducted with GLP-1 RAs and CVOTs present considerable differences in and enrolment which limits comparisons among designthem. Liraglutide and semaglutide showed superiority in cardiovascular benefit compared with placebo, both in the presence of standard treatment. 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 liraglutideandsemaglutide produce a cardiovascular benefit are still unknown (the antiatherosclerotic action hypothesis is prevailing), it would be desirable for these benefits to be incorporated 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 cardiovascular 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.

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