

Role of SGLT2 Inhibitors and GLP-1 Analogs in Cardiovascular Risk Reduction in Type 2 Diabetes

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Received: October 2021; Accepted: November 2021; Published: December 1, 2021.

Citation: Mostafa Hamdy Rashed et al. Role of SGLT2 Inhibitors and GLP-1 Analogs in Cardiovascular Risk Reduction in Type 2 Diabetes. *World Family Medicine*. 2021; 19(12): 119-128 DOI: 10.5742/MEWFM.2021.94188

Abstract

The leading cause of morbidity and mortality in patients with type-2 diabetes mellitus is cardiovascular (CV) disease, which makes it an important target in management. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1 RA) are both two new anti-diabetic drug classes that showed significant reduction in major cardiovascular events (MACE). With the introduction of these drugs, comprehensive CV risk reduction has been achieved in addition to glucose control. Both drugs work in different ways; the SGLT-2 Inhibitors lead to urinary excretion of 60-90 grams of glucose as well as sodium leading to osmotic diuresis. On the other hand, GLP-1 agonists affect postprandial glucose by enhancing insulin secretion in the beta cells and inhibition of glucagon secretion in the alpha cells in a glucose dependent manner. Different types of drugs are discussed in detail according to different trials such as

EMPA-REG, EMPEROR REDUCED, CANVAS, CREDENCE, VERTIS-CV, DAPA-HF and DECLARE TIMI 58 for SGLT-2 Inhibitors, while for GLP-1 agonists, trials such as ELIXA, FREEDOM, EXCEL, LEADER, SUSTAIN, PIONEER 6, REWIND and HARMONY. According to U.S. Drug and Food Administration guidance in 2008, it is required that all new oral hypoglycemic agents undergo cardiovascular outcome trials to evaluate CV safety. Both the SGLT2 inhibitors and GLP-1 agonists have undergone large trials that have led to massive evidence on their cardiovascular safety and renal benefits. The decision on using which drug from both classes depends on different factors like atherosclerotic disease and chronic Kidney disease.

Key words. diabetes, cardiovascular, reduction

Introduction

Cardiovascular (CV) disease remains the leading cause of morbidity and mortality in patients with type-2 diabetes mellitus (DM) and is thus an important target for management. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA) are two antidiabetic drug classes that have been demonstrated to significantly reduce the risk of major adverse cardiovascular events (MACE) and with introduction of these drugs there has been a paradigm shift to ensuring comprehensive CV risk reduction in addition to the glucose control previously accorded with initial oral antidiabetic drug classes (Das et al., 2020).

Their mechanism of action is as outlined in the table below :

SGLT-2 Inhibitors	SGLT-2 is a low affinity, high capacity glucose transporter in the proximal tubules of the kidney responsible for filtering approximately 90% of glucose. Inhibition of SGLT-2 leads to urinary excretion of 60-90 grams of glucose as well as sodium, leading to osmotic diuresis (Feingold, 2020)
GLP-1 RAs	GLP-1 is cleaved from the pro-glucagon molecule by pro-converterase enzymes in the gastrointestinal tract. Most of GLP-1 is stored in L-cells of the ileum and colon and is released at mealtime in response to neurohumoral signals and presence of food in the gut. GLP-1 affects postprandial glucose by enhancing insulin secretion in the beta-cells and inhibits glucagon secretion in the alpha-cells in a glucose dependent manner (Feingold, 2020)

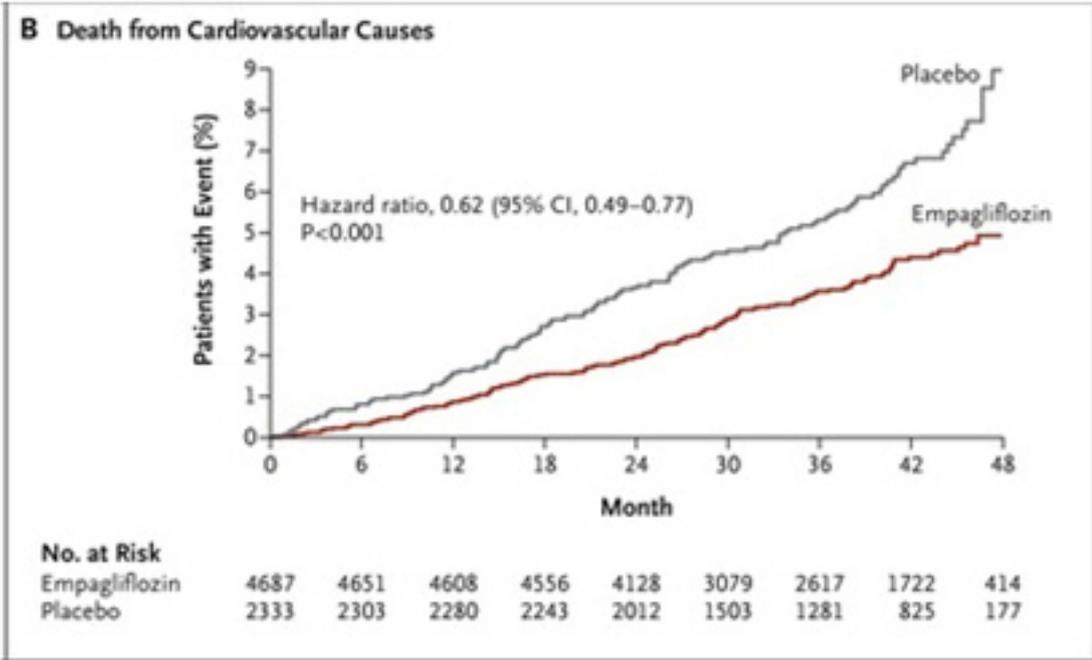
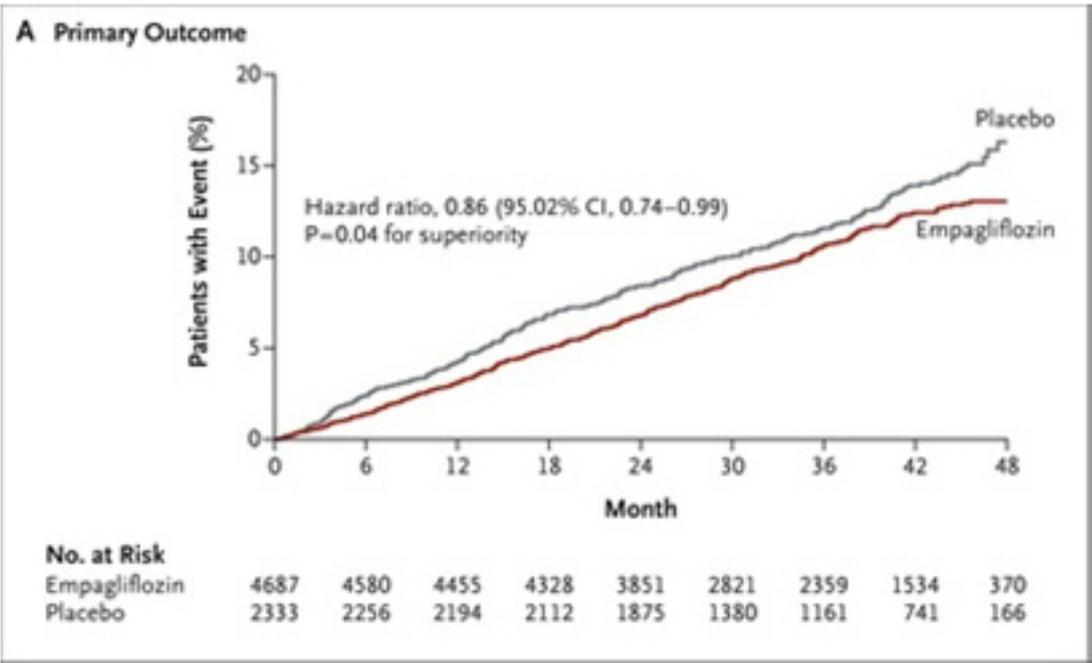
SGLT2-Inhibitors

This drug class has 4 major drugs as outlined in the table below:

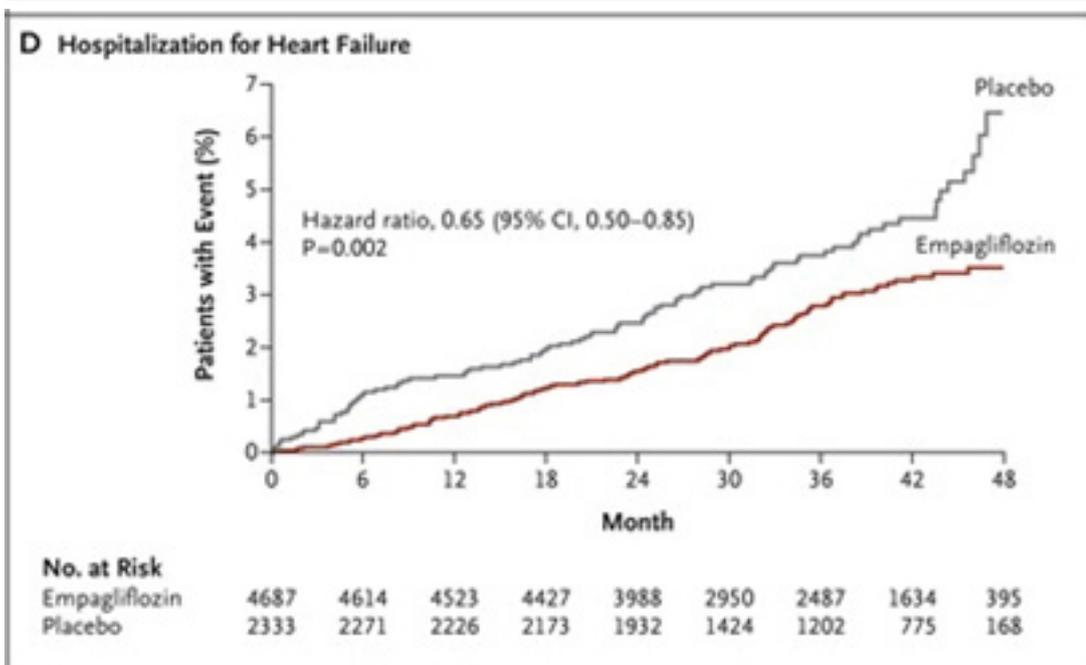
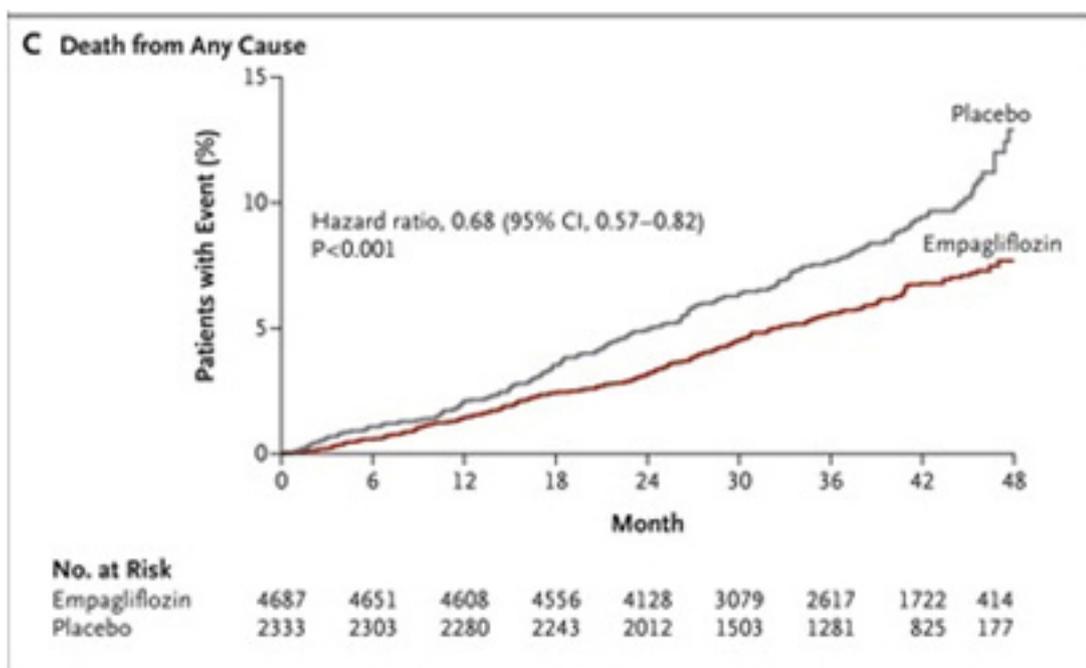
Year	Trial	Drug	Dosage Recommendations
SGLT-2 Inhibitors			
2015 2020	EMPA-REG EMPEROR REDUCED	Empagliflozin	10mg PO daily for CV benefit (ACC, 2020)
2017 2019	CANVAS CREDENCE	Canagliflozin	100mg PO daily for CV benefit (ACC, 2020)
2019	VERTIS -CV	Ertugliflozin	5mg PO daily, can be increased to 15mg (Feingold, 2020)
2019 2019	DAPA-HF DECLARE TIMI 58	Dapagliflozin	10mg PO daily for CV benefit (ACC, 2020)

1. Empagliflozin

Empagliflozin has been shown to have favourable effects on weight reduction, reduction in blood pressure without raising the pulse, improves markers of arterial stiffness and vascular resistance, has benefit on visceral adiposity, albuminuria, plasma urate levels and favourable effect on LDL and HDL levels. The EMPA-REG outcome trial examined the above favorable effects of empagliflozin compared to placebo. Primary outcomes evaluated included cardiovascular death, nonfatal Myocardial infarction (MI), and nonfatal stroke. Secondary outcomes included composite endpoints of the primary outcomes and hospitalization for unstable angina. The conclusions are summarized below: primary outcome was lower in the empagliflozin group (Figure A), decreased cardiovascular death (B), decreased all-cause mortality (C) and decreased hospitalization due to HF (D) (Zinman, et al., 2015).



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The EMPEROR-Reduced trial concluded that empagliflozin had improved outcomes in patients with heart failure with symptomatic stable ejection fractions of < 40%. This was superior to the placebo group and irrespective of whether a patient had diabetes or not (Kumbhani, et al., 2020).

2. Canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS) assessed Canagliflozin at reducing risk of MACE: cardiovascular (CV) death, non-fatal stroke or non-fatal myocardial infarction (MI) (Carbone and Dixon, 2019). The study participants were 10,420 patients with HbA1c \leq 10.5% and \geq 7% as well as established CV disease or two or more risk factors of it.

The effects of Canagliflozin were as depicted in the table below:

Cardiovascular risk factor	Observed effect of canagliflozin
HbA1c	Reduced by 0.58%
Body weight	Reduced by 1.60 kg
Systolic blood pressure	Reduced by 3.93 mm Hg
Diastolic blood pressure	Reduced by 1.39 mm Hg
High-density lipoprotein (HDL) cholesterol	Increased by 2.05 mg/dL
Low-density lipoprotein (LDL) cholesterol	Increased by 4.68 mg/dL
LDL/HDL cholesterol ratio	Remained unchanged

(Carbone and Dixon, 2019)

Canagliflozin significantly reduced CV risk factors in patients followed up for a period of 3-7 years. MACE risk reduced by 14% in the control versus placebo group: with CV death outcome reducing from 12.8 to 11.6/1000 patient-years; nonfatal stroke from 8.4 to 7.1/1000 patient-years, nonfatal MI from 11.6 to 9.7/100 patient-years and statistically insignificant reduction in all-cause mortality from 19.5 to 17.3/1000 patient-years. Other benefits of canagliflozin treatment included a 33% relative risk reduction in heart failure hospitalisations, a 30% reduction in fatal HF outcomes and a 22% reduction in composite CV death or HF hospitalization (Carbone and Dixon, 2019). Of the latter, patients with previous HF, BMI \geq 30 kg/m², HbA1c \geq 8%, on diuretics, and those who were not on metformin had suggested considerable benefits on canagliflozin treatment.

The Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical Evaluation (CREDENCE) trial focused on renal outcomes in patients with more advanced diabetic kidney disease. The trial showed Canagliflozin to have a significant benefit in both renal and cardiovascular outcome especially in patients who had advanced diabetic kidney disease (Robin, et al., 2020).

3. Ertugliflozin

According to Feingold (2020), the VERTIS-CV RCT randomized type-2 DM patients with atherosclerotic CV disease in three groups – 5mg ertugliflozin (n=2752), 15mg ertugliflozin (n=2747) and placebo (n=2747) added to the standard of care for diabetes (Consentino, et al., 2020). It focused on the 3 point MACE of CV death, nonfatal MI or nonfatal stroke after a mean duration follow-up of 3.5 years (Feingold, 2020; Zannad and Cowle, 2020). The heart failure hospitalizations were significantly reduced in patients treated with ertugliflozin (2.5% vs. 3.6%, p=0.006) (Feingold, 2020; Consentino et al., 2020). According to Williams, et al., 2021, this trial has a CV inferiority for the 3 point MACE compared to the CV superiority trials like EMPA-REG, CANVAS, CREDENCE and DECLARE-TIMI because the participants in this trial had a higher proportion of patients with heart failure (~ 24%).

4. Dapagliflozin

The DECLARE-TIMI 58 aimed to assess if the use of Dapagliflozin in patients with type 2 diabetes and at risk for cardiovascular disease reduces the risk of MACE. The study was a randomized, double-blind, multinational, placebo-controlled, phase 3b trial conducted in 33 countries. Participants were 17,160 patients with T2DM and a history of either established ASCVD (n = 6,971) or multiple risk factors for ASCVD (n = 10,189) (Wiviott et al., 2019).

The primary safety outcome was a composite of MACE: cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and the composite of cardiovascular death or hospitalization for heart failure. The secondary safety outcomes were renal dysfunction and death from any cause. They showed that dapagliflozin use among patients who had or were at risk for atherosclerotic cardiovascular disease reduced hospitalization without significant effect on MACE (Wiviott et al., 2019).

Later on, The DAPA-HF trial, a double-blinded, multicentre RCT that looked at a once daily dose of dapagliflozin at 10mg against a placebo in 4,744 subjects with heart failure with reduced ejection fraction (HFrEF) with type II diabetes, pre-diabetes and without diabetes was conducted. Inclusion criteria included heart failure patients with a NYHA class II or more, an ejection fraction of 40% or less and an elevated NT-proBNP level who were receiving standard heart failure therapy (McMurray, et al., 2019) (Docherty, et al., 2020). As opposed to prior HF trials, this RCT had a wide age gap including subjects between ages of 18 and 130 years (Rich, et al., 2020).

The trial concluded use of dapagliflozin at 10mg OD was beneficial to patients with HFrEF with or without diabetes in decreasing composite outcomes of cardiovascular mortality and hospitalization associated with heart failure. As compared to the DECLARE-TIMI 58 trial which looked at the same drug, this trial had the benefit of specifically looking at subjects with HFrEF and was the initial trial that showed benefit dapagliflozin, an SGLT2 inhibitor, in use for patients with HFrEF but without diabetes (McMurray, et al., 2019) (Wivott, et al., 2019).

Lo, et al., (2020) conducted a systematic review and meta analysis of 4 major trials, EMPA-REG, CANVAS, DECLARE-TIMI 58 and CREDENCE looking at the overall cardiovascular and renal outcomes following treatment with SGLT-2 inhibitors as second line therapy addition to metformin. The trials did not have enough data on diabetics with an estimated glomerular filtration rate between 30 and 45 mL/min/1.73m² but the meta analysis included data on those with an eGFR above and below 60 mL/min/1.73m². Regardless of atherosclerotic cardiovascular risk the meta analysis demonstrated that overall, SGLT-2 therapy is associated with a 7% reduction in MACE (major adverse cardiovascular event), an 11% reduction in cardiovascular death, a 29% reduction in heart failure hospitalization, a 35% reduction in the progression of renal disease in those with an eGFR above and below 60 mL/min/1.73m² and a reduction in all cause mortality (Lo, et al., 2020). The efficacy of SGLT-2 inhibitors is affected by the renal function. The evidence for cardiovascular benefit from SGLT-2 therapy was weakest in patients with an eGFR below 60 mL/min/1.73m² but there was clearer evidence of a lower adverse renal event in this group (Lo, et al., 2020). SGLT-2 inhibitors are reno-protective, implicating benefits for cardiovascular health. Of note, African Americans made up less than 10% of the participants in these large trials affecting the generalisability of these findings to them.

GLP -1 Receptor Agonists

This drug class can be divided into short-acting and long-acting agents:

Short-acting GLP-1 RAs			
2015	ELIXA	Lixisenatide	10ug or 0.01mg daily, after 14-days increase to 20ug or 0.02 mg daily (Feingold, 2020)
2016	FREEDOM	Exenatide	5ug or 0.005mg twice daily and after 1 month increase to 10ug or 0.01mg twice daily (Feingold, 2020)
2017	EXSCEL		
Long-acting GLP-1 RAs			
2016	LEADER	Liraglutide	0.6mg SC daily for CV benefit* (ACC, 2020)
2016	SUSTAIN		0.25mg SC per week for CV benefit *(ACC, 2020)
2018	PIONEER 6	Semaglutide	
2018	REWIND	Dulaglutide	0.75mg SC per week for CV benefit* (ACC, 2020)
2018	HARMONY	Albiglutide	30mg SC per week, can increase to 50mg (Trietley and Skef, 2017)
* can be titrated slowly to higher doses or maximally tolerated			

1. Lixisenatide

According to the results of the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, which was the first CVOT for the GLP-1 receptor agonists class following 6,068 type 2 diabetic patients with history of ACS (MI or hospitalization for unstable angina within the previous 180 days) over a period of 25 months, lixisenatide did not affect the rate of cardiovascular events (measured as composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina) compared to placebo among the patients studied, type 2 diabetics with history of ACS (Pfeffer, et al., 2015).

2. Exenatide

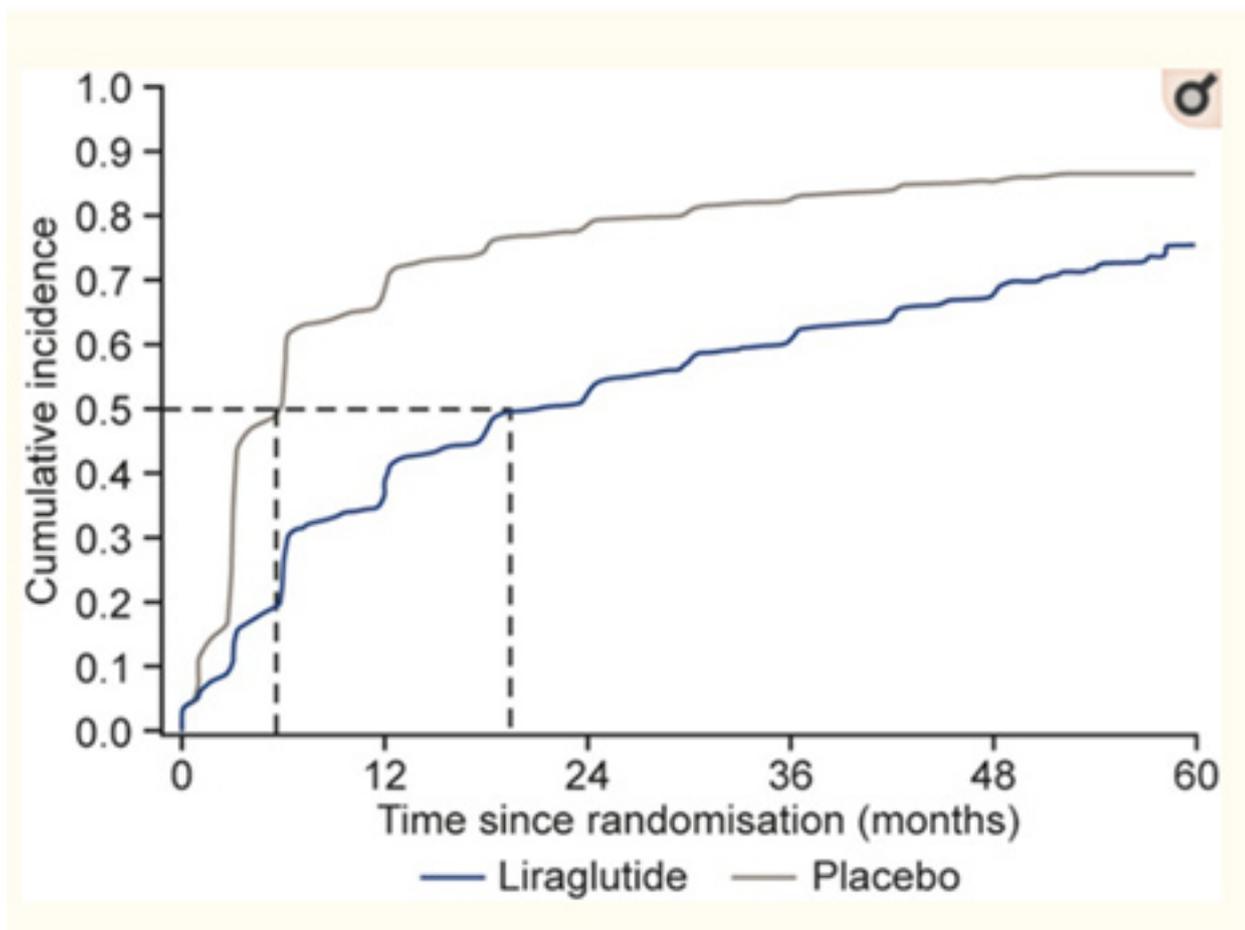
Effects of Once Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXSCEL) trial, a randomized, double-blind, placebo-controlled trial which was conducted in 687 sites in 35 countries with a total of 14,752 patients for a median duration of 3.2 years followed up type 2 diabetic patients with HbA_{1c} between 6.5 and 10% with (70%) or without (30%) prior cardiovascular events (coronary artery disease, ischaemic CVA, or atherosclerotic peripheral arterial disease) (Sheahan, et al., 2020). Patients were assigned 1:1 to either 2 mg of extended released exenatide or a volume-matched placebo once weekly (Holman & et al., 2017). Primary outcomes evaluated included occurrence mortality due to cardiovascular causes, nonfatal MI or nonfatal stroke. The trial concluded Exenatide use in diabetic patients with or without prior cardiovascular disease did not have any significant difference in occurrence of MACE between the study and placebo arm (Holman, et al., 2017).

3. Liraglutide

The LEADER trial, a double-blinded, placebo-controlled, event and duration based trial with a follow up of 32 to 60 months comparing use of Liraglutide (n= 4668) and a Placebo (n= 4672) found significant reduction of cardiovascular death, non-fatal MI and non-fatal stroke. Further analysis of the data was able to extrapolate the glycaemic deterioration over time. The end point was measured as HbA_{1c} >8 or change of 0.5 % on the next visit and intensification of oral hypoglycaemics and insulin as supportive treatment (Zinman, et al., 2018) (Marso, 2016).

The study shows that liraglutide reduces the HbA_{1c} and lessens the need for drug intensification when compared to a placebo in T2DM with High Cardiovascular risk. The trial followed the patients up over a mean period of 3.8 years and found that even though the Liraglutide lessens glycaemic deterioration, there is a convergence of HbA_{1c} control after 5 years. This is in keeping with the natural progression of T2DM (Figure 1).

Figure 1 (Image extracted from Marso, et al., 2016)



Cumulative incidence plot of time to HbA_{1c} ≥ 8% and reduction < 0.5% since previous visit or substantial intensification* in insulin or OAD treatment. Aalen-Johansen plot, with death as a competing risk factor.

* Substantial intensification of insulin or OAD defined as: start of new OAD; start of insulin; increase in insulin dose ≥ 10 units; or addition of mealtime bolus insulin to basal insulin or a shift from basal insulin to premixed insulin.

HbA_{1c} glycated haemoglobin, OAD oral antihyperglycaemic drug.

4. Semaglutide

SUSTAIN-6 and PIONEER 6 studies both are noninferiority cardiovascular outcomes trials of oral semaglutide whose primary outcome measures included the first occurrence of a major CV event defined as deaths arising from cardiovascular causes, non-fatal MI or stroke) (Marso, et al., 2016) (Husain, et al., 2019).

In the SUSTAIN-6 trial, the majority of T2DM individuals' (83%) who either had chronic kidney disease, established CV disease or both, were randomized to receive semaglutide once a week (0.5mg or 1.0 mg) or placebo for a duration of 104 weeks. At the end of the study period, the risk of the primary outcome was 42% lower in the semaglutide arm, and this was significant for noninferiority. With regards to the individual components of the primary outcome, the risk of nonfatal MI was 26% lower in the treatment arm, but this was not statistically significant while the risk of mortality from CV causes was the same in both groups. The risk of nonfatal stroke was 39% lower in the active treatment group and this attained statistical significance (Marso, et al., 2016).

In the PIONEER-6 trial, subjects with T2DM who either had a high cardiovascular risk or established cardiovascular disease were randomized to receive semaglutide given as a once-daily dose or placebo (Husain et al., 2019). At the end of the study period of 15.9 months, the occurrence of MACE was reduced by 21% in the treatment arm thus demonstrating that oral semaglutide was non-inferior. In the analysis of the various primary outcome components, the treatment arm had a reduction of 51% in CV deaths, as well as a 26% and a 49% reduction in non-fatal strokes and all-cause deaths, respectively (Husain, et al., 2019).

5. Dulaglutide

The REWID trial looked at the CV safety of addition of dulaglutide to diabetic patients with HbA1c \leq 9.5%, above the age of 50 years with established vascular disease receiving a maximum of 2 or more oral agents with or without basal insulin over a median period of 5.4 years which was the longest known for a GLP-1 RA. The trial showed dulaglutide has a safety profile comparable to the other GLP-1 RA studied in previous trials, and is superior to placebo in reducing cardiovascular events for diabetic patients with high CV risks when added on top of other oral hypoglycemic agents (Doupis, 2019).

6. Albiglutide

In 2018, the harmony outcomes trial, a randomized, double-blinded, placebo-controlled trial, with 9,463 patients in 28 countries with over 610 study sites looked into efficacy of once weekly albiglutide in type 2 diabetic patients with established cardiovascular disease and HbA1c levels of above 7% over a period of 1.6 years. Patients who received albiglutide had better improvement in their glycaemic control compared to the placebo group. The study control group also showed a major reduction in cardiovascular events and weight. Furthermore, in patients who were already receiving standard diabetic care, the inclusion of albiglutide contributed to a significant reduction in stroke, MI, cardiovascular events (22%), and hypoglycaemic episodes (Hernandez, et al. 2018).

While most trials on GLP-1 receptor agonists demonstrate beneficial effects in reducing MACE, results have been inconsistent regarding the effects of GLP-1 analogues on stroke and MI. Additionally, data on individuals with DM but without established CVD is limited though recent CVOTs have included many subjects without CVD. In a recent meta-analysis by Marsico, et al. (2020), data from 7 RCTs of GLP-1 analogues involving 56,004 patients with T2DM were analyzed. In this analysis, GLP-1 receptor agonists were associated with a significant decrease of 12% in the risk of three-point MACE. There was also a significant decrease in the risk of all-cause death (11%), CV mortality (12%), fatal and non-fatal stroke (16%), and HF hospitalization (8%) as well as a trend towards a reduction in the risk of MI. There was no significant difference in the efficacy of GLP-1 analogues between individuals with and without established CVD (Marsico, et al., 2020).

Conclusion

Following the U.S. Drug and Food Administration guidance in 2008, that required all new oral hypoglycemic agents to undergo cardiovascular outcome trials to evaluate for their cardiovascular safety (Regier, et al., 2016), the newer classes of SGLT2 inhibitors and GLP-1 RA have undergone relatively extensive large trials that have brought forth a wealth of information on their cardiovascular safety and additional renal benefits for particular drugs in those classes providing the clinician with excellent options of add-on 2nd line therapy. Keeping in mind diabetes already provides an inherent cardiovascular risk as the disease process progresses, it cannot be stressed enough that the drugs used to control hyperglycemia need to show benefit of reducing these cardiovascular risks especially in patients that already possess multiple cardiovascular risk factors or already have ongoing evidence of cardiovascular disease as can be seen in most cases in clinical practice. Ultimately, the decision to use which drug amongst the two classes depends on several factors including presence of atherosclerotic disease, and Chronic kidney disease which will guide which medication can or cannot be added, and the need to provide weight loss benefit to patients and cost and it is up to the clinician to individualize treatment.

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