Hormones (2018) 17:83–95
https://doi.org/10.1007/s42000-018-0017-5

REVIEW

The effect of antidiabetic medications on the cardiovascular system: a critical appraisal of current data

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Received: 27 October 2017 / Accepted: 23 January 2018 / Published online: 24 April 2018

Abstract
Both type 1 and type 2 diabetes are associated with increased risk for cardiovascular disease (CVD) events. This risk seems to be reduced by achievement of euglycemia. However, after the withdrawal of rosiglitazone from the market, the question arose as to whether this risk concerns simply a matter of euglycemia or the distinct role played by each antidiabetic drug with respect to its effect on CVD risk. To address this issue, many studies have been published during the last decade involving old and new antidiabetic agents, which however yielded contradictory results. Briefly, metformin is still considered safe and confers a beneficial effect on CVD risk. Conflicting data exist as concerns sulfonylureas, although the second and third generation representatives are regarded as relatively safe. Pioglitazone use seems to be associated with a reduction in CVD risk, whereas the dipeptidyl-dipeptidase-4 inhibitors (DPP-4i), lixisenatide and exenatide-LAR [from the category of glucagon-like-peptide-1 receptor (GLP-1R) agonists], confer a neutral effect. Two other GLP-1R agonists, liraglutide and semaglutide, as well as the sodium-glucose transporter-2 (SGLT2)-inhibitors, empagliflozin and cangliflozin, have shown an additional effect on CVD risk reduction, although their safety is in doubt. Insulin analogues and newer long-acting compounds are also safe for the cadiovascular system. The aim of this narrative review is to present and critically analyse the current data for each antidiabetic drug category with regard to their effect on CVD risk.

Keywords Metformin · Sulfonylureas · DPP-4i · GLP-1 · Empagliflozin · Canagliflozin · Cardiovascular risk

Introduction

An accumulating body of evidence during the last few decades has established an association between diabetes mellitus [both type 1 (T1DM) and type 2 (T2DM)] and increased risk of cardiovascular disease (CVD) in both genders [1–3]. In general, a two- to fivefold risk of myocardial infarction (MI) exists in T2DM compared with the general population [1]. The relative risk (RR) seems to be higher in women than in men (up to nine and three times, respectively, compared with the general population), although the exact absolute difference in CVD risk between diabetic genders in a given glycemic state is not known [3]. The same risk exists in patients with T1DM compared with individuals without diabetes [adjusted hazard ratio (HR) 3.6, 95% confidence interval (CI) 2.8–4.6) in men and 9.6, 95% CI 6.4–14.5 in women] [1].

Glycemic control is associated with a reduction in CVD risk in both types of diabetes. In T1DM, intensive insulin treatment and achievement of HbA1c levels of 7.4 ± 1.1% for a mean period of 6.5 years resulted in 42% reduction in the risk of any CVD event and 57% in the risk of non-fatal MI, stroke or death from CVD after 17 years of follow-up, compared with conventional treatment (HbA1c levels 9.1 ± 1.5%) [4]. Similarly, in T2DM, the United Kingdom Prospective Diabetes Study (UKPDS), the landmark study conducted on T2DM (from 1977 to 1991), showed a CVD risk reduction of 15% after 10 years of follow-up in patients previously treated with intensive therapy (either sulfonylurea, insulin, or metformin) compared with conventional therapy (dietary restriction) for 5 years (without having reached statistical significance at this time-point and without any attempt to maintain the

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assigned therapies thereafter) [5]. Thus, undoubtedly maintenance of euglycemia results in a reduction of CVD risk in both diabetes types. A large meta-analysis, including three other studies apart from the UKPDS, showed a HR for CVD events of 0.91 (95% CI 0.84–0.99) and HR 0.85 (95% CI 0.76–0.94) for MI in patients who reached glycemic targets [6].

However, after these hallmark studies, it was not clear whether the CVD risk reduction was merely a matter of euglycemia or if it was dependent on the drug used. In 2007, a large meta-analysis of 42 trials demonstrated that rosiglitazone use is associated with increased CVD risk [odds ratio (OR) 1.43, 95% CI 1.03–1.98, $p = 0.03$) for MI] compared with other antidiabetic agents (metformin, sulfonylureas, insulin) or placebo or usual care, as well as with CVD-related death (OR 1.64, 95% CI 0.98–2.74, $p = 0.06$) [7]. These results were confirmed in prospective randomised controlled trials (RCTs) and led the European Medicines Agency (EMA) in September 2010 to completely withdraw rosiglitazone from the market due to CVD safety concerns [8]. These concerns have led the pharmaceutical companies to conduct studies focusing on the CVD safety of antidiabetic drugs as a primary endpoint. Since the rosiglitazone story, many studies have emerged.

The aim of this narrative is to present and critically analyse the current data regarding each antidiabetic drug category in the context of their effect on CVD risk.

Metformin and sulfonylureas and their effect on CVD risk

Metformin and CVD risk

Metformin, the most widely used oral antidiabetic medication, is recommended as a first-line agent for T2DM by both the American Diabetes Association (ADA) and the European Association of the Study of Diabetes (EASD) [9]. Metformin's primary mechanism of action is to decrease hepatic glucose production, mainly by inhibiting gluconeogenesis. This process is mediated through the AMP-activated serine-threonine protein kinase (AMPK), an intracellular sensor of energy and a regulator of energy homeostasis, which plays a crucial role in protecting cellular functions under energy-restricted conditions. AMPK is a key therapeutic target in patients with diabetes as it regulates lipid, cholesterol, and glucose metabolism in specialised tissues, such as the liver, muscle, and adipose tissue [10, 11]. Moreover, metformin targets the mitochondria by inhibiting respiratory chain complex I, with a subsequent decrease in the production of adenosine triphosphate (ATP) and an increase in the accumulation of adenosine diphosphate (ADP) and adenosine monophosphate (AMP). Both AMP and ADP regulate AMPK function by preventing its dephosphorylation and inactivation. In addition, metformin can lead to the inhibition of glucose production by disrupting gluconeogenesis gene expression through AMPK-dependent and AMPK-independent regulatory points. In patients with T2DM, the final result of these metabolic changes is a reduction in insulin resistance and blood glucose levels [10, 11]. Beyond its beneficial effect on glycemic control, metformin could also confer CVD risk protection, although the exact pathogenetic mechanisms have not to date been fully elucidated. Briefly, these include the reduction in total cholesterol (TC) (mean difference −0.52 mmol/l, 95% CI −0.83 to −0.22 mmol/, $p = 0.002$), low-density lipoprotein-cholesterol (LDL-c) (mean difference −0.40 mmol/l, 95% CI −0.64 to −0.16 mM, $p = 0.002$) and triglyceride (Tg) concentrations (median difference −0.2 mmol/l, interquartile range −0.6 to 0.1 mmol/l, $p = 0.034$). However, metformin has no significant effect on blood pressure [12, 13]. Furthermore, treatment with metformin is associated with enhanced fibrinolysis, reduced platelet aggregation, and reduction in plasminogen activatory inhibitor-1 (PAI-1), clotting factor VII, and C-reactive protein [14, 15]. Another pathway could also be the reduction of hyperinsulinemia per se, in insulin-resistant T2DM subjects that might account for metformin's beneficial effects on CVD risk [16].

With respect to CVD risk reduction at the clinical level, there are no RCTs designed for this purpose as a primary endpoint. The UKPDS included 3867 newly diagnosed patients with a median age of 54 years. The UKPDS reported that intensive blood glucose control by either sulphonylureas or insulin for over 10 years, despite its beneficial effect on microvascular disease (RR 0.75, 95% CI 0.60–0.83, $p = 0.0099$, compared with conventional therapy), did not show significant reduction in all-cause mortality and stroke but was only of borderline significance for MI (RR 0.84, 95% CI 0.71–1.00, $p = 0.052$). Moreover, intensive treatment with either sulphonylureas or insulin increased the risk of hypoglycemia [16].

On the other hand, in a subgroup analysis of the UKPDS, metformin was compared with diet alone with regard to their effect on CVD risk reduction [17]. Seven hundred and fifty-three obese patients were randomised to either diet alone ($n = 411$) or metformin ($n = 342$), aiming at a fasting plasma glucose (FPG) of < 6 mmol/L. Additionally, a secondary analysis compared these 342 patients treated with metformin with 951 overweight patients who were treated with chlorpropamide ($n = 265$), glibenclamide ($n = 277$), or insulin ($n = 409$). Compared with diet alone, patients allocated metformin displayed a 32% CVD risk reduction (95% CI 13–47, $p = 0.002$) as well as 42% reduction in risk for diabetes-related death (95% CI 9–63, $p = 0.017$) and 36% for all-cause mortality (95% CI 9–55, $p = 0.011$). Among patients randomised to intensive blood glucose control, metformin showed a greater effect than chloropropamide, glibenclamide, or insulin for any diabetes-related endpoint, all-cause mortality, and stroke. However, it was difficult to determine whether the difference in adverse CVD events seen in these trials was due to a benefit

of metformin or a deleterious effect of sulphonylurea therapy or both [17].

A meta-analysis of 35 RCTs examined the effect of metformin on CVD events and mortality. The number of participants treated with metformin or comparator (placebo, insulin, sulphonylureas, pioglitazone, vildagliptin, rosiglitazone, acarbose) was 7171 and 11,301, with 451 and 775 CVD events, respectively [18]. Metformin therapy was associated with a significant reduction in CVD events in comparison with placebo or no therapy (OR 0.79, 95% CI 0.64–0.98, $p = 0.031$), although no effect was observed when compared with the other drugs (OR 1.03, 95% CI 0.72–1.77, $p = 0.89$), in general. More specifically, no significant difference with metformin was observed regarding the incidence of MI, stroke, or heart failure [OR 0.90 (95% CI 0.71–1.14), 0.92 (95% CI 0.65–1.29) and 1.12 (95% CI 0.25–9.04), respectively]. Meta-regression analysis showed that metformin's beneficial effect was more evident in trials of longer duration and those enrolling younger patients. Finally, this meta-analysis also suggests a potential association between metformin monotherapy and improved survival (OR 0.801, 95% CI 0.625–1.024, $p = 0.076$) [18].

Similar data have been derived from studies in patients with prediabetes. A long-term intervention study, the Diabetes Prevention Program (DPP) and its Outcome Study (DPPOS) ($n = 3234$, mean age 64 ± 10 years, mean follow-up time of 14 years), revealed that men, but not women, with prediabetes having been treated with metformin demonstrated lower coronary artery calcium (CAC) scores than their placebo group counterparts. In particular, the age-adjusted mean CAC severity in metformin versus placebo was 39.5 and 66.9 Agatston units ($p = 0.04$), respectively, and 75 versus 84% ($p = 0.02$), respectively, for CAC presence. In multivariate analysis, this effect in men was not influenced by demographic, anthropometric or metabolic factors, development of diabetes, or concomitant use of statin therapy. No difference in CAC scores was observed in the group receiving a lifestyle intervention as compared with the placebo group in either gender [19].

Additionally, a recent RCT compared metformin ($n = 219$) with placebo (=209) in T1DM patients with regard to its effect in delaying the development of atherogenesis as measured by the progression of the diameter of intima-media thickness of the common carotid artery (primary outcome). Metformin therapy did not reduce diameter progression (− 0.005 mm per year, 95% CI − 0.012 to 0.002, $p = 0.1664$) compared with placebo. However, as a secondary outcome, metformin caused a significantly greater reduction in other CVD risk factors such as body weight (− 1.17 kg, 95% CI − 1.66 to − 0.69, $p < 0.0001$) and LDL-c (− 0.13 mmol/L, − 0.24 to − 0.03; $p = 0.0117$) as well as an increase in estimated glomerular filtration rate (eGFR) (4.0 mL/min/1.73m^2, 2.19–5.82, $p < 0.0001$) [20].

All these observations suggest that metformin is not only safe with respect to CVD risk but may also slow or delay the progression of atherosclerotic independently of the effect of modern cardioprevention strategies in both prediabetes (mainly men) and T2DM patients.

Sulfonylureas and CVD risk

Sulfonylureas are a class of organic compounds used in the management of T2DM for more than five decades. Sulfonylureas act by binding to a regulatory protein, also known as the "SU receptor" (SUR). There are three SUR subtypes: SUR1 located in the β pancreatic cells, SUR2A found in the cardiac and skeletal muscles, and SUR2B found in smooth muscles and epithelial cells [21]. The binding of sulfonylureas to SUR1 results in the closure of ATP-sensitive K^+ channels on the cell membrane, which in turn leads to membrane depolarisation by preventing potassium from exiting. The latter process opens voltage-gated Ca^{2+} channels and the concomitant rise in intracellular calcium leads to increased transposition of insulin granules to the cell membrane, degranulation, and concomitant increased release of (pro)insulin [22].

The cardiovascular safety of sulfonylureas is a matter of debate. In a large retrospective comparative study [23], sulfonylureas seemed to be inferior to metformin in terms of all-cause (RR 1.43, 95% CI 1.15–1.77) and CVD mortality (RR 1.70, 95% CI 1.18–2.45). However, no significant difference was found with regard to the risk of hospital admissions due to CVD events (RR 1.30, 95% CI 0.71–2.40) [23]. Moreover, another comparative study concluded that metformin monotherapy was superior to sulfonylurea monotherapy with respect to all-cause and CVD-related mortality (RR 0.78, 95% CI 0.65–0.92) and (RR 0.84, 95% CI 0.66–1.07), respectively [24]. Notably, in the aforementioned meta-analysis, concomitant use of sulphonylureas was associated with reduced survival compared with metformin alone (OR 1.43, 95% CI 1.068–1.918, $p = 0.016$) [18].

A recent meta-analysis of 30 RCTs of at least 6 month duration compared the use of sulfonylurea with placebo or other antidiabetic medications [rosiglitazone, metformin, pioglitazone, dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like-peptide-1 receptor (GLP-1R) agonists, and/or insulin]. There was no difference in the incidence of major adverse cardiovascular events (MACE), including CVD death, non-fatal MI, stroke, and/or heart failure (OR 1.08; 95% CI 0.86–1.36, $p = 0.52$) when sulfonylurea use was compared with placebo and active comparators, except for DPP-4i (OR 1.85, 95% CI 1.20–2.87, $p = 0.005$). However, a significant increase in mortality was shown with sulfonylureas (OR 1.22, 95% CI 1.01–1.49, $p = 0.047$), although it was not clear if it was the result of increased risk of hypoglycemia [25]. On the other hand, another meta-analysis of 47 RCTs of at least 13-months' duration noted that the most frequently used sulfonylureas (of the second and third generations) were not associated with all-cause mortality (OR 1.12, 95% CI 0.96–

1.30) when compared with placebo or diet (OR 0.97, 95% CI 0.71–1.33) or with active comparators (OR 1.16, 95% CI 0.98–1.38). The same results also emerged from the comparisons regarding CVD mortality, MI, and stroke [26]. These results that conflicted with the previous meta-analysis may be explained by the differences regarding the inclusion of studies with first-generation sulfonylureas, observational studies, and studies of short duration.

The combination of metformin with sulfonylureas has been studied with respect to its effect on CVD. A meta-analysis, which was published in 2008 and included nine studies, did not show a significant effect on CVD and all-cause mortality [RR 1.29 (95% CI 0.73–2.27) and RR 1.19 (95% CI 0.88–1.62), respectively], although it increased the risk of a composite endpoint of CVD hospitalisations or mortality [RR 1.43 (95% CI 1.10–1.85)]. These results were irrespective of the reference group (diet therapy, metformin monotherapy, or sulfonylurea monotherapy) [27]. A prospective cohort study, the Fremantle Diabetes Study ($n = 1271$, mean age 64.2 ± 11.2 years, 48.8% males, mean follow-up 10.4 ± 3.9 years), compared the effect of metformin-sulfonylurea combination with diet, metformin monotherapy, sulphonylurea monotherapy, or insulin with or without an oral antidiabetic regimen. Although the combination was associated with higher CVD and all-cause mortality compared with diet or metformin monotherapy, and lower CVD and all-cause mortality compared with insulin, these differences were not evident after adjustment for confounders [28]. In another prospective cohort study, metformin-sulphonylurea combination was compared with metformin-DPP-4i combination with regard to their risk for severe hypoglycemia, CVD, and all-cause mortality ($n = 52{,}760$, median follow-up 3.4 years for the first group and 2.5 years for the second). Sulphonylurea-DPP-4i combination was associated with a higher risk of severe hypoglycemia, fatal and non-fatal CVD, and all-cause mortality [adjusted HR 2.07 (95% CI 1.11–3.86); 1.17 (95% CI 1.01–1.37); and 1.25 (95% CI 1.02–1.54), respectively] [29].

In conclusion, sulfonylureas do not appear to be associated with a significant increase in CVD risk compared with placebo, but they seem to be inferior to metformin and other classes of antidiabetic agents, such as DPP-4i, in this regard.

Thiazolidinediones and CVD risk

Thiazolidinediones (TZDs) constitute a widely prescribed antidiabetic drug category mainly targeting the reduction of insulin resistance. After withdrawal of rosiglitazone due its aforementioned association with increased CVD risk, pioglitazone remains the only representative of the TZD class at the moment. The main mechanism of function is the modification of expression of numerous metabolic-related genes via activating one or more nuclear transcription factors, known as peroxisome proliferator-activated receptors gamma (PPAR-γ) [30]. Pioglitazone also partially activates PPAR-α receptors, a fact that may explain its different way of action compared with rosiglitazone [30]. In general, TZDs decrease insulin resistance especially in the liver and adipose tissue and may also improve the β cell response to glucose. Besides lowering blood glucose levels, TZDs also have pleiotropic effects, most of which are associated with a reduction in CVD risk. First, they induce body fat redistribution from the visceral to the less atherogenic subcutaneous storage depots [27]. Second, various studies have shown a reduction in systolic blood pressure by 1.6–20 mmHg and in diastolic blood pressure by 1.4–17 mmHg [31]. Furthermore, they may reduce plasma levels of a wide range of inflammation markers, such as C-reactive protein (CRP), thus contributing to the retardation of the development of atherogenesis [30, 31]. With respect to lipid profile, TZDs increase HDL-c and, specifically, pioglitazone lowers Tg levels while shifting low-density lipoprotein (LDL) particles from the smaller to the less atherogenic larger ones [32]. Finally, TZDs can reduce urinary albumin excretion [33] and improve liver function tests in patients with non-alcoholic fatty liver disease (NAFLD) and the histological parameters of non-alcoholic steatohepatitis (NASH) [30].

A landmark study with regard to the effect of pioglitazone on CVD risk was the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, which randomised 5238 patients with T2DM and a history of macrovascular disease to receive either pioglitazone 15–45 mg/day ($n = 2605$) or placebo ($n = 2633$) additionally to their previous treatment [34]. The primary outcome was the composite of all-cause mortality, non-fatal MI, stroke, acute coronary artery (ACS), endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The main secondary endpoint was all-cause mortality, non-fatal (excluding silent) MI and stroke. After a mean observational time of 34.5 months, there was no difference between the two groups regarding the primary endpoint (HR 0.90, 95% CI 0.80–1.02, $p = 0.095$). However, pioglitazone significantly reduced the risk of the main secondary endpoint by 16% (HR 0.84, 95% CI 0.72–0.98, $p = 0.027$), indicating a beneficial effect on CVD [34].

More recently, another RCT carrying out a similar investigation, the Insulin Resistance Intervention after Stroke (IRIS) study, was published. This study included patients with insulin resistance and recent stroke or transient ischemic attack (TIA) who were randomised to pioglitazone 15–45 mg/day ($n = 1939$) or placebo ($n = 1937$). The observational period was 4.8 years and the primary outcome was fatal or non-fatal stroke or MI, which was recorded in 9% of patients in the pioglitazone group versus 11.8% in the placebo group (HR 0.76, 95% CI 0.62–0.93, $p = 0.007$) [35]. Another recent study, the Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial

(TOSCA.IT), compared the cardiovascular safety of pioglitazone ($n = 1535$) with that of sulfonylureas ($n = 1493$) as an add-on treatment in T2DM patients inadequately controlled with metformin monotherapy. The primary outcome (all-cause death, non-fatal MI, non-fatal stroke, or urgent coronary revascularisation) occurred equally between the two groups (HR 0.96, 95% CI 0.74–1.26, $p = 0.79$). Pioglitazone, however, was associated with fewer hypoglycemic episodes [36].

Despite its beneficial effect on glucose and lipid metabolism and concomitant CVD risk, pioglitazone use has also been linked to some side effects. These include an increased risk of heart failure (not associated with increased mortality) and peripheral edema. Along with that, pioglitazone can cause a noticeable increase in body weight and the risk of macular edema. Furthermore, there is growing evidence suggesting that PPAR-γ agonists decrease bone mineral density (BMD) and thus increase fracture risk, particularly in women [37]. There is also a notable decrease in hematocrit that surprisingly enough does not reverse after discontinuation of the drug. Finally, there are some concerns about increased bladder cancer risk, potentially dependent on dose exposure and duration of administration. However, pioglitazone's CVD benefit far outweighs this risk [38].

In conclusion, pioglitazone still remains a reliable second-line drug in diabetes management after failure with metformin monotherapy, especially in patients with increased insulin resistance and NAFLD, a quite common feature in obese T2DM patients. Its pleiotropic effects may account for its potential cardioprotective role, although further data are needed, especially in patients without established CVD. However, one should always be cautious about pioglitazone's adverse effects, especially in patients at increased risk of heart failure and fractures. The results of the above trials are briefly presented in Table 1.

Incretin-based therapies and CVD risk

GLP-1R agonists and CVD risk

The "incretin effect" is the phenomenon whereby a greater insulin secretion is induced by oral than by intravenous glucose intake. This phenomenon has been attributed to two intestinal insulinotropic hormones, so-called glucose-dependent insulinotropic peptide (GIP) and GLP-1 [49]. In T2DM patients, the "incretin effect" is substantially impaired due to both decreased secretion and to a relatively fast degradation of these two hormones [50]. GLP-1 exerts multiple actions in peripheral tissues. Apart from stimulation of insulin and inhibition of glucagon secretion, it promotes proliferation of β cells and prevents their apoptosis. It also slows gastric emptying, decreases food intake and plays a potential neuroprotective role [51]. The currently available GLP-1R agonists in the USA and Europe are exenatide, liraglutide, albiglutide, lixisenatide, and dulaglutide [52, 53].

Exenatide and liraglutide lower HbA1c by 0.81 to 1.13% and FPG by 21 to 33 mg/dL. They also reduce postprandial blood glucose levels by 16 to 41 mg/dL [54]. Weight loss is another well-established property of GLP-1R agonists [54]. Exenatide has also shown antihypertensive effects in a number of trials, attributed to the accomplished weight reduction, its natriuretic effect, and vasodilation [55]. Likewise, liraglutide lowers blood pressure either administered alone [56] or along with sulphonylureas [57] or with metformin and TZDs [58]. Adding exenatide to metformin and/or sulphonylurea has also shown a beneficial effect on lipid metabolism by reducing TC, LDL-c and Tg levels by 5, 6 and 12%, respectively, while increasing HDL-c levels by 24% [55]. On the other hand, liraglutide has demonstrated a greater reduction in Tg levels (by 22%) but with little or no effect on the other components of the lipid profile [56]. Potential anti-atherosclerotic properties may also be attributed to GLP-1 via increased activity of nitric oxide (NO) related and NO-independent vasodilation as well as inhibition of monocyte/macrophage accumulation [55].

Four studies have been published so far with regard to the cardiovascular safety of GLP-1R agonists as a primary outcome: ELIXA (Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) and EXSCEL (Exenatide Study of Cardiovascular Event Lowering).

The ELIXA trial assessed the impact of lixisenatide on CVD risk in patients with T2DM and ACS. It was a randomised, double-blind, placebo-controlled trial including 6068 patients with a history of ACS within the last 180 days. Participants were treated with any antidiabetic regimen besides incretin-based therapies (mean duration of T2DM 9.3 ± 8.2 years). Patients were randomised to lixisenatide ($n = 3034$) at a starting dose of 10 μg/day (maximum dose 20 μg/day) or placebo ($n = 3034$). The primary endpoint was the composite of death from cardiovascular causes, non-fatal myocardial infraction, hospitalisation for unstable angina, and non-fatal stroke [49]. After a mean follow-up time of 25 months, the primary outcome occurred in 406 patients (13.4%) and 399 patients (13.2%) in the lixisenatide group and placebo group, respectively (HR 1.02, 95% CI 0.89–1.17, $p < 0.001$). The separate components of the primary outcomes did not differ between the two groups [49]. The same applied to secondary endpoints, such as hospitalisation for heart failure alone or for coronary revascularisation [39].

Liraglutide's cardiovascular safety has been tested in the LEADER trial. This study followed 9340 patients (average age 64) for 3.8 years. Inclusion criteria were T2DM and high

Table 1 Comparison of randomized placebo-controlled trials with CVD safety of available antidiabetic drugs, as a primary end-point

First author/year of publication	Name of study	Drug/dose	Number/mean age (years)	Follow-up time (years)	CVD effect (positive/neutral)	HR for primary endpoint*	Hospitalization for heart failure
Dormandy et al./[34]	PROActive	Pioglitazone/15–45 mg/day	5238/61.8	2.8	Positive	0.90 (95% CI 0.80–1.02), $p = 0.095$	N/A
Kernan et al./[35]	IRIS	Pioglitazone/15–45 mg/day	3876/63	4.8	Positive	0.76 (95% CI 0.62–0.93), $p = 0.007$	N/A
Pfeffer et al./[39]	ELIXA	Lixisenatide/10–20 μg/day	6068/60.3	2.1	Neutral	1.02 (95% CI 0.89–1.17), $p < 0.001$	0.96 (95% CI 0.75–1.23), $p = 0.75$
Marso et al./[40]	LEADER	Liraglutide/1.8 mg/day	9340/64	3.8	Positive	0.87 (95% CI 0.78–0.97), $p < 0.001$	0.87 (95% CI 0.73–1.05), $p = 0.14$
Marso et al./[41]	SUSTAIN-6	Semaglutide/0.5 mg or 1 mg/w	3297/64.6	2.1	Positive	0.74 (95% CI 0.58–0.95), $p < 0.001$	1.11 (95% CI 0.77–1.61), $p = 0.57$
Holman et al./[42]	EXSCEL	Exenatide/2 mg/w	14,000/63	3.2	Neutral	0.91 (95% CI 0.83–1.00), $p < 0.001$	0.94 (95% CI 0.78–1.13)
Green et al./[43]	TECOS	Sitagliptin/100 mg/day	14,671/65	3	Neutral	0.98 (95% CI 0.88–1.09), $p < 0.001$	1.00 (95% CI 0.83–1.20), $p = 0.98$
White et al./[44]	EXAMINE	Alogliptin/25 mg/day	5380/61	1.5	Neutral	0.96 (95% CI ≤ 1.16), $p = 0.36$	N/A
Scirica et al./[45]	SAVOR-TIMI 53	Saxagliptin/5 mg/day	16,492/65	2.1	Neutral	1.00 (95% CI 0.89–1.12), $p = 0.99$	1.27 (95% CI 1.07–1.51), $p = 0.007$
Zinman et al./[46]	EMPA-REG OUTCOME	Empagliflozin/10 mg or 25 mg/day	7020/63	3.1	Positive	0.86 (95% CI 0.74–0.99), $p = 0.04$	0.65 (95% CI 0.50–0.85), $p = 0.002$
Neal et al./[47]	CANVAS	Canagliflozin/100 mg or 300 mg/day	10,142/63.3	8	Positive	0.86 (95% CI 0.75–0.97), $p < 0.001$	0.67 (95% CI 0.52–0.87)
Gerstein et al./[48]	ORIGIN	Insulin glargine/100 UI/mL/day	12,537/63.5	6.2	Neutral	1.02 (95% CI 0.94–1.11), $p = 0.63$	0.90 (95% CI 0.77–1.05), $p = 0.16$

*In most studies, the primary endpoint was the composite of cardiovascular death, non-fatal myocardial infarction and stroke

CVD risk, defined as established CVD, chronic heart failure [New York Heart Association (NYHA) class II or III], chronic kidney failure (stage > 3) or age above 60 accompanied by CVD risk factors [40]. At the time of study initiation, patients were either not being treated or were receiving one or more oral antidiabetic drugs (OADs) and/or insulin, excluding incretin-based therapies (mean duration of T2DM was 13 years) [40]. Patients were randomised to either liraglutide ($n = 4668$) 1.8 mg/day or placebo ($n = 4672$). Primary outcome was the first occurrence of cardiovascular death, non-fatal MI or stroke. Secondary outcomes were death from CVD causes, death from any cause, non-fatal MI, non-fatal stroke, and hospitalisation for heart failure. After a median follow-up time of 3.8 years, 608 patients (13%) of the liraglutide group and 694 (14.9%) of the placebo group (HR 0.87, 95% CI 0.78–0.97, $p < 0.001$) met the criteria of primary endpoint. Deaths both from CVD and any other cause were also fewer in patients taking liraglutide than in those on placebo [HR 0.78 (95% CI 0.66–0.93, $p = 0.007$) and HR 0.85 (95% CI 0.74–0.97, $p = 0.02$), respectively]. However, the reduction in non-fatal MI, stroke, and heart failure-associated hospitalisations was non-significant compared to the placebo group [50].

The SUSTAIN-6 study investigated the cardiovascular safety of semaglutide in 3297 patients with T2DM. Inclusion criteria were the same as for liraglutide [41]. Participants were randomly assigned to a once-weekly dose of 0.5 mg (or 1 mg) semaglutide or placebo. Primary and secondary endpoints were the same with the other GLP-1R agonists. The primary endpoint was recorded in 6.6% (108 of 1648) of the semaglutide group compared with 8.9% (146 of 1649) of the placebo group (HR 0.74, 95% CI 0.58–0.95, $p < 0.001$) [41]. More specifically, the risk of non-fatal MI decreased by 26% and non-fatal stroke by 39% in the semaglutide group. Nonetheless, no significant reduction in CVD mortality was demonstrated [41]. Additionally, semaglutide showed a protective effect against new or worsening nephropathy [3.8 versus 6.1% in the placebo group (RR 0.64, 95% CI 0.46–0.88, $p = 0.005$]. However, higher rates of retinopathy complications were observed in the semaglutide group (RR 1.76, 95% CI 1.11–2.78, $p = 0.02$) [41].

The CVD safety trial for exenatide (EXSCEL) has very recently been completed, including 14,000 patients with T2DM [52]. Most of the participants (73.1%) had a history of CVD. Eligible patients were those who had received up to three OADs, insulin alone or concomitant with up to two antidiabetic drugs, while GLP-1R agonist treated patients were excluded. Patients were randomised to a once-weekly dose of 2 mg exenatide or placebo (median follow-up time of 3.2 years) [42]. The primary and secondary outcomes were the same as those of the other GLP-1R agonist studies. Primary outcome events occurred in 839 (11.4%) patients on exenatide and in 905 (12.2%) patients on placebo (HR 0.91, 95% CI 0.83–1.00, $p < 0.001$). Rates of death from any cause

were 6.9% in the exenatide group and 7.9% in the placebo group (HR 0.86, 95% CI 0.77–0.97). The percentage of deaths attributed to CVD causes was 45.4% in the exenatide group and 41.3% in the placebo group. Rates of fatal or non-fatal MI (HR 0.97, 95% CI 0.85–1.1), fatal or non-fatal stroke (HR 0.85, 95% CI 0.7–1.03), and heart failure hospitalisation (HR 0.94, 95% CI 0.78–1.13) were similar between the two groups. Patients on exenatide achieved better glycemic control, greater weight loss and lower blood pressure counts. Rates of serious adverse events did not differ between groups [42].

In conclusion, lisixenatide, liraglutide, semaglutide, and exenatide have a proven CVD safety record in patients with T2DM. However, the three component MACE outcomes occurred at lower rates in the LEADER and SUSTAIN-6 trials. The rate of death from any cause was lower for liraglutide (by 15%) and exenatide (by 14%, although it did not show any significant benefit in the primary outcomes). These differences may be attributed to many factors. The median follow-up in LEADER was longer (3.8 years) compared with that of EXSCEL (3.2 years). Discontinuation of the trial regimen in EXSCEL led to shorter exposure duration (2.4 years) compared with that of the LEADER study (3.5 years) [52]. Baseline HbA1c was lower in EXSCEL (8.0%) and ELIXA (7.7%) compared with the other studies (8.7% in LEADER and SUSTAIN-6). Additionally, antidiabetic drugs with beneficial effects on CVD (such as SGLT-2 inhibitors, as will be presented below) were used in the placebo group of the EXSCEL study, which might have affected the results. Furthermore, there were differences in the proportion of patients with established CVD (72.2% in SUSTAIN-6, 73.1% in EXSCEL, 81% in LEADER, whereas all participants in ELIXA had a history of a recent ACS). Of note, the increase in retinopathy risk with semaglutide use warrants further investigation, although a plausible explanation could be based on the worsening of retinopathy after rapid glucose lowering. The comparative results between these trials are briefly presented in Table 1.

DPP-4 inhibitors and CVD risk

Dipeptidyl peptidase-4 (DPP-4) is a proteolytic enzyme encoded by the DPP-4 gene and cleaves GLP-1 and GIP. DDP4-i constitute a class of antidiabetic drugs that delay the inactivation of these two hormones, prolonging their aforementioned glucose-lowering properties [59, 60]. The available DDP-4i are sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin [61, 62]. DDP-4i reduce HbA1c by 0.5 to 0.9% [63]. They are weight-neutral [50] and the risk of hypoglycemia is low, especially when they are not used concomitantly with sulfonylureas [64]. DDP-4 inhibition is also associated with a wide spectrum of anti-atherosclerotic properties, such as increased NO activity and vasodilation. Lipid profile may be improved, since a reduction in TC and postprandial Tg, along with an increase in HDL-c levels, has been reported [65]. DDP4-i may also lower blood pressure via renal artery vasodilation, modification of sympathetic angiotenstin-II mediated hypertensive response, induction of natriuresis, and inactivation of brain-derived natriuretic peptide (BNP) [65].

With respect to the cardiovascular safety of DDP-4i, three trials have been conducted so far: SAVOR-TIMI 53 (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53), EXAMINE (Examination of Cardiovascular Outcomes: Alogliptin vs. Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome) and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin).

The SAVOR-TIMI 53 study included 16,492 T2DM patients (mean age 65 ± 8.6 years and mean HbA1c 8 ± 1.4%) with established CVD and CVD risk factors [60]. The participants were randomised to saxagliptin ($n = 8280$) 5 mg/day (2.5 mg for those with eGFR ≤ 50 ml/min) and placebo ($n = 8212$) for a median follow-up of 2.1 years. The primary endpoint was CVD death, non-fatal MI, and non-fatal ischemic stroke. The secondary endpoints consisted of the primary endpoint plus hospitalization for unstable angina, heart failure, or coronary revascularisation [45]. The rates in the primary endpoint in the two groups were similar (HR 1.00, 95% CI 0.89–1.12; $p = 0.99$). The secondary endpoint rates also did not differ between the two groups (HR 1.02, 95% CI 0.94–1.11, $p = 0.66$). However, more hospitalisations for heart failure occurred in the saxagliptin group (3.5 vs 2.8%, RR 1.27, CI 1.07–1.51, $p = 0.007$). Patients on saxagliptin achieved better glycemic control, although the rates of at least one hypoglycemic episode in this group were higher (15.3 vs 13.4%, $p < 0.001$) [45].

The EXAMINE study enrolled 5380 T2DM patients with an acute MI or unstable angina requiring hospitalisation within the previous 15–90 days (mean patients' age 61 years and mean HbA1c 8%). According to their renal function status, patients were randomly assigned to a daily dose of 25 mg (if eGFR was ≥ 60 ml/min), 12.5 mg (if eGFR was 30–60 ml/min), 6.25 mg (with eGFR < 30 ml/min) alogliptin or placebo for a median follow-up of 1.8 years [64]. Primary and secondary endpoints were the same as with saxagliptin. Rates of primary endpoint events did not differ between the alogliptin and the placebo group (HR 0.96, 95% CI ≤ 1.16, $p < 0.001$) [44]. The same applied for the secondary endpoint between the two groups (HR 0.95, 95% CI < 1.14). By the end of the study, significantly lower levels of HbA1c were observed (− 0.36%, 95% CI, − 0.43 to − 0.28; $p < 0.001$) but without differences in the incidence of hypoglycaemia or other adverse events between the two groups [44].

The TECOS study included 14,671 patients with T2DM (mean age 65 years, mean HbA1c 7.2%) and established CVD for a median follow-up of 3 years. Patients were randomly

assigned to 100 mg/day sitagliptin ($n = 7332$) or placebo ($n = 7339$). Inclusion criteria were a history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease [65]. Primary and secondary endpoints were the same with the other DPP-4i. No differences in primary (HR 0.98, 95% CI 0.89–1.08; $p = 0.65$) and secondary outcomes (HR 0.99, 95% CI 0.89–1.10, $p = 0.84$) were observed between the two groups [43]. With HbA1c values 0.29% lower in the sitagliptin group by the end of the trial, patients in the sitagliptin group received fewer antidiabetic drugs and were less likely to be treated with insulin. Sitagliptin did not affect the rates of hospitalisation due to heart failure. The two groups did not differ in terms of the safety outcomes [43].

In conclusion, all three trials were able to establish CVD safety. The three DDP-4i were non-inferior to placebo in terms of major CVD events. However, none of them reduced the rates of these events despite the improved glycemic control. On the other hand, increased concern has arisen due to the observed increased rates of hospitalisation due to heart failure with saxagliptin, albeit without differences in death rates due to heart failure. In a post hoc analysis of the EXAMINE trial, alogliptin did not increase the risk of recurrent hospital admission due to heart failure compared with placebo (HR 1.05, 95% CI 0.82–1.34, $p = 0.707$), which remained non-significant, independently of the history of heart failure before randomisation, without interaction between treatment and history of heart failure [66]. Sitagliptin use was not associated with increased risk of heart failure. In another study, the risk of heart failure was comparable between incretin-based drugs (including both DPP-4i and GLP-1R) and other OADs [67]. The comparative results between these trials are briefly presented in Table 1.

Sodium-glucose cotransporter 2 and CVD risk

Sodium-glucose cotransporters (SGLTs) are membrane proteins located across the apical membranes of the kidney's proximal convoluted tubules (PCT). They are responsible for the reabsorption of glucose and sodium from the lumen to the intracellular space by active transport. Eventually, glucose moves passively through the basolateral transporters and leads to blood circulation. There are two types of SGLTs: SGLT1 (located not only in the late PCT but also in the small intestine and heart) and sodium-glucose cotransporter 2 (SGLT2) (located in the early PCT). The latter reabsorbs 90% of the filtered glucose, whereas the former are responsible for a less significant percentage [68]. Therefore, the inhibition of SGLT2 appeared as a promising approach in the treatment of T2DM [68].

The main representatives of this drug category are canagliflozin, dapagliflozin, and empagliflozin. These agents block the reabsorption of filtered glucose and allow its excretion in the urine [65]. A meta-analysis including comparative studies on SGLT2 inhibitors versus placebo or OADs (particularly sulfonylureas and sitagliptin) showed that SGLT2 inhibitors are superior with regard to HbA1c lowering (by 0.4916% in the first and 0.503% in the second year of treatment compared with placebo, and by 0.12 and by 0.13% in the second year compared with OADs) [69]. They also decrease systolic (SBP, − 2.8 mmHg for the first and − 7.5 mmHg for the second year) and diastolic blood pressure (DBP, − 1.95 and − 2.197 mmHg for the first and second year, respectively, compared with placebo) and body weight (− 2.47 kg for the first year, − 2.99 kg for the second year compared with placebo) [66]. However, patients treated with SGLT2 inhibitors are at a higher risk of urinary and genital infections compared with placebo or OADs [70].

Two RCTs have been conducted with respect to the effect of SGLT2 inhibitors on the cardiovascular system. The first was the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular outcome event trial in type 2 diabetes mellitus patients) during which 7020 T2DM patients (mean age 63.1 years, mean HbA1c level 8.1%) with a history of CVD were randomised to empagliflozin 25 mg/day ($n = 2345$), 10 mg/day ($n = 2342$) or placebo ($n = 2333$). The primary outcome was death due to CVD events, non-fatal MI, or non-fatal stroke. The secondary endpoint comprised the primary outcome plus hospitalisation due to unstable angina. After a median observation time of 3.1 years, patients treated with empagliflozin exhibited lower rates in the primary endpoint compared with placebo (HR 0.86, 95% CI 0.74–0.99, $p = 0.04$), which was attributed mainly to the lower risk of CVD death (HR 0.62, 95% CI 0.49–0.77, $p < 0.001$), without differences in the risk of MI or stroke. Moreover, lower rates of heart failure were observed in the empagliflozin group (HR 0.65, 95% CI 0.5–0.85, $p = 0.002$). Except for the differences in HbA1c (− 0.5%), empagliflozin, compared with placebo, was associated with small reductions in body weight, SBP, DBP, and uric acid levels, with small increases in both LDL-c and HDL-c concentrations. Empagliflozin was generally well-tolerated, with higher rates of genital infections being the only significant adverse effect compared with placebo. Diabetic ketoacidosis occurred at a similar rate in the empagliflozin and placebo groups [46]. Empagliflozin also slowed the progression of albuminuria (HR 0.62, 95% CI 0.54–0.72, $p < 0.001$) [71].

The second study was the Canagliflozin Cardiovascular Assessment Study Program (CANVAS Program) which included the CANVAS and the CANVAS-Renal (CANVAS-R) trials. It recruited 10,142 patients with T2DM (mean age 63.3 years, mean HbA1c 8.2%) at increased CVD risk who were randomised to canagliflozin 100 or 300 mg/day ($n = 5795$) or placebo ($n = 4347$). The primary endpoint was death due to CVD events, non-fatal MI, or non-fatal stroke. The

secondary endpoint was death from all causes, CVD death, progression of albuminuria, and the primary outcome plus hospitalisation for heart failure. After a mean follow-up of 8 years, patients treated with canagliflozin exhibited lower rates in the primary endpoint compared with placebo (HR 0.86, 95% CI 0.75–0.97, $p < 0.001$ for non-inferiority, $p = 0.02$ for superiority). Significant adverse effects of canagliflozin were a higher risk of the lower limb amputations (HR 1.97, 95% CI 1.41–2.75, $p < 0.001$), observed mainly in patients with previous amputations or peripheral vascular disease, as well as an increased risk of fractures (HR 1.26, 95% CI 1.04–1.52, $p = 0.02$) and diabetic ketoacidosis (HR 2.33, 95% CI 0.76–7.17, $p = 0.14$) compared with placebo [47].

Thus, empagliflozin and cangliflozin appear to be not only safe but also cardioprotective. Regarding their latter effect, some mechanisms may be considered beyond glycemic control, such as a mild diuretic and natriuretic action which leads to an increased delivery of sodium to juxtaglomerular apparatus causing constriction of afferent arterioles, and a reduction of intraglomerular pressure. As a consequence, plasma volume and extracellular fluid decrease, resulting in a reduction of SBP and DBP. Despite the preload and afterload reduction, heart rate remains unaffected, a fact that is attributed to a potential inhibition of the cardiac sympathetic nervous system [72]. An interesting hypothesis is also the alteration from glucose to fat oxidation in the liver, increasing the produced ketone levels that concentrate and are oxidized by the myocardial cells [72]. Other factors such as weight loss due to glucosuria, reduced systemic inflammation oxidative stress, and uric acid levels as well as improvement of arterial stiffness also contribute to the cardiovascular benefit, although more data are needed for safe conclusions [72].

In conclusion, SGLT2 inhibitors seem to be beneficial both for the cardiovascular system and renal function. However, the higher rates of leg amputations, fractures, and diabetic ketoacidosis in patients treated with canagliflozin need to be taken into account when selecting this drug category. Of note, in a recent study, canagliflozin compared with DPP-4i doubled the possibility of diabetic ketoacidosis but hospitalisation was rarely observed (HR 2.2, 95% CI 1.4–3.6) [73].

Insulin and CVD risk

It is almost a century since insulin has been used to treat diabetes, this completely changing the course of the disease in T1DM patients. In T2DM patients, diet and OADs often fail to sustain satisfactory euglycaemic targets. In fact, early introduction of insulin in a T2DM patient's therapeutic algorithm assists in achievement and maintenance of tight glycemic control which has proven to lower the risk of vascular complications [74], as long as hypoglycemia episodes are minimised [75]. Furthermore, possible effects of insulin on the cardiovascular system independently of its action on blood glucose control need to be taken into account. Various insulin products have been developed and, despite increased cost, the benefit scale tilts towards newer insulin analogues in regard to efficacy and safety [76–80].

Today, when we attempt to compare the effect of insulin on CVD with that of other OADs, we discover a plethora of observational studies claiming to show insulin's increased CVD morbidity and mortality risk association in T2DM patients [48, 81–87,]. In a recent large open cohort study [86] including 469,688 patients with T2DM (aged 25–84 years, 19,791 on insulin therapy), insulin use was associated with a 47% increase in all-cause mortality, a 32% increase in the risk of heart failure, and a 23% increase in the risk of CVD events compared with no insulin use. Indeed, insulin seemed to have the most unfavorable results surpassing even sulfonylureas. On the other hand, all other antidiabetic drugs, except for insulin and sulfonylureas, significantly reduced the risk for all the above factors.

In contrast to this observational evidence, the verdict of the following trials seems to be different. Starting with UKPDS, which displayed evidence of insulin's CVD risk reduction [16], it included no indication of any cardiovascular harm. In the post-trial 10-year follow-up of the study, the T2DM patient group that was randomised to insulin therapy demonstrated a reduction in micro- and macrovasular complications and overall mortality risk [5]. More recently, two RCTs have been conducted with regard to long-acting insulins and CVD outcomes: the ORIGIN (outcome reduction with initial glargine intervention) trial and the DEVOTE trial (a trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with T2D at high risk of cardiovascular events). In the ORIGIN study, 12,537 patients with prediabetes or primary T2DM and CVD risk were randomised to insulin glargine 100 IU/mL ($n = 6264$) or OADs $n = 6273$) and omega-3 fatty acids or placebo (mean age 63.5 years, mean HbA1c 6.4%). The primary endpoint was non-fatal MI, non-fatal stroke or CVD death and these events plus hospitalization or revascularization due to heart failure. The secondary endpoint was mortality from all causes and microvascular outcomes. After a median observation time of 6.2 years, there was no difference in the primary outcome between the groups of antidiabetic treatment (HR 1.02, 95% CI 0.94–1.11, $p = 0.63$). Severe hypoglycaemia occurred in 1.00/100 person-years in the insulin glargine group versus 0.31/100 person-years in the OADs group. Moreover, there was greater weight gain in the glargine group, with no difference in microvascular outcomes between the groups of antidiabetic treatment [48].

The DEVOTE trial was also a randomised, controlled, double-blind trial that included 7637 patients with T2DM (mean age 65 years, mean HbA1c 8.4%) at increased CVD risk, who were randomized to insulin deglutec ($n = 3818$) or insulin glargine ($n = 3819$) 100 IU/mL injected in a single

dose after dinner. The primary endpoint was a significant CVD episode including CVD death, non-fatal stroke, or non-fatal MI. The secondary endpoint was the number of severe hypoglycemic incidents as well as the alteration of HbA1c levels. After a mean follow-up time of 1.99 years, lower rates regarding the primary outcome occurred in the degludec group ($n = 325$ or 8.5%) than in the glargine group ($n = 356$ or 9.3%) (HR 0.91, 95% CI 0.78–1.06, $p < 0.001$ for non-inferiority). Severe hypoglycemic episodes occurred less often in the deglutec group, with greater reductions in FPG levels (estimated treatment difference, − 7.2 mg/dL, 95% CI, − 10.3 to − 4.1, $p < 0.001$) [88].

In general, long-acting insulin analogues, such as glargine, have neutral effects with regard to CVD risk and low risk of hypoglycaemia. Deglutec seems to be superior to glargine in this regard, although the differences observed in the DEVOTE trial may be attributed to such factors as the duration of diabetes and the rate of insulin use. It must also be underlined that the DEVOTE trial lasted only 2 years and patients were at high risk of CVD, which limits the generalisation of its results.

In conclusion, the CVD safety issues of insulin are still not fully elucidated given the contradictory evidence from epidemiological studies and RCTs [89]. However, one possible confounder explaining the unfavorable outcomes of observational data could be the risk profile of the patients who receive insulin. These are patients not easily controlled with metformin or other OADs and at a more advanced stage of diabetes progression accompanied by more severe insulin resistance. This means that this group might already have been at a higher risk of complications regardless of therapy, also taking into account the higher risk of hypoglycemia in these patients, which may augment CVD risk.

Current recommendations

According to the ADA, metformin accompanied by lifestyle modification should be considered the initial treatment, unless it is contraindicated. After a follow-up of 3 months, if HbA1c levels fail to remain below 9%, dual therapy is initiated. Any of the aforementioned antidiabetic agents (sulfonylureas, pioglitazone, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors, basal insulin) can be added after taking the patient's individual characteristics into consideration. Each additional non-insulin agent is estimated to lower HbA1c by 0.7–1%. In patients with established CVD, empagliflozin and liraglutide are the most appropriate second-line agents. When dual therapy fails to decrease HbA1c levels below 9% after 3 months from its initiation, a third agent can be introduced, again based on its properties and patient characteristics. If failure occurs of the triple therapy or when HbA1c at initial diagnosis is ≥ 10% (or blood glucose levels ≥ 300 mg/dL), combination injectable therapy should be considered. During this therapy, basal insulin and metformin should be maintained, while other oral antidiabetic agents should be discouraged in order to avoid side effects, complexity, and excessive costs. The addition of a rapid-acting insulin injection before the largest meal, a GLP-1 analogue (if not yet added) or alteration to premixed analogue insulin three times per day (injection per meal) can be used [90].

Conclusions

Both T1DM and T2DM are associated with increased CVD risk, which seems to be reduced by maintenance of euglycemic control. Whether it is just a matter of euglycemia or a distinct role of each antidiabetic drug is a matter of debate. In this concept, many studies have been published during the last decade (most during the last 2–3 years), with old and new antidiabetic agents, yielding contradictory results. Metformin remains safe and confers a beneficial effect on CVD risk, with conflicting data regarding sulfonylurea use. Pioglitazone is beneficial on CVD risk, whereas DPP-4i and, from GLP-1R agonists, lixisenatide, and exenatide, appear to be safe but without a reduction in CVD risk. In contrast, liraglutide and semaglutide, as well as SGLT2 inhibitors, empagliflozin, and cangliflozin, have shown a significant reduction in CVD risk and attenuate the deterioration of renal function, except for their CVD safety. Despite contradictory evidence, insulin analogues and newer long-acting insulins appear also to be safe for the cardiovascular system. All these data and the exact mechanisms need to be further validated in future studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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