Peer-reviewed version available at *J. Clin. Med.* **2020**, *9*; doi:10.3390/jcm9040912

Review

Impact of Glucose-Lowering Medications on Cardiometabolic Risk in Type 2 Diabetes

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Abstract: Type 2 Diabetes Mellitus (T2DM) is associated with a high risk of atherosclerotic cardiovascular (CV) disease. Contributing pathophysiologic factors include endothelial dysfunction caused by excessive production of reactive oxygen species (ROS), increased activity of nuclear factor kB (NFkB), altered macrophage polarization, and reduced synthesis of endothelial progenitor cells (EPC). Consequently, there can be a potentially rapid progression of the atherosclerotic disease with a higher propensity to unstable plaque, leading to increased cardiovascular mortality. Management is aimed at prevention, early diagnosis, and treatment of hyperglycemia and vascular complications. Innovative therapeutic approaches for T2DM seek to customize the antidiabetic treatment to each patient in order to optimize glucose-lowering effects, minimize hypoglycemia and adverse effects, and prevent cardiovascular events. The newer drugs (Glucagon Like Peptide-1 Receptor Agonists, GLP-1 RAs; Sodium GLucose coTransporter-2 inhibitors, SGLT2is; DiPeptidyl Peptidase-4 inhibitors, DPP4is) impact body weight, lipid parameters, and blood pressure, as well as endothelial function, inflammatory markers, markers of oxidative stress, and subclinical atherosclerosis. The present review summarizes the results of trials that evaluated the cardiovascular safety of these drugs and found them to be safe 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 (CVD) is a leading cause of death in diabetic patients. Hyperglycemia activates multiple maladaptive signalling pathways involving endothelial dysfunction, which leads to the emergence and rapid progression of the atherosclerotic disease with distinct characteristics. The choice of a drug to reduce blood glucose is based not only on its effectiveness but also on its cardiovascular safety; further, the prevention and control of CVD in patients with Type 2 Diabetes Mellitus (T2DM) are imperative. Data obtained from recent clinical studies attest to the cardiovascular benefits of therapeutic approaches that are currently available. These trials have had the advantage of expanding our knowledge on the efficacy and safety of innovative antidiabetic drugs; they also revealed some undesirable effects on specific aspects of cardiovascular (CV) risk.

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD); in the past, the only treatment that was able to attenuate DKD was a renin-angiotensin system blockade (ACEi or ARB) but for the partial effectiveness of these agents is needed to delay or prevent progression to ESRD. Recently reno-cardiovascular safety profile of SGLT2 inhibitors and GLP-1RAs in diabetic patients has been suggested as a second line treatment in type 2 diabetic patients when it is not contraindicated [1]. Although they have shown a reassuring safety profile, unfortunately, the current guidelines do not fully allow us to identify the most appropriate drug according to a specific patient phenotype and attendant co-morbidities. The results of the CV safety trials, as well as those of the older efficacy trials, facilitates clinical efforts to not only achieve and maintain optimal glycemic targets, but also minimize adverse effects such as weight gain, hypoglycemia, and heart failure.

2. Search Strategy

We searched the electronic databases [MEDLINE (1975 - 2019), EMBASE and SCOPUS (2000 - 2019), DARE (1980 - 2019)], and Web of Science Core Collection (up to 1997) and abstracts from national and international meetings. When necessary, we contacted the authors to obtain other information. The main search terms in studies, trials, meta-analyses were: 'Incretins', 'Glucagon Like Peptide-1 Receptor Agonists, GLP-1RA', 'DiPeptidyl Peptidase-4 inhibitors, DPP4-i', 'Sodium GLucose coTransporter-2 inhibitors, SGLT2-i', 'kidney disease' and their association with cardiovascular risk and prevention of CVD.

3. Traditional Ant-Diabetic Drugs

Metformin is the drug of the first choice in treatment of T2DM; in UK Prospective Diabetes Study (UKPDS study), patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13-47, p=0.002) for any diabetes-related endpoint, 42% for diabetes-related death (9-63, p=0.017), and 36% for all-cause mortality (9-55, p=0.011) in overweight patients [2]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE; CT. gov identifier: NCT00949286) study highlighted that intensive glycemic treatment based on the use of modified-release gliclazide reduced a combined endpoint of macro- and microvascular complications, mainly due to the reduction of new nephropathy or worsening of the same [3]. As regards the thiazolidinediones, in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive; CT. gov identifier: NCT00174993) study, pioglitazone reduced CV events 16% (p=0.027) despite an increase in the incidence of heart failure [4]. In the Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention (TOSCA; CT. gov identifier: NCT00700856) trial, the incidence of CV events was similar with sulfonylureas (glimepiride and gliclazide) and pioglitazone when used as add-on treatments to metformin, although pioglitazone was associated with fewer hypoglycemic events [5]. The primary outcome (a composite of the first occurrence of all-cause death, non-fatal myocardial infarction, urgent coronary revascularisation, or non-fatal stroke, assessed in the modified intention-to-treat population) occurred in 105 patients (1.5 per 100 person-years) who were given pioglitazone and 108 (1.5 per 100 person-years) who were given sulfonylureas (Hazard Ratio, HR 0.96, 95% Confidence Interval, CI 0.74-1.26, p=0.79). However, the best treatment option for patients with T2DM in whom treatment with metformin alone fails to achieve proper glycaemic control is debated [5]. In the trial: Insulin Resistance Intervention After Stroke (IRIS; CT. gov identifier: NCT00091949), pioglitazone [6] reported a significant 24% (p=0.02) diminution in its composite end point of MI, fatal or nonfatal stroke compared with placebo after 4.8 years of follow-up in 3,876 insulin-resistant subjects with a transient ischemic attack or recent ischemic stroke but without diabetes.

In the study Outcome Reduction With an Initial Glargine Intervention (ORIGIN; CT. gov identifier: NCT00069784.), early use and titration of basal insulin did not have any untoward effect on CV events when compared with standard strategies [7].

The study Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes (DEVOTE; CT.gov identifier: NCT01959529), a Trial Comparing Cardiovascular Safety of Insulin Degludec

Versus Insulin Glargine in Patients With T2DM at High Risk of Cardiovascular Events involving 7,637 patients with established CVD and a mean diabetes duration of 16 years [8], confirmed the CV safety of insulin degludec compared with insulin glargine (HR 0.91 [95% CI 0.78–1.06], p=0.21). Degludec was statistically superior with a lower rate of both severe and nocturnal severe hypoglycemia (by 40 and 53%, respectively; p<0.001 for both comparisons); despite the differences in severe hypoglycemia, no differences in CV mortality were found [8].

4. Novel Anti-Diabetic Drugs

Incretins are intestinal hormones that, after secretion by the enteroendocrine cells in response to oral glucose intake, stimulate the secretion of insulin from the pancreatic ß-cells. Glucagon-like peptide 1 (GLP-1) and Glucose-dependent insulinotropic peptide are two incretins, which once released in the blood are rapidly degraded by dipeptidyl peptidase-4 (DPP-4) and cleared by the kidney [9]. The insulinotropic effect of GLP-1 is more preserved in patients affected by T2DB, compared to glucose-dependent insulinotropic peptide.

In this respect, Incretin-Based Therapies (IBTs), including Glucagon Like Peptide-1 Receptor Agonists (GLP-1RA), DiPeptidyl Peptidase-4 inhibitors (DPP-4is), and Sodium/GLucose coTransporter 2 inhibitors (SGLT2is), have become popular and more widely used for the treatment of T2DM in recent years. Clinical studies highlight their actions beyond glucose-lowering effects (reduction of lipids, blood pressure, inflammatory markers, oxidative stress, endothelial dysfunction, and subclinical atherosclerosis and in body weight), which are achieved without any increase in hypoglycemia. Analyzing data on a large number of patients with T2DM, it appears that sulphonylureas and basal insulin are associated, though not necessarily causatively, with an increase in heart attacks, strokes and amputations [10]. Because of this association, clinicians could consider prescribing GLP-1 receptor agonists, SGLT-2 inhibitors, or DPP-4 inhibitors rather than sulfonylureas or basal insulin more routinely after metformin. The short-term CV outcomes with GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors were similar [10].

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

GLP-1 improves the glycemic control by stimulating pancreatic insulin synthesis and secretion in a glucose-dependent manner, inhibiting glucagon secretion from pancreatic α-cells via a paracrine effect promoted by somatostatin release and slowing the rate of endogenous glucose production; moreover, GLP-1 inhibits gastric emptying and promotes satiety.

Synthetic GLP-1 receptor agonists are structurally similar to GLP-1 but resist dipeptidyl peptidase 4 (DDP-4) degradation. Several data ensured their cardiovascular safety and efficacy. Besides their ability to decrease the levels of blood glucose, GLP-1RAs showed several positive cardiovascular and metabolic effects, such as improved control of blood pressure and cholesterol/dyslipidemia, promotion of weight loss and reduced food intake, finally reducing the impact of these known atherosclerotic risk factors [11]. Further, GLP-1 RAs may favorably affect CV risk through direct actions on the myocardium and blood vessels [12].

To date, five GLP-1 RAs have received FDA approval and include exenatide, dulaglutide, lixisenatide, semaglutide and liraglutide [11]. With respect to this latter, Rizzo et al. [13] have hypothesized possible explanations in understanding the beneficial actions of liraglutide beyond glycemic control, which seems to exert significant effects at the early stage of atherosclerosis and slows its progression [13]. Circulating Low-Density Lipoproteins (LDL) particles are transported from the vascular space into the arterial wall and retained in the extracellular matrix, where they are prone to form oxidized LDL, an early event in atherosclerosis that further contributes to atherosclerotic plaque formation [14]. Decreased clearance by LDL-R, increased arterial entry, arterial retention and increased oxidation have been proposed as the primary mechanisms, leading to endothelial dysfunction, foam cell formation, smooth muscle cell migration and proliferation and induction of platelet adhesion and aggregation [13]. In this respect, liraglutide exerts its potential

cardiovascular protective mechanism through a direct effect on plaque formation and progression, as reviewed in [13].

The results of Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results-A Long Term Evaluation (LEADER; CT. gov identifier: NCT01179048) trial showed that liraglutide (1.8 mg) significantly reduced the rates of major adverse CV events in T2DM patients at elevated CV risk [15]. In an 8-month prospective study in subjects with T2DM without Coronary Artery Disease (CAD) [16], Carotid Intima Media Thickness (CIMT) decreased independent of the effects of liraglutide on glucose and lipids [17]. In subsequent clinical studies, liraglutide was found to reduce CIMT over 18 months in subjects with Metabolic Syndrome (MetS). Moreover, the prevalence of the MetS was significantly reduced since 26% of the subjects no longer fulfilled the criteria for it ($p<0.0001$) [18].

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL; CT. gov identifier: NCT01144338) met the goal of CV safety but failed to show any significant cardiovascular benefit [19]. Torimoto et al. showed that exenatide (10 μg) inhibited postprandial vascular endothelial dysfunction beyond lipid and glucose metabolism in subjects with T2DM who underwent a meal tolerance test [20]. The clinical development program for Exenatide once Weekly (EQW), Diabetes Therapy Utilization: Researching Changes in HbA1c, Weight and Other Factors Through Intervention with Exenatide ONce Weekly (DURATION; CT. gov identifier: NCT00308139), consisted of 8 multicenter, multinational, prospective, phase 3 comparator-controlled clinical trials in more than 5000 patients with T2DM [21]. In studies lasting 24 to 30 weeks, EQW reduced glycated hemoglobin (HbA1c) (average 1.4%, [95% CI-1.5% to -1.4%]), fasting blood glucose (average 1.94 mmol/L, [95% CI-1.5% to -1.4%]) and body weight (average 2.5 kg, [95% CI-2.8 kg to -2.3 kg]) [21]. These effects were sustained for up to 5 years in the clinical study [22] and improved several cardiometabolic risk factors in subjects with T2DM and the MetS [23]. Treatment with exenatide Long Acting Release (LAR) led to improved cardio-metabolic parameters, including CIMT and Flow-Mediated Dilation (FMD), independently of glucometabolic control in sixty subjects with T2DM treated with exenatide LAR as an add-on to stable doses of metformin for 8 months in an open-label study [24]. Exenatide significantly improved fasting glycemia (from 8.8 ± 2.8 to 7.3 ± 2.2 mmol/L, $p<0.0001$), HbA1c (from 8.0 ± 0.4 to 6.9 ± 1.1%, $p<0.0001$), waist circumference (from 109 ± 13 to 106 ± 13 cm, $p= 0.0105$ and body mass index (from 33 ± 9 to 31 ± 6 kg/m2, $p= 0.0348$). There was a significant improvement in the lipid profile, except in triglyceride (TG) levels where no changes were observed. CIMT and FMD were also improved (from 0.98 ± 0.14 to 0.87 ± 0.15 mm and from 5.8 ± 1.3 to 6.8 ± 1.7%, respectively; $p<0.0001$ for both) [24].

ITCA 650 (exenatide implant) is an innovative delivery system that provides continuous subcutaneously exenatide for up to 6-12 months after sub-dermal placement of a small, 44 mm titanium osmotic mini-pump [25]. In 2016, Intarcia Therapeutics, Inc. published successful results involving more than 4000 patients in Cardiovascular Safety Study (FREEDOM-CVO trial; CT. gov identifier: NCT01455896) for ITCA 650 at 60 micrograms per day vs. placebo over a period of 3 years [26]. ITCA 650 represents the first once or twice-yearly GLP-1 in development, where exenatide is delivered by a matchstick-size, miniature osmotic pump (DUROS®) that is placed sub-dermally to provide continuous and consistent drug therapy. The inclusion criteria were: age greater than 40 years, HbA1c> 6.5%, a history of coronary, cerebrovascular or peripheral artery disease (PAD), or multiple CV risk factors. Continuous delivery of exenatide improved medication adherence, compliance and control rates over time, which are important aspects in the management of a chronic disease like T2DM. Exenatide, liraglutide, and taspoglutide achieved a significant reduction in LDL-C ([95% CI, -0.08 to -0.16 mmol/L or [95% CI, -3.08 to -6.18mg/dL) [27]. However, although significant, this is probably clinically irrelevant: according to the Cholesterol Treatment Trialists' (CTT) collaboration, it translates into only a 3% reduction in CVD events after 5 years [28]. A significant reduction in triglyceride levels was shown with liraglutide 1.8 mg once daily ([95% CI, -0.49 to -0.11]) vs. placebo [27] in patients with a mean baseline HbA1c of 8.2% (66.1 mmol/mol). In

comparison with insulin, long-acting GLP-1 RAs were shown to decrease LDL-C levels (-0.18 to -0.09 mmol/L or -6.95 to -3.47 mg/dL), but the difference between short-acting agents and insulin was not significant [29].

Semaglutide has shown CV benefit in the pre-marketing phase of the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes CardioVascular Outcome Trial-CVOT (SUSTAIN-6; CT. gov identifier: NCT01720446). This trial also demonstrated a strong positive effect on non-fatal stroke [30]. Additional data will be available from the new post-marketing CVOT with the use of semaglutide designed to test CV benefit in a much larger cohort of patients than those included in the LEADER study [31].

In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA; CT. gov identifier: NCT01147250), a randomized, double-blind, placebo-controlled, parallel-group, multicenter study, 6,068 subjects with T2DM and a recent Acute Coronary Syndrome (ACS) [32] were treated with lixisenatide. The median follow-up period was 25 months. The primary aim was to evaluate its effects on CV morbidity and mortality in a population at high CV risk, while the primary efficacy endpoint was a composite of time to CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina [32]. Once-daily lixisenatide administration demonstrated safety but not superiority over placebo for the composite primary outcome [33].

Albiglutide is another long-acting GLP-1RA that is administered by weekly injection and has a chemical structure different from that of other marketed GLP-1 RAs [34]. The efficacy and safety of once-weekly albiglutide were evaluated in a series of eight large, prospective, multicentre, multinational, phase 3, controlled clinical trials (HARMONY 1-8 trials; CT. gov identifier: NCT00849056, NCT00849017, NCT00838903, NCT00838916, NCT00839527) that randomized 4838 patients with T2DM [35]. The cardiovascular outcome study with albiglutide provides additional and important data on cardiovascular safety and benefit within the GLP-1 analogue/agonist class. In patients with T2DM and cardiovascular disease, albiglutide was superior to placebo for Major Adverse Cardiovascular Events (MACE). In the HARMONY study, albiglutide shows a cardiovascular benefit with a 25% reduction in the relative risk for fatal or non-fatal myocardial infarction but the mechanisms involved remain to be understood [36].

The Effect of Dulaglutide on Major Cardiovascular Events in Patients With Type 2 Diabetes: Researching Cardiovascular Events With a Weekly INcretin in Diabetes (REWIND; CT. gov identifier: NCT01394952) trial is a phase three, double-blind, randomized, placebo-controlled study designed to assess the effects of once-weekly dulaglutide 1.5 mg on the incidence of cardiovascular outcomes [37]. The patients were aged ≥ 50 years with T2DM, HbA1c ≤ 9.5%, and, depending on age category (≥ 50 years, ≥ 55 years, or ≥ 60 years), had either a prior cardiovascular event, evidence of cardiovascular disorder, or at least 2 other cardiovascular risk factors, like as dyslipidemia, hypertension or tobacco use. The primary cardiovascular outcome included the first occurrence of MACE; secondary outcomes include cardiovascular death, nonfatal MI, nonfatal stroke, a composite outcome of renal or retinal diseases, hospitalization for unstable angina, heart failure requiring hospitalization or an urgent heart failure visit, and all-cause mortality. There is data from a large meta-analysis that considered the cardiovascular risk of dulaglutide from 9 randomized phase 2 and 3 clinical efficacy and safety trials ranging from 12 to 104 weeks in duration (mean treatment duration, 333 days) [38]. The baseline cardiovascular risks were similar between dulaglutide and comparator groups; a composite MACE endpoint of death due to cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina occurred in 0.67% of patients in the dulaglutide group compared with 1.18% in the comparator group (active treatment or placebo). The estimated hazard ratio for dulaglutide versus comparators was 0.57, with an adjusted 98.02% CI of 0.30-1.10 (p=0.046). The relative risk of experiencing a nonfatal MI was significantly lower in the dulaglutide group versus the comparator group (estimated HR= 0.35; adjusted 98.02% CI= 0.13-0.95;

p=0.014). While awaiting the final REWIND data, this meta-analysis confirms that dulaglutide does not increase the risk of MACE in patients with T2DM based on the meta-analysis findings [38].

IdegLira (Degludec + Liraglutide) [39] and iGlarLixi (Glargine 100 + Lixisenatide) [40], a titratable fixed-ratio combination of insulin (Degludec or Glargine) plus GLP1-RA (Liraglutide or Lixisenatide), reduced the risk of hypoglycemia unawareness or hypoglycemia-associated complications such as acute cardiovascular events. iGlarLixi achieved significantly greater reductions in HbA1c ($p<0.001$) and post prandial glycemia ($p<0.001$) at week 30 than comparators and mitigated insulin-associated weight gain and lixisenatide-associated gastrointestinal events [40]. IdegLira, in the DUAL program studies (CT. gov identifier: NCT01952145), achieved significantly greater reductions in waist circumference (p=0.0494), blood pressure (p=0.0146), LDL-C (p=0.0323) and tryglicerides (p=0.0130) [39].

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

SGLT2 proteins are transporters expressed in the proximal convoluted tubule of the kidneys, where they contribute to the reabsorption of approximately 90% of renal glucose. Thus, SGLT2 inhibitors exert their glucose-lowering effects by reducing the renal threshold for glucose reabsorption and inducing urinary excretion of glucose. A crucial aspect is that SGLT2 inhibitors, due to the fact that they do not modify insulin sensitivity, are slightly associated with hypoglycemic phenomena [41].

To date, four SGLT-2-inhibitors have been FDA approved: Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin.

SGLT-2is, as a drug class, exert beneficial metabolic actions such as reduced blood pressure and decreased extracellular volume, which can be manifested as early as within the first 3 months of treatment [42,43]. Small mean changes in HDL-C (+2.1% to +9.3%), triglyceride (−0.9% to −10.6%), and LDL-C (−0.5% to +9.5%) levels were observed overall in patients undergoing dapagliflozin therapy, although did not achieve the statistical significance. The overall LDL-C to HDL-C ratio decreased with dapagliflozin therapy [44]. Two placebo-controlled studies of dapagliflozin (10 mg) for 12 [45] and 24 weeks [46] have reported the drug's effects vs. sitagliptin on LDL-C and HDL-C subfractions; dapagliflozin significantly reduced small dense LDL-C (-19.9%, $p<0.005$ vs. sitagliptin -6.7%, $p<0.368$; $p<0.003$ for intergroup comparison) but not the far less atherogenic large LDL-C (-17.75%, $p<0.026$ vs. sitagliptin -2.9%, $p<0.671$; $p<0.029$ for intergroup comparison). There was a significant increase in HDL-2-C (+18%, $p<0.001$ vs. sitagliptin +3.4%, $p<0.334$; $p<0.013$ for intergroup comparison), a marker inversely associated with triglycerides and insulin resistance [45]. In a further comparison of linagliptin and gemigliptin vs. dapagliflozin as add-on therapy to metformin and/or sulfonylurea for 24-weeks, a significant increase in HDL-C levels was reported in subjects treated with SGLT-2is [46].

In Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG CT. gov identifier: NCT01131676.), MACE was reduced by 14%, with a reduction of 38% in CVD death and a 35% reduction in heart failure requiring hospitalization [47]. Canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS; CT. gov identifier: NCT01032629) also reduced 3-point MACE and Hospitalization for Heart Failure (HHF) by 14 and 23%, respectively, but there was an increased risk of amputation (HR: 1.97; 95% CI, 1.41 – 2.75) [48]. In the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL Nordic trial), a multinational observational study, new use of SGLT-2is vs. new use of other glucose-lowering drugs was associated with decreased risk of CVD mortality (HR: 0.53; 95% CI, 0.40-0.71]), major adverse CVD events (HR: 0.78; 95% CI, 0.69–0.87) and HHF (HR: 0.70; 95% CI, 0.61–0.81) ($p<0.0001$ for all) [49,50]. In a sub-analysis comparing dapagliflozin with DPP4is, the former was associated with a lower risk of MACE and HHF vs. DPP4i [50]. The results of DPP4-is in

CVOT are reminiscent of the rather disappointing effects of thiazolidinediones [51-53] on heart failure, and their controversial CV outcomes [53].

The treatment with dapagliflozin did not result in a different rate of MACE than placebo but did result in a lower rate of CV death or hospitalization for heart failure. In the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE; CT. gov identifier: NCT01730534) [54], the primary safety outcome was a composite of MACE defined as a myocardial infarction, ischemic stroke or cardiovascular death. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. The secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause. The cohort of 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, were followed for a median of 4.2 years. In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% CI, <1.3; p<0.001 for noninferiority); in the two primary efficacy analyses, dapagliflozin in a lower rate of cardiovascular death or HHF (4.9% vs. 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; p=0.005), which reflected a lower rate of HHF (HR, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17). A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (HR, 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (HR, 0.93; 95% CI, 0.82 to 1.04). Renal studies with SGLT-2is and CV outcomes are in progress; CANVAS-R (CANVAS-Renal; CT. gov identifier: NCT01032629) [55], data from which were included in the combined report on the overall CANVAS Program [48], and the ongoing 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] will also evaluate CV death or HF-related hospitalizations in addition to the primary composite renal outcome; 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]), both of which are looking at heart failure patients with reduced ejection fraction; and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction [59]), which involves patients with preserved ejection fraction. The EMPagliflozin compaRative effectIveness and SafEty (EMPRISE; CT. gov identifier: NCT03363464) study aims to assess empagliflozin's effectiveness, safety, and healthcare utilization in routine care for 5 years; It investigated the risk of HHF among T2DM patients initiating empagliflozin vs. sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i) [60]. The initiation of empagliflozin decreased the risk of HHF-specific by 50% (HR = 0.50; 95% CI = 0.28-0.91), and the risk of HHF-broad by 49% (HR: 0.51;95% CI: 0.39-0.68), over a mean follow-up of 5.3 months. The results were similar in patients with and without baseline cardiovascular disease treated with both 10 mg or 25mg doses of empagliflozin daily. Finally, analyses comparing empagliflozin vs. the DPP-4i class, and the SGLT2i vs. DPP-4i classes also produced consistent findings [60].

Sotagliflozin, a novel dual sodium-glucose co-transporter-1 (SGLT1) and -2 (SGLT2) inhibitor, enhanced the efficacy of SGLT2 inhibitors by additionally reducing intestinal glucose absorption [61]. A range of phase II and III clinical trials showed that improves glycaemic control in both Type 1 and Type 2 diabetes, such as smaller postprandial plasma glucose excursions, lower insulin requirements, appetite suppression and weight loss have been documented [61]. For this drug, a cardiovascular outcome study that can prove its effectiveness in preventing the risk of heart attack or stroke has not yet been performed.

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

DDP-4 is the enzyme involved in the degradation and inactivation of GLP-1. Furthermore, DPP-4 exerts both enzymatic activity against chemotactic molecules and hormones and biological activities independent from its catalytic activity, which overall modulate inflammatory, vascular and immune processes.

DPP-4 inhibitors, neutralizing the DPP-4 enzymatic activity, prevent the peripheral inactivation of incretins (glucose-dependent insulinotropic polypeptide (GIP) and GLP-1), finally increasing the half-life and promoting the insulinotropism of GLP-1 in T2DM patients.

FDA-approved DDP-4is include sitagliptin, saxagliptin, linagliptin and alogliptin; vildagliptin has been approved from the European Medicines Agency (EMA).

Given the plethora of biological substrates of DDP-4, its inhibition could lead to several effects, ranging from metabolic (improved glycemic control, improved total cholesterol and triglyceride levels, and weight neutrality) to cardiovascular (reduced risk factors, ameliorated cardiac function and vascular repair) improvements [1,9,10,62].

The DPP-4i, though not ideal as initial therapy, have nevertheless been studied in patients with T2DM and HF. The four trials with DPP-4i (SAVOR-TIMI 53 with saxagliptin [63], EXAMINE with alogliptin [64], TECOS with sitagliptin [65] and CARMELINA with linagliptin [66]) failed to show any significant decrease in HF risk in patients with T2DM. The Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus (SAVOR-TIMI 53; CT. gov identifier: NCT01107886.) trial showed a 27% increase in the risk for HF-related hospitalizations with saxagliptin vs. placebo [63], while the EXamination of cArdiovascular outcoMes with alogliptIN vs. standard of carE (EXAMINE; CT. gov identifier: NCT00968708) in patients with T2DM and acute coronary syndrome) showed a non significant difference in risk with alogliptin vs. placebo [64].

In the Sitagliptin Cardiovascular Outcomes (TECOS; CT. gov identifier: NCT00790205) study (n=14,671) sitagliptin or placebo was added to existing therapy with a median follow-up of 3.0 years. There was a little difference in glycated hemoglobin levels (least-squares mean difference for sitagliptin vs. placebo, -0.29 percentage points; 95% CI, -0.32 to -0.27). The primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years), with sitagliptin being noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; p<0.001) [65].

Other study, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA; CT. gov identifier: NCT01897532) recruited people with previous CV events and micro or macroalbuminuria, reduced eGFR (<75 ml min−1 [1.73 m]−2) with macroalbuminuria, or with more severe renal impairment (eGFR <45 ml min−1 [1.73 m]−2) alone [66]. 6979 patients (mean age, 65.9 years; eGFR, 54.6 mL/min/1.73 m2; 80.1% with Urine Albumin:Creatinine Ratio UACR >30 mg/g) received at least 1 dose of study medication and 98.7% completed the study. During a median follow-up of 2.2 years, the primary outcome occurred in 434 of 3,494 (12.4%) and 420 of 3,485 (12.1%) in the linagliptin and placebo groups, respectively, (absolute incidence rate difference, 0.13 [95% CI, -0.63 to 0.90] per 100 person-years) (HR, 1.02; 95% CI, 0.89-1.17; p< .001 for noninferiority) and the renal outcome occurred in 327 of 3,494 (9.4%) and 306 of 3,485 (8.8%), respectively (absolute incidence rate difference, 0.22 [95% CI, -0.52 to 0.97] per 100 person-years) (HR, 1.04; 95% CI, 0.89-1.22; p= 0.62) [66].

The OMNeON study (randomized, double-blind, placebo-controlled, multicenter study to assess cardiovascular outcomes following treatment; CT. gov identifier: NCT01703208) [67], evaluating the investigational once-weekly omarigliptin in 4,202 patients with type 2 diabetes and CVD, was

terminated as a business decision [68] but reported an HR of 1.00 (95% CI 0.77–1.29) for its primary 3-point MACE end point [67].

5. Discussion and Conclusions

Recent CVOTs in patients with diabetes have focused attention on the pressing problem of HF, which complicates the disease more frequently than MI [69]. The use of glargine, degludec, sitagliptin, alogliptin, saxagliptin, lixisenatide, and once-weekly exenatide shown neutral effects on MACE. Thus, they improve glycemic control and reduce microvascular complications without increasing CV risk. Empagliflozin [70-73], canagliflozin [48], liraglutide [15] and semaglutide [30] have been shown to reduce CV events and deaths in similar populations in clinical trials, while the former two were associated with a reduction in HF-related hospitalizations and deaths (HR 0.61 [95% CI 0.47–0.79], p<0.001) [69]. Another important effect of these drugs is the improvement in renal function. Empagliflozin slowed the deterioration of renal function (HR 0.61 [95% CI 0.53–0.70], p<0.001) [72], canagliflozin (HR 0.60 [95% CI, 0.47–0.77], p<0.0001) [56]. Interestingly, it has been suggested that injured renal and myocardial tissues may benefit from access to the energy supplied by modestly higher circulating ketone levels during treatment with SGLT2 inhibitors [41,58].

In the DPP4 inhibitor class, the linagliptin (CARMELINA) [66] has the least impact, with no benefit beyond glucose-lowering, except in confirming the absence of a class adverse effect on heart failure and assuring safety in the presence of renal impairment. Saxagliptin and alogliptin are associated with an increased propensity to HF [63,64,74] probably because they block cleavage of many circulating peptides and may have various downstream effects.

Studies with the GLP-1RAs indicate that there is an improvement in kidney function with liraglutide (HR 0.78 [95% CI 0.67–0.92], p=0.003) and semaglutide (HR 0.64 [95% CI 0.46–0.88], p=0.005) [15,30]. Reduced progression of renal disease, notable macroalbuminuria, may be secondary to the improvements in glucose and blood pressure provided by these drugs. This class of molecules does not have a pancreatitis signal. Semaglutide's deleterious effect on diabetic retinopathy can be explained based on rapid and significant improvement of glycemic control in patients with preexisting retinopathy; a similar trend was seen with liraglutide [15,30]. GLP-1RAs appear to have a relatively early beneficial effect on the vasculature that persists over time, with evidence of protection against both MI and stroke. GLP-1RAs are not clearly indicated in people with diabetes and extant CVD, whether a weight-loss effect is desired or not.

Important CVOTs assessing CV safety of glucose-lowering medications (Figure 1) reached their primary outcomes and confirmed previous studies that indicated no increased CV risk (Table 1). Future data should provide additional insights into the efficacy and safety of these drugs.

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Peer-reviewed version available at J. Clin. Med. 2020, 9; doi:10.3390/jcm9040912

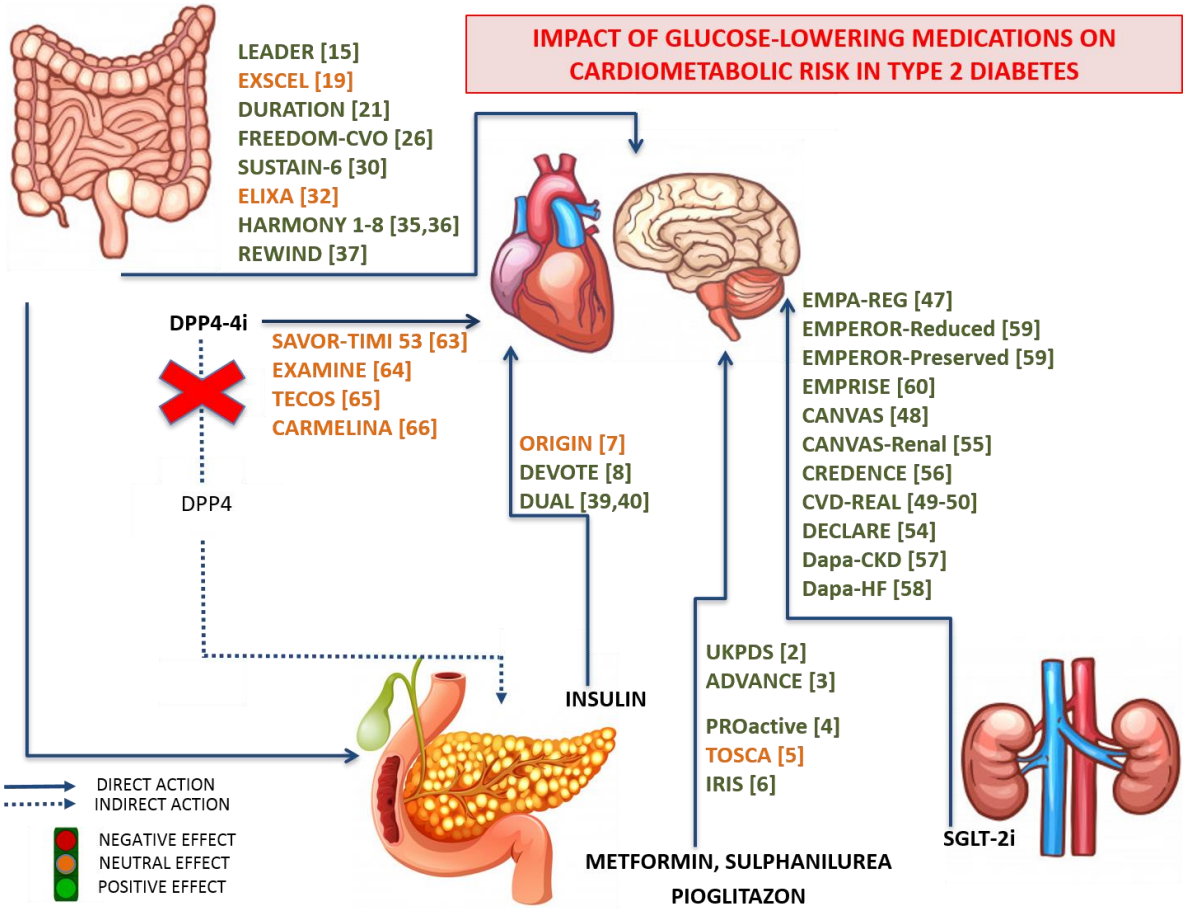

Figure 1. Schematic representation of the main routes, tissue biotargets, mode of actions and effects of glucose-lowering medications, and their impact on cardio-metabolic risk in patients with Type 2 Diabetes. The data are obtained from both scientific literature and CardioVascular Outcome Trials, carefully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

Table 1. Hypoglycemic drugs and cardiovascular disease (CVD)-reduction: an overview

Agent	Study	Patients (N. and type)	CVD-reduction (HR, CI and p value)	Reference
Metformin	UK Prospective Diabetes Study (**UKPDS study**)	**4,075** 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**)	**5,238** 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]*
Pioglitazone	Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention (**TOSCA**)	**3,028** patients with type 2 diabetes inadequately controlled with metformin monotherapy	HR 0.96 [95% CI 0.74-1.26] **p=0.79**	*[5]*

Peer-reviewed version available at J. Clin. Med. 2020, 9; doi:10.3390/jcm9040912

Pioglitazone	Insulin Resistance Intervention After Stroke (**IRIS**)	**3,876** 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**)	**7,637** patients with type 2 diabetes; 3,818 patients with insulin degludec and 3,819 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**)	**9,340** 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 to 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**)	**3,297** 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**)	**6,068** 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	**9,901** 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]*

	(**REWIND**)			
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 a 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]*
Sitagliptin	Sitagliptin Cardiovascular Outcomes (**TECOS**)	**14,671** patients with type 2 diabetes and cardiovascular disease	HR 0.98 [95% CI, 0.88 to 1.09] **p<0.001**	*[65]*
Linagliptin	Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (**CARMELINA**)	**6,991** 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)**	**4,202 patients with type 2 diabetes mellitus and established cardiovascular disease**	**HR 1.00 [95% CI 0.77–1.29] p=0.77**	*[67,68]*

Author Contributions: Conceptualization, A.M.P., R.V.G. and F.M.; data curation, A.M.P., A.S.P., and A.A.R.; writing—original draft preparation, A.M.P., R.V.G. and D.L.; writing—review and editing, D.L., F.M., and A.M.P.; visualization and editing of figures, D.L., and R.V.G.; supervision, F.M., S.A.P., A.A.R.

All Authors read and approve the final version of manuscript.

Funding: "This research received no external funding. The Authors did not receive financial or professional help with the preparation of the manuscript"

Acknowledgments and Conflicts of Interest: "The authors declare no conflict of interest. This review was written independently. The authors have given talks, attended conferences and participated in advisory boards and trials sponsored by various pharmaceutical companies, that had no role in the design of the review; in the interpretation of data and in the writing of the manuscript, or in the decision to publish the results." "The Authors are heartily thanks to Prof. Rizzo Manfredi for his invaluable and outstanding scientific support.

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