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In type 2 Diabetes: The Impact Of Lowering Glucose Level On Cardiovascular Risk Is Significant

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Abstract
Diabetes type 2 diabetes mellitus is characterized by a high cardiovascular risk, which includes atherosclerotic cardiovascular disease. Some of the well-known pathophysiologic factors which play a crucial role include endothelial dysfunction due to oxidative stress and inflammation, hyperglycemia, increased activity of nuclear factor kappa B, altered macrophage polarization and reduced synthesis of resident endothelial progenitor cells. Therefore, it is reasonable to suggest that the atherosclerotic disease may progress more rapidly with increased tendency for unstable plaque formation, culminating in high mortality from cardiovascular diseases. The main strategies are therefore to prevent or diagnose it at the earliest, through management of hyperglycaemia and vascular complications. The new strategies for the management of T2DM are aimed at developing individualized treatment strategies for each patient with the goal of enhancing glucose lowering effects and minimizing the incidence of hypoglycemia and other side effects as well as prevention of cardiovascular diseases. New drugs (e. g. GLP-1 RAs, SGLT2is, DPP4is) have effects on body weight, lipids and blood pressure and also influence endothelium (dis)function, inflammatory markers, OS biomarkers and SAS. The present review summarizes the results of the main trials focused on the cardiovascular safety of these drugs from the CV standpoint.
Keywords: cardiovascular risk; dipeptidyl peptidase-4 inhibitors; glucagon like peptide-1 receptor agonists; sodium glucose cotransporter-2 inhibitors; type 2 diabetes mellitus

1. Introduction

Cardiovascular disease is the [1,2]. leading Hyperglycemia the cause activates development of numerous and blood death detrimental progression glucose in signaling of is prevention diabetic pathways atherosclerosis based and patients that with not treatment according affect certain only of to the endothelial features. on CVD the findings function The in its literature of and choice patients efficacy recent lead with of but clinical to T2DM a also trials are drug on which crucial to its provide [3]. lower cardiovascular new The the information safety. following regarding Of are the course, cardiovascular effect the of the therapeutic approaches that available are at the moment. These trials added knowledge on the effectiveness and the safety of the new antidiabetic drugs and highlighted some adverse effects of certain aspect of CV risk. Diabetic kidney disease is the most common cause of end stage renal disease. The most common treatment approach that can prevent the progression of DKD includes the use of ACEi or ARBs. However, it has been recommended that in T2DM patients, the SGLT2i and GLP-1 RAs should be used as the second-line treatment owing to their reno-cardiovascular benefits (Figure 1). Although they have shown a reassuring safety profile, unfortunately, the current guidelines do not enable us to determine the right drug for the right patient with the right co-morbidities (Table 1).

Findings from all the available CV safety trials enhance and support the clinical practices not only to control and keep the glycaemia in the healthy range but also to reduce the risks of the well-known complications (e.g. weight gain, hypoglycaemia and heart failure).

Table 1. The main glucose-lowering medications and their mechanisms of action for Type 2 **diabetes, which were** implicated in **the** cardiovascular outcome trial (CVOT**), are listed below**

Class Drug	Agent	Administration	Mechanism of Action	Reference
Biguanides	Metformin	oral	↑ Insulin sensitivity by activating Adenosine Mono Phosphate-activated protein kinase (AMP-k) ↓ Hepatic glucose production	[2]
Thiazolidinediones	Pioglitazone	oral	↑ Insulin sensitivity by activation of Peroxisome Proliferator Activated Receptor gamma (PPAR-γ) ↓ Peripheral glucose uptake	[4–6]
Sulfonylureas	Glimepiride Gliclazide	oral oral	↑ Insulin secretion	[1,5]
Insulin	Glargine Degludec	injective	↑ Glucose disposal ↓ Hepatic glucose production	[7,8]
Dipeptidyl Peptidase-4 Inhibitors (DPP4-is)	Sitagliptin Linagliptin Omarigliptin	Oral oral oral	↓ Half-life and promoting the insulinotropism of Glucagon Like Peptide-1(GLP-1) ↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent) Enzymatic activities against chemotactic molecules and hormones modulating the intricate inflammatory, vascular and immune processes Improving glycemic control ↓ Total cholesterol and triglyceride levels Improve weight neutrality ↓ Risk factors Ameliorating cardiac function and vascular repair Block cleavage of many circulating peptides ↑ Control of cholesterol/dyslipidemia	[9,10]
Glucagon Like Peptide-1 Receptor Agonists (GLP-1RAs)	Liraglutide Exenatide Semaglutide Lixisenatide Albiglutide Dulaglutide	Injective Injective oral / injective Injective Injective Iniective	↑ Insulin secretion (glucose-dependent) ↑ ß-cell proliferation ↑ Insulin biosynthesis ↓ ß-cell apoptosis ↓ Glucagon secretion (glucose-dependent) from pancreatic α-cells ↓ Rate of endogenous glucose production ↓ Gastric emptying ↑ Satiety ↓ Food intake ↓ Weight loss Improved blood pressure ↑ Low Density Lipoproteins particles oxidised (ox-LDL) ↓ Carotid Intima Media Thickness (CIMT) ↓ Flow-Mediated Dilation (FMD) ↓ Artery endothelial dysfunctions ↓ Atherosclerotic risk factors direct effects on both plaque initiation/formation and progression	[11–40]
Sodium Glucose coTransporter-2 Inhibitors (SGLT2-is)	Empagliflozin Canagliflozin Dapagliflozin	Oral oral oral	↓ Renal threshold for glucose reabsorption increasing glycosuria Modify insulin sensitivity lower insulin requirements ↓ Body weight ↓ Blood pressure ↓ Extracellular volume little changes in High Density Lipoprotein-Cholesterol (HDL-C), triglyceride, and Low Density Lipoproteins-Cholesterol (LDL-C) ↓ Small dense LDL-C	[41–73]

2. Search Strategy August 2024

We searched by using domestic and international electrical databases of medical literature (i. e., MEDLINE (1975 – 2019), EMBASE and SCOPUS (2000 – 2019), DARE (1980 – 2019) and Web of Science Core Collection (since search 1997) terms and used by were: reviewing trials, the meta-analyses, abstracts Incretins, of Glucagon-like national and international meetings. The major Peptide-1 receptor antagonists, DiPeptidyl Peptidase-4 inhibitors, Sodium-glucose transporter-2, 'kidney disease' and its relation to cardiovascular risk and CVD prevention.

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The main and very important Cardiovascular Outcomes Trials (CVOTs) assessing CV safety of glucose-lowering medications reached their primary outcomes and confirming previous studies that indicated that no increased CV risk are detailed in Table 2.

Table 2. An introduction to CVOTs and their relationship to reducing CVD with hypoglycemic drugs.

Agent	Study	Patients (N. and Type)	CVD-Reduction Interval CI, and *p*-Value) (Hazard Ratio HR, Confidence	Reference
Metformin	UK Prospective Diabetes Study (UKPDS study)	4075 overweight patients with newly diagnosed type 2 diabetes recruited in 15 centres	−32% HR (95% CI 13-47) $p = 0.002$	[2]
Pioglitazone	Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive)	5238 patients with type 2 diabetes who had evidence of macrovascular disease	−16% HR 0.84 (95% CI 0.72–0.98) $p = 0.027$	[4]
Thiazolidinediones or Sulfonylureas	Cardiovascular Accidents Intervention (TOSCA)	3028 patients with type 2 diabetes inadequately controlled with metformin monotherapy	HR 0.96 Pioglitazone (95% CI 0.74–1.26) $p = 0.79$	[5]
Pioglitazone	Insulin Resistance Intervention After Stroke (IRIS)	3876 participants and 12% with a history of coronary artery disease	−24% HR 0.71 (95% CI 0.54–0.94) $p = 0.02$	[6]
Degludec	Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes (DEVOTE)	7637 patients with type 2 diabetes; 3818 patients with insulin degludec and 3819 patients with insulin glargine U100	HR 0.91 (95% CI 0.78–1.06) $p = 0.21$	[8]
Liraglutide	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results-A Long Term Evaluation (LEADER)	9340 patients with type 2 diabetes with a previous cardiovascular problem or chronic heart failure or at least one cardiovascular risk factor	−13.9% HR 0.87 (95% CI 0.78–0.97) $p < 0.001$	[15]
Exenatide LAR	Exenatide Study of Cardiovascular Event Lowering (EXSCEL)	14,752 patients; 10,782 had previous cardiovascular disease	−12% HR 0.91 (95% CI 0.83–1.00) $p = 0.061$	[19]
Semaglutide	Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes CardioVascular Outcome Trial-CVOT (SUSTAIN-6)	3297 patients with type 2 diabetes	−6.6% HR 0.74 (95% CI 0.58–0.95) $p < 0.001$	[30]
Lixisenatide	Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)	6068 patients with type 2 diabetes who had had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 days	HR 1.02 (95% CI 0.89–1.17) $p = 0.81$	[32]
Albiglutide	Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (HARMONY 1-8 trials)	21,135 patients. Most patients had, or were at high risk for, cardiovascular disease.	−25% HR 0.78 (95% CI 0.68–0.90) $p < 0.0001$	[35,36]
Dulaglutide	Dulaglutide on Major Cardiovascular Events in Patients with Type 2 Diabetes: Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)	9901 participants occurred in 370 sites located in 24 countries with type 2 diabetes; 31% had prior cardiovascular disease	HR 0.88 (95% CI 0.79–0.99) $p = 0.026$	[37]
Empagliflozin	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG CT)	22,830 diabetic patients	−38%; HR 0.62 (95% CI, 0.49–0.77) $p < 0.001$	[47]
Canagliflozin	Canagliflozin Cardiovascular Assessment Study (CANVAS)	10,142 participants with type 2 diabetes and high cardiovascular risk	HR 0.86 (95% CI, 0.75–0.97) $p < 0.001$	[48]

Dapagliflozin	Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL Nordic trial)	40,908 patients with type 2 diabetes; 23% had cardiovascular disease	HR 0.59 (95% CI, 0.49–0.72) $p < 0.001$	[49,50]
Dapagliflozin	Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE)	17,160 patients, including 10,186 without atherosclerotic cardiovascular disease	HR 0.83 (95% CI, 0.73–0.95) $p = 0.005$	[54]

Agent	Study	Patients (N. and Type)	CVD-Reduction (Hazard Ratio HR, Confidence Interval CI, and *p*-Value)	Reference
Sitagliptin	Sitagliptin Cardiovascular Outcomes (TECOS)	14,671 patients with type 2 diabetes and cardiovascular disease	HR 0.98 (95% CI, 0.88–1.09) $p < 0.001$	[65]
Linagliptin	Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA)	6991 diabetic patients with high cardiovascular risk	HR 1.02 (95% CI, 0.89–1.17) $p < 0.001$	[66]
Omarigliptin	A Study to Assess Cardiovascular Outcomes Following Treatment with Omarigliptin (OMNeON study)	4202 patients with type 2 diabetes mellitus and established cardiovascular disease	HR 1.00 (95% CI 0.77–1.29) $p = 0.77$	[67,68]

3. Traditional Anti-Diabetic Drugs

Metformin is the most effective pharmacological treatment for T2DM; in the United Kingdom Prospective Diabetes Study (UKPDS study), for example, the risks of developing any diabetes-related complication, diabetes-related death or all-cause death were reduced by 32%, 42%, and 36% respectively in the group of overweight patients treated with metformin when compared with the 'conventional' group (i.e. patients treated with diet only or diet plus chlorpropamide, glibenclamide or insulin) [2]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE; study number: NCT00949286) revealed that the intensive glycemic control with gliclazide (modified release) reduced the combined macro and microvascular events mostly because of the new nephropathy or worsening of the same. Concerning thiazolidinediones, the study called Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive; study number: NCT00174993) which revealed although there was more heart failure, pioglitazone was effective in reducing the CV events by 16% ($p = 0.027$) [4]. On the other hand, the trial Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention (TOSCA; study number: NCT00700856) showed that the rate of CV events was comparable between the sulfonylureas (i. e. glimepiride and gliclazide) and pioglitazone with less hypoglycemic events observed with pioglitazone [5]. No significant difference (1.5 per 100 person-years) was revealed in the primary outcomes (defined as all-cause death, myocardial infarction, urgent coronary revascularisation or stroke in the modified intention-to-treat population) between patients treated with pioglitazone and sulfonylureas ($p = 0.79$). However, in T2DM patients in which metformin failed to provide adequate glycaemic control, the best treatment option is actually not well defined and remains a subject of vigorous debate [5].

Interestingly, pioglitazone [6] demonstrated a significant improvement in the major clinical events (MI, fatal or nonfatal stroke) (24%, $p = 0.02$) after 4. 8 years of follow-up in 3876 subjects with insulin resistance and transient or recent ischemic attack or stroke but without diabetes (the trial: Insulin Resistance Intervention After Stroke (IRIS; study number: NCT00091949) performed vs. placebo).

In the study Outcome Reduction with an Initial Glargine Intervention (ORIGIN; study number: NCT00069784.), it was stated that the use of basal insulin as an add on to the regular management improved the glycemic control without negative impact on the CV events [7].

The study named Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes (DEVOTE; CT. gov identifier: NCT01959529), a large randomized controlled trial of 7637 patients with CV disease and with diabetes duration of 16 years [8], supported the CV safety of insulin degludec when compared with insulin glargine. Degludec was in fact statistically superior with a lower rate of both severe and nocturnal severe hypoglycemia (by 40 and 53% respectively; $p < 0.001$ for both comparisons); there were no differences in CV mortality although differences in severe hypoglycaemia were also described and discussed [8].

4. Novel Anti-Diabetic Drugs

Incretins are hormones secreted by the intestinal cells that, when secreted into the circulation in response to oral glucose challenge, stimulate insulin release from the pancreatic ß-cells. The two main classes of incretins are the glucagon like peptides (GLP-1) and the glucose dependent insulinotropic polypeptides (GIPs); these are degraded in the blood by dipeptidyl peptidase-4 (DPP-4). Finally, they are removed from the circulation by the kidneys [9]. Of the two, GLP-1 has a better preserved insulinotropic potency in patients with T2DM as compared to GIDP.

During the past years, the Incretin-Based Therapies (IBTs) of T2DM (through Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA), DiPeptidyl Peptidase-4 inhibitors (DPP-4is), and Sodium/GLucose coTransporter 2 inhibitors (SGLT2is)) have been simplified and widely used. The effects of these treatments have been supported by clinical researches, which go beyond the glucose control improving several biomolecular targets (i.e. lipid levels, blood pressure, inflammatory markers, oxidative stress, endothelial dysfunction, subclinical atherosclerosis and weight). More and more T2DM patients have been found to be associated with heart attack, stroke, and amputation with sulfonylureas and basal insulin at significantly higher rates [10]. Consequently, it may be useful for the clinicians to prefer GLP-1 receptor agonists, SGLT-2 inhibitors or DPP-4 inhibitors instead of sulfonylureas or basal insulin after metformin as these drugs have shown similar or better short-term CV outcomes with GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors.

[10].

4.1. Glucagon Like Peptide-1 Receptor Agonists (GLP-1RAs)

GLP-1 enhances the insulin secretion and synthesis through the glucose-dependent pancreatic beta cell insulin secretory pathways and also suppresses the glucagon release from the pancreatic alpha cells; in addition, GLP-1 suppresses the glucose production and slows down the gastric emptying and thus increase the feeling of fullness.

Interestingly, the synthetic GLP-1 receptor agonists are structurally very close to the native GLP-1, but they are less sensitive to the enzymatic degradation by dipeptidyl peptidase 4 (DDP-4). Nevertheless, some data supported their safety and effectiveness on the cardiovascular system. In addition to the effects on glycaemia, GLP-1RAs have several other beneficial effects on the cardiovascular and metabolic systems including blood pressure, cholesterol/dyslipidaemia, body weight and food intake, which in turn reduces the burden of these traditional atherosclerotic risk factors (11). In addition, GLP-1 RAs may also have beneficial effects on the CV risk by modulating the physiology of the heart and the vasculature. [12].

To date, five GLP-1 RAs received FDA approval and include: exenatide, dulaglutide, lixisenatide, semaglutide, and liraglutide [11].

Also, been posited beyond found by the to Rizzo well-known have et effect a al. of marked in improving impact the glycemic on original control, the paper, liraglutide progression liraglutide has of has atherosclerosis the in its early phase; as potential Lipoproteins gotten to (LDL) into slow particles the down that arterial the are endothelial progression present wall of in where atherosclerotic the LDLs disease. blood are Low-Density are essential taken to up be from converted the into vascular ox-LDL. space and These modified lipoproteins were specifically engulfed by the activated macrophages which are in a position of initiating the inflammatory and proteolytic pathways which are well known early biological-biomolecular events in degradation and animal via enhanced models, LDL-receptors in ox-LDL results vitro trapping in and and enhanced in fixation penetration vivo within and atherosclerosis the trapping [14]. intima of The with ox-LDL impaired enhanced within ox-LDL ox-LDL the arterial intima peroxidation. The bio-molecular events have been postulated and documented to be among the major mechanisms that cause endothelial dysfunction, foam cell formation and accumulation, smooth muscle cell activation, migration and proliferation within the extracellular matrix as well as platelet activation/adhesion and aggregation. Among these events, liraglutide exerts its potential cardiovascular protective mechanism through direct effects on both plaque initiation/formation and progression (exhaustively reviewed in [13]).

The trial named Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results-A Long Term Evaluation (LEADER; CT. gov identifier: NCT01179048) clearly demonstrated in T2DM patients at elevated CV risk that liraglutide (1.8 mg) significantly reduces the rates of major adverse CV events [15]. In a prospective study performed on subjects with T2DM but without CAD [16], Carotid Intima-Media Thickness (CIMT) decreased independently to the well-known effects of liraglutide on both glucose and lipids [17]. Moreover, further studies demonstrated that liraglutide reduced CIMT also in subjects with metabolic syndrome, highlighting that its prevalence may be significantly reduced of about 26% in these subjects ($p < 0.0001$) [18].

According to the results obtained by Exenatide Study of Cardiovascular Event Lowering (EXSCEL; CT. gov identifier: NCT01144338), Exenatide reached the full CV safety but unfortunately failed to show any significant cardiovascular benefit [19], even though exenatide (10 µg) was able also to inhibit endothelial dysfunction in subjects with T2DM undergoing a meal tolerance test [20].

The clinical program development for “Exenatide once Weekly” (EQW) is based on multicenter, multinational, prospective, and phase 3 comparator-controlled clinical trial involving more than 5000 patients with T2DM (Diabetes Therapy Utilization: Researching Changes in HbA1c, Weight and Other Factors Through Intervention with Exenatide ONce Weekly; DURATION; CT. gov identifier: NCT00308139). The EQW program (24–30 weeks of treatment) demonstrated the ability to reduce by about 1.4% the levels of glycated hemoglobin (HbA1c), with an average of 1.94 mmol/L fasting blood glucose and 2.5 kg the body weight [21]. These significant effects were observed for up to five years in the some clinical studies, improving cardiovascular risk factors in subjects with both T2DM and the metabolic syndrome [22,23].

On the other hand, the therapeutic approach with exenatide Long-Acting Release (LAR) led to improved CIMT and Flow-Mediated Dilation (FMD), independently of glucometabolic status, suggesting that this therapy may represent an “add-on” to stable doses of metformin [24]. Interestingly, Exenatide significantly augmented fasting glycemia ($p < 0.0001$), HbA1c ($p < 0.0001$), waist

circumference ($p = 0.0105$) and also body mass index ($p = 0.0348$), revealing unexpectedly a crucial amelioration in the lipid profile, except in triglyceride (TG) [24].

The innovative delivery version of exenatide implant (named ITCA 650) provided significant continuous subcutaneous injection of Exenatide for up to 12 months after a sub-dermal placement of a small mini-pump [25]. The FREEDOM-CVO trial (CT. gov identifier: NCT01455896) in a cardiovascular safety study demonstrated very successful results in more than 4000 patients receiving 60 micrograms per day vs. placebo for over three years [26]. This study suggests ITCA 650 as the optimal condition for once or twice-yearly sub-dermal osmotic pump for delivering continuously and consistently GLP-1 drug therapy. It is worth noting that the continuous delivery of exenatide significantly improved medication adherence, compliance, and control rates over time, crucial aspects in the management of a chronic disease like T2DM.

Exenatide, liraglutide, and taspoglutide were able to achieve a significant reduction in total LDL-Cholesterol amount [27]. However, although at significant levels this biological effect probably is not clinically relevant, in fact, according to the Cholesterol Treatment Trialists' collaboration, it gives only a 3% of reduction in CV events after five years [28]. A significant reduction in triglyceride levels was also shown with liraglutide 1.8 mg once daily vs. placebo [27] in patients with a mean baseline HbA1c of 8.2% (66.1 mmol/mol). Although the long-acting GLP-1 RAs showed an ability to decrease LDL-Cholesterol levels, the difference between short-acting agents and insulin did not reach statistically significant levels [29].

Interestingly, Semaglutide showed a CV benefit in the pre-marketing phase of the SUSTAIN-6 trial involving patients with T2DM (Cardiovascular Outcome Trial-CVOT; CT. gov identifier: NCT01720446). The trial demonstrated a very positive effect on non-fatal strokes [30]. Data of post-marketing CVOT are actually in itinere and the results will be available from a larger number of patients than those included in the previous LEADER study [31].

In the multicenter, randomized, double-blind, placebo-controlled, parallel-group study named Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA; CT. gov identifier: NCT01147250), 6068 subjects with both T2DM and recent Acute Coronary Syndrome (ACS) [32] received lixisenatide. After a median follow-up period of 25 months, once daily dose of lixisenatide was safe but not superior to placebo for the composite primary endpoint (defined as CV death, myocardial infarction, stroke, and/or hospitalization for unstable angina). $$32,33$$

Another long-acting GLP-1RA is Albiglutide, given as a weekly subcutaneous injection and is a drug with different structure to other marketed GLP-1 RAs. HARMONY 1–8 trials: The HARMONY 1–8 trials are prospective, multicentre, multinational, phase 3, controlled clinical trials (ClinicalTrials. gov identifier: NCT00849056, NCT00849017, NCT00838903, NCT00838916, and NCT00839527) which involved 4838 patients with T2DM to assess the efficacy and safety of once weekly Albiglutide. However, $$35$$ it produced more substantiate the cardiovascular safety and benefit within the GLP-1 analogue/agonist class. Indeed, Albiglutide revealed its superiority vs placebo in patients with concomitant T2DM and cardiovascular disease, with a significant cardiovascular risk reduction (25% for myocardial infarction, fatal or not); nevertheless, the mechanisms behind these effects are still unclear. $$36$$

The REWIND study on the effects of Dulaglutide on major cardiovascular events in T2DM patients with the acronym of Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND; https://clinicaltrials. gov; identifier: NCT01394952) of is once a weekly randomized, dulaglutide double-blind, 1. placebo-controlled 5 study mg that on aimed the at major testing cardiovascular the events. effect

Although there are previous data from a large meta-analysis evaluating the cardiovascular risk of dulaglutide from randomized clinical efficacy and safety trials; the baseline cardiovascular risks were relatively balanced between the dulaglutide and the comparator groups; The primary endpoints of MACE, defined as the incidence of death from a cardiovascular cause, myocardial infarction, stroke, or unstable angina requiring hospitalization, was 0. 67% in the dulaglutide group and 1. 18% in the control group. The risk of non-fatal MI was also found to be significantly lower in the dulaglutide group as compared to the comparator group (p = 0. 014). However, the final REWIND data is yet to be obtained; this meta-analysis also reveals that dulaglutide does not increase the risk of MACE in patients with T2DM as concluded from the meta-analysis of the study. $$38$$

IdegLira (Degludec+Liraglutide) [39] and iGlarLixi (Glargine 100+lixisenatide) [40], a titratable fixed-ratio combination of insulin (Degludec or Glargine) with GLP-1 receptor agonist (Liraglutide or Lixisenatide), has the potential of minimizing the risk of hypoglycemia symptoms or hypoglycemia related risks such as acute CV events. In addition, iGlarLixi provided greater improvements in HbA1c ($p < 0.001$) and PPG glucose ($p < 0.001$) lixisenatide-associated than GI the symptoms. comparators $$40$$ while It preventing is insulin-related important weight to gain note and that in the DUAL program studies (DUAL 1, DUAL 2, DUAL 3; NCT01952145), IdegLira produced greater reductions in waist circumference ($p = 0.0494$), 0. blood 0323), pressure and (p triglycerides = (p 0. = 0146), 0. LDL-C 0130) [39].

4.2. Sodium Glucose coTransporter-2 Inhibitors (SGLT2-is)

The inhibitors SGLT2 are carrier proteins which are located in the proximal convoluted tubule of the kidney where they are involved in the reabsorption of glucose which is about 90%. Therefore, SGLT2 inhibitors work by decreasing the tubular maximum for glucose reabsorption and hence promote urinary glucose excretion. ANOTHER IMPORTANT THING TO REMEMBER IS THAT SGLT2 INHIBITORS SINCE THEY DO NOT AFFECT INSULIN SENSITIVITY ARE SLIGHTLY RELATED TO HYPOGLYCEMIC METABOLIC EVENTS. [41].

To date, four SGLT2-inhibitors have been FDA approved: Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin.

The metabolic beneficial effects obtained by SGLT2-is are primarily related to the capability of decreasing blood pressure and reducing the extracellular volume and such effects are seen in the first three months of treatment [42,43]. However, in patients treated with dapagliflozin the changes in HDL-C, triglyceride and LDL-C levels although not statistically significant showed a consistent reduction in the LDL-C/HDL-C ratio [44].

Two other studies of dapagliflozin (10 mg) double blinded and placebo controlled for a period of 12 weeks [45] and 24 weeks [46] proved that this drug has the potential of lowering the small dense LDL-C particles ($p = 0.005$ when compared with sitagliptin and $p = 0.003$ for between group comparison) while the larger LDL-C particles were not affected ($p = 0.026$ when compared with sitagliptin while the inter group comparison was insignificant, $p = 0.671$). Interestingly, HDL-2-C (an another marker which is inversely related with triglyceride levels and insulin resistance) was also found to be elevated to a significant level ($p < 0.001$ vs sitagliptin; $p < 0.013$ for intergroup comparison) [45].

However, when other DPP-4 inhibitors such as linagliptin and gemigliptin were administered with dapagliflozin as add-on to metformin and/ or sulfonylurea for 24 weeks, the level of HDL-C was found to be higher in patients treated with SGLT-2is [46].

The EMPA-REG trial (acronym of Empagliflozin cardiovascular outcome events in T2DM patients; CT. gov identifier: NCT01131676.) revealed that empagliflozin could lead to major adverse cardiovascular event MACE by 14%, CVD death by 38% and heart failures by 35%.

Also, the CANVAS study (Canagliflozin cardioVascular Assessment Study; CANVAS: NCT01032629) found that canagliflozin could decrease the incidence of MACE and HHF by 14% and 23%, respectively, although it was associated with the higher risk of acute limb neural compression.

The CVD-REAL Nordic trial conducted in multiple countries showed a marked difference in the outcomes between the new use of SGLT-2is and other glucose lowering drugs highlighting the led SGLT-2is to reduction in the risk of CVD mortality, MACE and HHF ($p < 0.0001$ for all conditions) [49, 50]. It should be noted that an analysis of these significant data revealed that dapagliflozin was associated with lower risk of MACE and HHF [50], which may explain the opposite findings of DPP4-is in CVOT and the CV effects of thiazolidinediones that are similar to heart failure [51-53].

Interestingly, the effect of Dapagliflozin therapy in patients with T2DM did not affect the rate of MACE as compared to placebo but it was observed that this therapeutic approach was associated with lower rate of CV death or hospitalization for heart failure. The DECLARE trial (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes; CT. gov identifier: NCT01730534) [54], based on a large cohort of 17160 patients (including 10186 patients without atherosclerotic cardiovascular disease followed up for a median of 4.2 years) revealed that dapagliflozin met the primary safety outcome criteria with regards to the placebo for MACE (myocardial infarction, ischemic stroke or

cardiovascular death). In the primary efficacy analyses (MACE and a composite of cardiovascular death or hospitalization for heart failure HHF), dapagliflozin produced a lower rate of cardiovascular death or HHF (p=0.005).

No differences between-group in terms of cardiovascular death were observed.

In relation to the kidney disordered functioning, renal harmful events were observed to have occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group and with regards to death from any cause it was seen that 6.2% died in the dapagliflozin group and 6.6% in the placebo group.

Currently there are ongoing studies on the effects of SGLT-2is on renal function abnormalities and CV outcomes (CANVAS-Renal; CT. gov identifier: NCT01032629 [55], which is part of the CANVAS Program [48]) and the results are awaiting.

Some trial studies also evaluated CV death or HF-related hospitalizations in addition to the primary composite renal outcome: e.g., Evaluation of the effects of Canagliflozin on Renal and Cardiovascular Outcomes in participants with Diabetic Nephropathy (CREDENCE; CT. gov identifier: NCT02065791) trial [56]; Dapa-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease) [57]; Dapa-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure [58]) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced; CT. gov identifier: NCT03057977 [59]); and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction [59]).

The EMPagliflozin compaRative effectIveness and SafEty (EMPRISE; CT. gov identifier: NCT03363464) study was aimed to assess empagliflozin's effectiveness, safety, and healthcare utilization in routine care for five years. It investigated the risk of HHF among T2DM patients initiating empagliflozin vs. sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i) [60] demonstrating that empagliflozin decreased the risk of HHF-specific by 50% and the risk of HHF-broad by 49%, independently of the doses of empagliflozin daily (10 mg or 25mg) for patients with and without baseline cardiovascular disease. Interestingly, also a comparative analyses among empagliflozin vs. the DPP4-i class, and the SGLT2i vs. DPP4-i classes revealed the same consistent findings [60].

4.3. *Dipeptidyl Peptidase-4 Inhibitors (DPP4-is)*

DDP-4 is the main enzyme that is involved in the biochemical pathways that control both the degradation and inactivation of GLP-1. Actually, DPP-4 is able to hydrolyze chemotactic factors and catalytic hormones, activity but that it can has affect also the other delicate biological balance functions of unrelated inflammation, to vascular its and immune processes.

DPP-4 inhibitors, by inhibiting the DPP-4 enzymatic activity, block the degradation of the incretins (GIP and GLP-1) and thus enhance the half-life and the insulinotropic effect of GLP-1 in patients with T2DM.

The DDP4-Is include sitagliptin, saxagliptin, linagliptin and alogliptin, of which vildagliptin has been recommended by the European Medicines Agency (EMA).

Based on the numerous biological substrates of the enzyme DDP-4, its crucial enzymatic inhibition may lead to a number of bio-molecular effects ranging from metabolic (enhancing glycaemic control, total cholesterol and triglyceride levels and being weight neutral) to cardiovascular (reducing risk factors, improving cardiac function and vascular repair) overall benefits [1, 9, 10, 62].

Although, the DPP4-Is were not deemed to be the most appropriate therapeutic option as an initial therapy these inhibitors have been evaluated in patients with T2DM and HHF. But the four DPP4-i trials (saxagliptin in SAVOR-TIMI 53 [63], alogliptin in EXAMINE [64], sitagliptin in TECOS [65], and linagliptin in CARMELINA [66]) did not reveal any significant reduction in HHF risk in the patients with T2DM. On the other hand, the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus vs. placebo; CT. gov identifier: NCT01107886) revealed a 27% risk of worsening of HF-related hospitalizations [63]; while in patients with T2DM and acute coronary syndrome EXAMINE trial (EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE; CT. gov identifier: NCT00968708) showed that there was no significant difference in the risk of developing HHF between alogliptin and placebo. [64].

In the TECOS study trial (Sitagliptin Cardiovascular Outcomes; CT. gov identifier:

NCT00790205), a study performed on 14,671 evaluating sitagliptin or placebo treatment added to existing therapy and for a median follow-up of 3.0 years was shown only a little difference in glycated haemoglobin levels, but, more interestingly, the primary cardiovascular outcomes in patients of the sitagliptin group demonstrated that sitagliptin was considered as noninferior to placebo ($p <$ 0.001) [65].

The further trial study named CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin; CT. gov identifier: NCT01897532), recruiting 6979 patients with previous CV events and micro and/or macroalbuminuria, was found to be able to reduce eGFR with macroalbuminuria [66], reporting that the primary outcome occurred in about 12% in both the linagliptin and placebo groups ($p < 0$ .001 for noninferiority), without significant differences in the renal outcome ($p =$ 0.62) [66].

Finally, the randomized, double-blind, placebo-controlled, multicenter OMNeON study (for assessing cardiovascular outcomes following omarigliptin treatment; the CT. gov identifier: NCT01703208) [67], however, demonstrated that once-weekly omarigliptin in 4202 patients with T2DM and CVD that revealed a hazard ratio (HR) of 1.00 for its primary MACE endpoint [67] was surprisingly terminated on the basis of business decisions [68].

5. Discussion and Conclusions

The CVOTs in patients with T2DM have shed light on the need to address the issue of HHF, which is now a more frequent and severe complication and progression of the diabetic disease than myocardial infarction. Based on the findings from several clinical trial studies, the application of glargine, degludec, sitagliptin, alogliptin, saxagliptin, lixisenatide, and once weekly exenatide had only neutral/negligible impact on the major adverse cardiovascular events. Hence, these drugs (i. e. glargine, degludec, sitagliptin, alogliptin, saxagliptin, lixisenatide and once weekly exenatide) have been observed to effectively enhance glycaemic control and prevent microvascular diseases without boosting the CV events.

Therefore, it is noteworthy that in a number of clinical trials, empagliflozin [70-73], canagliflozin [48], liraglutide [15], and semaglutide [30] have been found to lower CV events and deaths in very similar populations while both empagliflozin and canagliflozin were significantly associated with reduction in HF hospitalization and mortality ($p < 0.001$) [69].

Other imporant biological and clinical effects of empagliflozin and canagliflozin drugs were importantly linked to the improvement in renal function that was observed. Indeed, both empagliflozin ($p < 0.001$) [72], and canagliflozin ($p < 0.0001$) [56] were capable of slowing down the common progression of kidney disease in T2DM patients.

In addition, it has also been postulated that renal and myocardial tissues that are damaged may also gain from the supply of metabolic energy in the form of ketones in the circulation which results from the use of the SGLT2 inhibitor class [41, 58].

Within the class of DPP4 inhibitors, the linagliptin [66] has the least impact, with no benefit over the glucose-lowering control, only contributing to the proof of the lack of adverse effect on HF and proving the safety in patients with renal impairment.

However, both saxagliptin and alogliptin are known to have the undesirable effect of increasing the risk of HF [63, 64, 74], possibly due to the ability of both drugs to inhibit the release of many active peptides and may cause various bio-molecular effects which may not be well understood.

The results of the studies with the GLP-1RAs indicate that there is the improvement in the kidney function with both liraglutide ($p =$ 0.003) and semaglutide ($p = 0.005$) [15, 30]. However, it should be noted that the slower progression of renal disease (i. e. significantly low levels of macroalbuminuria) may be due to improvement in glucose control and renal handling as well as blood pressure control achieved with these drugs. However, the class of molecules, including liraglutide and semaglutide does not trigger the deleterious pancreatitis signals, which is an important clinical characteristic for patients with T2DM.

Finally, the deleterious effect shown by Semaglutide on diabetic retinopathy may represent a bias and could be explained on the basis of rapid and significant improvement of glycemic control in patients with pre-existing retinopathy; this clinical behavior and biological association with a similar trend was also seen with liraglutide treatment [15,30].

As for GLP-1RAs, it seems that they have an effect on all the vasculature, the body's physiological functions that are sustained with the potential for reducing the risk of MI and stroke. However, to the present day, GLP-1RAs are not proven to be effective in people with T2DM

CVD.

In the light of the recent ADA/EASD guidelines, the use of new glucose-lowering medications, SGLT-2i and GLP-1RAs, was emphasized, which was recommended to be used before metformin, even at the time of diagnosis of type 2 diabetes due to their protective effect on the cardiovascular system. The use of innovative therapies is thus marking a new era of drug therapy which is no longer based on the glycaemic control but rather on the individual needs of these patients. The potential advantages of these drugs have been analysed in this review; the adverse events (pancreatitis, thyroid diseases, ketoacidosis etc.) for the frequency of which these drugs do not raise concerns about non-use of these drugs but may require laboratory and possibly imaging investigations together with very close clinical monitoring for any adjustments of therapy. Important CVOTs assessing CV safety of glucose-lowering medications (as depicted in Figure 1) reached their primary outcomes and confirmed previous studies that indicated no increased CV risk (as detailed in Table 2). Future data should provide additional insights into the efficacy and safety of these drugs.

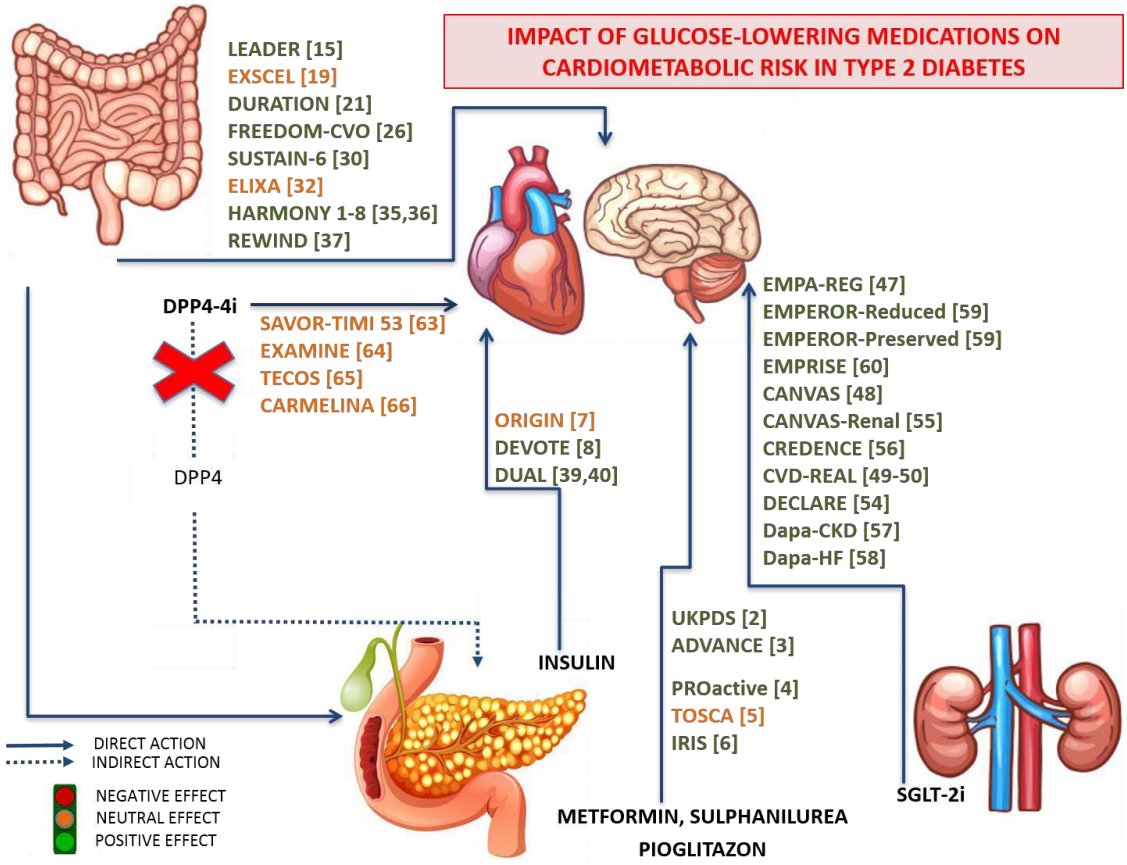

Figure 1. Schematic representation of the main routes, tissue biotargets, mode of actions, and effects of glucose-lowering medications, and their impact on cardiovascular risk in patients with Type 2 Diabetes. The data are obtained from both scientific literature and CardioVascular Outcome Trials, carefully assessing the cardiovascular safety of the main newest glucose-lowering medications;

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