Review

Cardiovascular safety of type 2 diabetes medications: Review of existing literature and clinical implications

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ABSTRACT

Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and the cardiovascular effect of antidiabetic drugs are today critical medical issues, with the prevalence of T2DM in particular showing a steep increase worldwide, mainly due to unhealthy lifestyle habits. T2DM in association with obesity and other cardiovascular risk factors, results in the development of CVD, the leading cause of morbidity and mortality in patients with T2DM. Thus, treatment of T2DM is an individualized and complex challenge in which targeting cardiovascular risk factors is an important component in the decision making. Given the cardiovascular adverse events associated with rosiglitazone, both the Food and Drug Administration and the European Medicines Agency currently require the demonstration of cardiovascular safety of new antidiabetic drugs. Consequently, clinical trials to guarantee their cardiovascular safety are now obligatory. This review aims to summarize the available evidence on the cardiovascular effects and safety of the major drugs used in T2DM treatment and also to provide an overview of upcoming and ongoing clinical trials in this field. Our belief is that this review will be of substantial assistance to all medical doctors who are treating diabetic patients, namely primary care physicians, internal medicine doctors, endocrinologists, diabetologists and less well experienced personnel such as young doctors in training.

Key words: Antidiabetic drugs, Cardiovascular side effects and safety, Diabetes mellitus, Treatment outcome

INTRODUCTION

Cardiovascular disease (CVD) remains the leading

cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM).[1] Given that drugs used in the treatment of T2DM may have either beneficial or harmful cardiovascular (CV) effects, it is vital to ensure that these drugs have no deleterious CV effects and may actually improve CV outcomes. On this account, the Food and Drug Administration (FDA) in

2008 and the European Medicines Agency (EMA) in 2010 recommended that new compounds being developed for T2DM should undergo clinical trials to guarantee CV safety.[2,3] However, the CV effects of most antidiabetic drugs are not as yet elucidated[4] and there is little evidence from randomized trials regarding how best to treat T2DM in the CVD affected population. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have reported a consensus algorithm for managing T2DM[5] in which metformin is the initial pharmacologic agent of choice combined with other drugs in double or triple therapy. Our review aims to summarize the CV issues related to the core drugs used in T2DM (Table 1) and to provide an overview of the status of the ongoing and upcoming clinical trials in this field.

INSULIN

Insulin is the primary treatment for type 1 diabetic patients and for type 2 diabetic patients whose hyperglycemia does not respond to other antidiabetic drugs.[6] The initial step of insulin action occurs after its binding to the insulin receptor, which leads to the activation of two major pathways of considerable complexity: the mitogenic pathway, mediating the growth effects of insulin through the mitogen-activated protein kinase (MAPK), and the metabolic pathway which regulates nutrient metabolism by activation of phosphatidylinositol 3-kinase (PI3K). Different types of insulin are now available and categorized by their source and time of action.[7] Some authors believe that individuals with insulin resistance, mainly affecting the PI3K pathway, need greater amounts of insulin to achieve a similar glycemic control, whilst MAPK pathway overstimulation leads to an acceleration of the atherosclerotic process within the vessel wall.[8] Older *in vivo* animal studies provided evidence of the atherogenic potential of insulin.[9] Conversely, several studies have pointed to a possible anti-atherosclerotic effect of insulin mediated by nitric oxide release[10] as well as inhibition of pro-apoptotic signals[11] and of platelet aggregation.[12] However, at present there are no unequivocal clinical data about these effects, which may also depend on the physiological or else experimental circumstances. The main side effects insulin are hypoglycemia and weight gain, while se-

vere hypoglycemia can increase the risk of dementia, CV events and death.[13]

CARDIOVASCULAR SAFETY OF INSULIN: EVIDENCE FROM STUDIES

Several studies have reported an increase in CV risk and higher mortality,[14] whereas others have demonstrated a reduction in CV events, apart of their raise in the incidence of hypoglycemia.[15] An observational study of patients on insulin plus metformin reported a higher risk of a composite effect of nonfatal CV and all-cause mortality among insulin therapy users compared to those administered sulfonylureas (SU) as an add-on therapy.[16] However, significant bias might be present considering that patients with more severe disease are more likely to be treated with insulin. A recently published post hoc analysis of the action to control cardiovascular risk in diabetes (ACCORD) trial suggests that insulin dose did not play a role in the greater CV mortality in patients randomized to intensive glycemic control.[17] In the sulfonylurea/insulin arm of the United Kingdom Prospective Diabetes Study (UKPDS), there was no association between the use of insulin and CVD incidents,[18] even after 10 years of follow-up.[19] The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial with the long-acting insulin glargine involved more than 12,000 patients with new-onset or early T2DM, impaired glucose tolerance or impaired fasting glucose, with a prior CV event or at high risk for CVD, who were randomized either to glargine or to standard care. The results demonstrated no association with macrovascular events in both groups. However, there was a positive link to both weight gain and hypoglycemia.[20] The ORIGIN trial and the recently published legacy effects (ORIGINALE) study followed up these patients for more 2.5 years and confirmed that insulin glargine had neutral effects on CV health.[21] The hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with type 2 diabetes mellitus (HEART2D) trial was designed to study the effects of either prandial (lispro) or basal (NPH twice daily or insulin glargine once daily) insulin on CV outcomes in 1,115 patients after myocardial infarction (MI). No differences in respect of CV events between prandial versus basal strategies were found.[22]

Table 1. Main cardiovascular effects of antidiabetic drugs

Drug	Weight	SBP	DBP	LDL-c	HDL-c	TG	Blood vessels	Heart	Inflammation	Overall CV effect
Insulin	Gain	Neutral	Neutral	Decrease	Mixed results	Decrease	May have anti-atherosclerotic effects	Risk of hypoglycemia induced CV effects	May inhibit platelet aggregation	Uncertain, studies aiming CV safety are needed
Metformin	Loss or neutral	Decrease or neutral	Decrease or neutral	Decrease	Increase	Decrease	Endothelial protection	May have cardioprotective effects (attenuation of MI size and improved LVF)	May have anti-inflammatory and anti-thrombotic effects	Appears to be beneficial
SU	Gain	Neutral	Neutral	Neutral or decrease	Decrease	Neutral or increase	-	May increase risk of CV events (gliclazide and glimepiride appear to be the safest); May prevent ischemic cardiac preconditioning after MI (except glimepiride); Risk of hypoglycemia induced CV effects	May inhibit platelet aggregation (gliclazide)	May increase CV risk, studies aiming CV safety are needed
TZD	Gain (fat redistribution, may decrease visceral adipose tissue)	Decrease or neutral	Decrease or neutral	Rosiglitazone – increases; Pioglitazone – neutral	Increase	Decrease	May have anti-atherosclerotic effects	Fluid retention and edema; Rosiglitazone - may increase risk of MI and HF; Pioglitazone - may increase risk of HF	May have anti-inflammatory effect	Pioglitazone appears to be a safer profile than rosiglitazone; caution in patients with heart disease
DPP-4i	Neutral	Neutral or modest decrease	Neutral or modest decrease	Neutral or decrease	Neutral or increase	Neutral or increase	May have anti-atherosclerotic effects; Vasodilation	May have cardioprotective effects; Hospitalization for HF (saxagliptin, results not confirmed with sitagliptin)	May have anti-inflammatory effect; May improve fibrinolysis	No additional CV risk; clinical trials ongoing
GLP-1 RA	Loss	Decrease	Decrease or neutral	Decrease	No significant improvements	Decrease	Vasodilation; May improve endothelial function	May have cardioprotective effect; May improve LVF and reduce arrhythmias; Increase in heart rate (small increases of uncertain significance)	Anti-inflammatory and antithrombotic properties	Appears to be beneficial; clinical trials ongoing
SGLT2i	Loss	Decrease	Decrease or neutral	Increase	Increase	Decrease	May improve endothelial function; Reduce arterial stiffness	No effect on heart rate; Risk of volume depletion	May decrease CV risk markers (ex: albuminuria, uric acid)	Appears to be beneficial; clinical trials ongoing

SU: sulfonylureas, TZD: thiazolidinediones; DPP-4i: dipeptidyl peptidase 4 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; SGLT2-i: sodium-glucose transporter-2 inhibitors; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-c: Low density lipoprotein cholesterol; HDL-c: high density lipoprotein cholesterol; TG: triglycerides; CV: cardiovascular; MI: myocardial infarction; LVF: left ventricular function, HF: Heart failure.

Insulin degludec is a novel basal insulin with a longer duration of action. In 2013, the FDA suspended approval of this insulin and requested additional CV outcomes data. The DEVOTE trial was designed to test its safety and efficiency in subjects with T2DM at high risk of CV events. Due to the satisfactory preliminary results, this trial has recently been approved by the FDA and is expected to be completed by September 2016.[23]

METFORMIN

Metformin acts by reducing insulin resistance, particularly in the liver and skeletal muscle, suppressing hepatic gluconeogenesis and increasing insulin sensitivity and peripheral glucose utilization.[24] This drug has beneficial effects on lipid metabolism,[24] causing a decrease in total cholesterol, Apo B concentrations and low-density lipoprotein (LDL) cholesterol (LDL-c)[25] and triglycerides (TG) and by increasing high-density lipoprotein (HDL) cholesterol (HDL-c).[26] It has also been reported to cause a decrease in the proportion of small dense LDL particles.[27] Metformin is also associated with weight loss.[26] Metformin may have a moderate blood pressure (BP) lowering effect,[28] although the majority of studies have failed to identify any effect on BP.[29] Metformin may be able to protect against diabetes-induced vascular disease,[30] since it is able to decrease inflammation[31] and preserve the endothelium,[32] while it exhibits anti-thrombotic effects.[33] On the other hand, metformin can cause folate malabsorption and vitamin B12 deficiency, which can lead to elevated homocysteine, an established risk factor for CVD.[34]

CARDIOVASCULAR SAFETY OF METFORMIN: EVIDENCE FROM STUDIES

The UK Prospective Diabetes Study (UKPDS) was a landmark study of the CV benefits of metformin, which demonstrated that, compared to the conventional-treatment group, metformin was able to reduce any diabetes-related endpoint, diabetes-related death and all-cause mortality. When compared to chlorpropamide, glibenclamide or insulin, metformin showed a more pronounced effect for any diabetes-related endpoint, all-cause mortality and stroke.[35] Moreover, the metformin treated group displayed a sustained risk reduction for any diabetes-related endpoint, MI and death from any cause in the post-trial follow-up.[36] Metformin has been shown to lower all-cause mortality compared with other oral agents and insulin[37] and to reduce composite CV endpoints compared with glipizide.[38] It also appears to reduce the risk of macrovascular disease.[39] Systematic reviews have revealed that treatment with metformin is associated with a decreased risk of CV mortality[40] and with a significant reduction of CV events, especially in younger patients.[41] However, in the A Diabetes Outcome Progression Trial (ADOPT) metformin did not demonstrate any advantage in terms of risk of death or CV events over glibenclamide or rosiglitazone.[42] Moreover, the CV safety of metformin has been questioned since there is evidence of greater CV mortality when it is added to sulfonylurea.[35] More specifically, a study found that patients treated with SU in combination with metformin were at higher risk of adverse CV outcomes than those treated with metformin alone.[43]

A number of studies have pointed to beneficial effects of metformin in heart failure (HF), namely lower rates of mortality,[44] mainly CV mortality,[45] and a lower risk of death and readmission for HF.[46] A recent systematic review has determined that metformin is at least as safe as other glucose-lowering treatments in patients with diabetes and HF, even in those with reduced left ventricular ejection fraction.[47] At present, metformin is recommended as first-line therapy in clinically stable patients with HF when their ventricular dysfunction is not severe.[48] Among T2DM patients with documented coronary artery disease (CAD), metformin appears to be associated with lower mortality and CV risk than secretagogues.[49]

Several studies are in progress evaluating the potential CV benefits of metformin. The METformin in DIastolic Dysfunction of MEtabolic syndrome (MET-DIME) trial aims to evaluate if metformin added to the standard treatment of patients with metabolic syndrome (MS) is able to improve diastolic dysfunction.[50] The Glycometabolic Intervention as an adjunct to Primary percutaneous intervention in ST elevation myocardial infarction (GIPS)-III trial aims to provide confirmation that metformin is able to decrease infarct size, prevent adverse remodeling and ultimately improve systolic function.[51] The Glucose Lowering In Non-

diabetic hyperglycemia Trial (GLINT) was designed to establish the effectiveness and cost-effectiveness of metformin in preventing CV events in non-diabetic individuals with high glucose levels.[52]

SULFONYLUREAS

Sulfonylureas (SU) act by stimulating insulin release from pancreatic β-cells.[53] SU also have a number of extra-pancreatic effects, although their clinical significance needs to be clarified.[54] These drugs can reduce hepatic glucose production and hepatic insulin uptake and increase glucagon secretion by pancreatic α-cells.[54,55] They increase insulin sensitivity in peripheral tissues[55] as well as stimulate glucose utilization by these tissues.[54,55] They may attenuate ischemically induced changes in cardiac electrical properties and prevent malignant arrhythmias.[53] Gliclazide is able to reduce platelet adhesion, aggregation and hyperactivity and increase fibrinolysis.[56] Gliclazide, in contrast to glyburide,[53] is also thought to scavenge reactive oxygen species, thereby protecting pancreatic β-cells from apoptosis. Sulfonylurea treatment causes adverse effects, such as weight gain and hypoglycemia. The former usually ranges from 2 to 5 kg, whereas the latter is more likely to affect older individuals, those with impaired renal function or irregular meal schedules.[57]

In respect to CV risk safety, the main CV adverse effects of SU are weight gain and hypoglycemia, two important risk factors for CV adverse outcomes. The profiles of the different SU seem to slightly vary. In fact, hypoglycemia appears to be more frequent with glyburide,[58] while glimepiride is associated with lower risk of hypoglycemia and less weight gain.[59] According to a 2013 meta-analysis, SU can cause a slight reduction of HDL-c with no effects on BP and on the remaining lipid profile.[60] However, a very recent meta-analysis revealed that SU have only a small effect on lipids, with a significant increase in both free fatty acids (FFA) and TG levels, and a decrease in LDL-c and HDL-c.[61]

CARDIOVASCULAR SAFETY OF SU: EVIDENCE FROM STUDIES

No consistent evidence exists as to the association between SU use and risk of CVD in patients with T2DM. A meta-analysis revealed an increased risk of

stroke and a significant increase in mortality, without affecting the overall incidence of major adverse cardiac events (MACE) with SU treatment.[62] Another study has shown an increase in CV risk and mortality with all SU, except for gliclazide which was associated with a lower risk.[63] In addition, in diabetic patients with documented CAD, glipizide and glyburide were associated with increased mortality,[49] the latter probably because of its ability to impair ischemic preconditioning.[64] SU have also been reported to reduce resting myocardial blood flow, to increase infarct size and to elicit proarrhythmic effects.[65] Glimepiride however may be safer in patients with CVD, since it has no detrimental effects on ischemic preconditioning.[59,64] SU seem to increase mortality when patients are submitted to elective[66] or emergency coronary angioplasty for acute MI.[67] Globally, several retrospective studies have demonstrated that all-cause mortality[68] and CV events and death[69] are significantly increased in patients treated with SU compared with metformin.

In the UKPDS, there was no increased mortality in the sulfonylurea-treated subjects;[18] however, the addition of metformin to this group of patients was associated with an increased risk of diabetes-related death compared with sulfonylurea alone.[70] A 2015 study confirmed that treatment with a sulfonylurea plus metformin was associated with increased risks of CVD, MI and ischemic stroke.[71] On the other hand, in the post-UKPDS, the sulfonylurea-insulin group exhibited a significant risk reduction of MI.[19] Overall, large prospective randomized clinical trials[72-74] did not report any increased CV mortality in patients treated with SU.

THIAZOLIDINEDIONES

Thiazolidinediones (TZD) are ligands of the transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ) and act as insulin sensitizers.[75] Rosiglitazone was withdrawn from the European market by the EMA in September 2010 because of its CV risks;[76] nonetheless, it continues to be used in the USA. In respect to pioglitazone, it is not recommended as first-line therapy either by the EMA[77] or by FDA.[78]

TZD have the potential to modulate several CV risk factors, including lipids, BP, inflammatory bio-

markers, endothelial function and fibrinolytic status.[79] Both pioglitazone and rosiglitazone can cause an increase in HDL-c.[75] LDL-c levels seem to remain unchanged with pioglitazone but to increase with rosiglitazone.[75] Interestingly, both drugs seem able to increase LDL-c size particles.[80] Pioglitazone decreases TG levels[75] but has no effect on postprandial TG.[81] Although reports on the effect of rosiglitazone on TG are conflicting,[75,80] it seems to be able to decrease their postprandial values.[82] Rosiglitazone is also able to decrease FFA.[82] TZD use is associated with weight gain,[80] in subcutaneous rather than in visceral adipose tissue, and causes a reduction in liver fat.[83] Data on the effect of TZD in BP have shown conflicting results, with some studies indicating improvements in BP control[84] and others exhibiting no effect.[85] Other studies have suggested potential anti-atherogenic effects for TZD.[86] TZD adverse effects also include fluid retention and edema and, in fact, an increased risk of HF is the main CV concern with TZD use.[87]

CARDIOVASCULAR SAFETY OF TZD: EVIDENCE FROM STUDIES

The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial found no increase in CV event rates with rosiglitazone, although the rosiglitazone group developed significantly more HF events.[88] The Rosiglitazone Evaluated for CV Outcomes in Oral Agent Combination Therapy for T2DM (RECORD) trial showed that rosiglitazone does not increase the risk of overall CV morbidity or mortality; nevertheless, it confirmed an increased risk of HF.[89] In spite of this, issues related to trial design and data integrity led FDA to call for an independent reevaluation of the RECORD data, which reported similar results.[90] A 2007 meta-analysis demonstrated that rosiglitazone was associated with a significant increase in the risk of MI and death from CV causes.[91] In 2010, the same authors repeated the meta-analysis and found an increased risk for MI, albeit less than before, and found no increased risk for CV mortality.[92] Other meta-analysis have suggested that rosiglitazone is associated with a significantly increased risk of MI and HF, without a significantly increased risk of CV mortality.[93,94] The bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial in 2013 reported that among patients with T2DM and CAD,

rosiglitazone is not associated with an increase in major ischemic CV events.[95]

The PROspective pioglitAzone clinical trial in macroVascular events (PROactive) study has shown that in T2DM patients at high risk for macrovascular events, pioglitazone significantly reduced a pre-specified secondary endpoint composed of death, non-fatal MI and stroke.[96] It is important to note that in the pioglitazone group, there was an increased rate of any reported HF and HF leading to hospitalization, even though the rate of fatal HF was similar in both groups.[96] In a subgroup analysis of the PROactive study, pioglitazone significantly decreased the risk of recurrent stroke[97] and of fatal and nonfatal MI and acute coronary syndrome[98] in high-risk patients with T2DM. Corroborating this, a meta-analysis has revealed that pioglitazone is associated with a significantly lower risk of death, MI or stroke in patients with T2DM.[99] HF is increased by pioglitazone, although there is no increase in the associated mortality.[99] However, a recent study reported that pioglitazone treatment did not produce any significant reductions in the rate of primary CV events.[100]

Both pioglitazone and rosiglitazone seem to increase the risk of HF; nonetheless, the risk of CV death is not increased.[101] Additionally, in a recent cochrane meta-analysis, PPAR-γ agonists were shown to reduce recurrent stroke and total events of CV death, as well as improving insulin sensitivity and carotid plaques stabilization.[102]

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Five dipeptidyl peptidase-4 (DPP-4) inhibitors (DPP-4i), also named gliptins, are now available in Europe and worldwide (except vildagliptin in the USA): sitagliptin, saxagliptin, linagliptin, vildagliptin and alogliptin. Other DPP-4i are available only in Asia, namely anagliptin and teneligliptin, which are licensed in Japan, and gemigliptin in Korea. Other members of this class are in clinical development, including trelagliptin.[103]

Incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released from the gut in response to meals and are rapidly degraded by DPP-4. GLP-1 stimulates insulin and suppresses glucagon secretion,

slows gastric emptying and enhances satiety leading to a decrease in food intake.[104] The pharmacologic inhibition of DPP-4 allows extension of the biological effect of incretins. In addition to metabolic effects, DPP4 inhibition has been described as having other pleiotropic effects in the CV system related to several non-incretin substrates, like cytokines, chemokines and neuropeptides involved in inflammation, immunity and vascular function.[105] One of the best known substrates is stromal-derived factor-1a responsible for endothelial progenitor cells recruitment and vascular repair following ischemic injury.[106] Potent vasodilators, as for example substance P and bradykinin, are also degraded by DPP-4 and may improve fibrinolysis by stimulating tissue plasminogen activator (tPA).[107] Due to the multiple functions of these substances their ultimate role in disease prevention is still unclear.[108]

DPP-4i may have a beneficial role both in hypertension and dyslipidemia, major risk factors for CVD. Human studies have indicated that DPP-4 inhibition allows endothelium-dependent relaxation mediated by nitric oxide, a molecule with important implications for BP.[109] A meta-analysis pointed to a favorable effect of DPP-4i on cholesterol reduction, providing a small but significant reduction of CV risk.[110] This class also has a low risk of causing hypoglycemia or weight gain.[111]

CARDIOVASCULAR SAFETY OF DPP-4 INHIBITORS: EVIDENCE FROM STUDIES

Although not all of them, several studies on experimental animals have found that DPP-4 inhibition improves cardiac function. In animal models with diabetes and atherosclerosis, DPP-4 inhibition reduced atherosclerotic lesions and the expression of proinflammatory cytokines in these lesions,[112] as well as monocyte activation and chemotaxis.[113] In humans, patients not responding to metformin treated with sitagliptin or vildagliptin had a decrease in the intima media thickness of the carotid artery, a surrogate marker for early atherosclerosis.[114]

Some studies have suggested an increased risk of hospital admission for HF in patients on DPP-4i,[115] albeit the mechanism of action remains controversial.[116] There is no clear evidence of differences among drugs of this class. It is likely that the risk is greater in certain sub-populations of patients; however, current evidence is not yet sufficient to identify susceptible patients.[117]

The Saxagliptin Assessment of Vascular Outcomes recorded in patients with diabetes mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) study evaluated 16,492 patients with T2DM, who had a history of, or were at risk for, CV events, that received saxagliptin or placebo. The study showed that the use of saxagliptin did not alter the rate of ischemic events; however, the rate of hospitalization for HF was increased.[118] It is important to note that this was a secondary composite endpoint and further evaluation is needed. The EXAmination of CV outcoMes with alogliptIN versus standard of carE (EXAMINE) study was a randomized, double-blind trial with 5,380 patients with T2DM who had required hospitalization during the previous 15 to 90 days due to either acute MI or unstable angina. Alogliptin did not increase MACE, including MI, stroke or HF, compared to patients receiving placebo.[119] The TECOS trial evaluating CV outcomes with sitagliptin was a randomized double-blinded trial involving 14,671 patients with T2DM and established CVD who added sitagliptin or placebo to their usual therapy. Recently published, this study showed that adding sitagliptin to therapy did not increase the risk of MACE, hospitalization for HF or other adverse events.[120] Another recent study has suggested that, according to a pooled analysis of trials, linagliptin is not associated with increased CV risk versus active comparators or placebo in patients with T2DM.[121]

Currently there are other ongoing randomized clinical trials comparing DPP-4i versus placebo added to conventional therapy in patients with T2DM. The CArdiovascular safety and renal microvascular outcomE study with LINAgliptin in patients with T2DM (CARMELINA), lasting till 2018, has been designed to assess the long-term impact on CV morbidity, mortality and renal function of treatment with linagliptin.[122] The CARdiovascular outcome trial of LINAgliptin versus glimepiride in patients with T2DM (CAROLINA) is a trial ongoing since 2010 comprising a comparison of a sulfonylurea with a DPP-4i. This trial is expected to provide considerable insight as it is unique in comparing head-to-head add-on therapy.[123]

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

The actions of GLP-1 are mediated through the GLP-1 receptor (GLP-1R) that is expressed in pancreatic islet cells and in peripheral tissues.[104] As a result of the wide distribution of GLP-1R, GLP-1 seems to exert extra-pancreatic actions that can have beneficial effects on the CV, gastrointestinal and central nervous systems.[124] Currently, the GLP-1R agonists (GLP-1 RA) approved for the treatment of T2DM are albuglutide, dulaglutide, exenatide and extended release exenatide, liraglutide and lixisenatide.[125] Taspoglutide was stopped in phase III studies due to the unexpectedly high hypersensitivity reactions reported.[126] Semaglutide and efpeglenatide are currently in development and are, respectively, in phase III and II of clinical trials.[127,128]

GLP-1 RA treatment seems to be associated with a favorable impact on several CV risk factors, namely BP, lipid profile and weight. In fact, several meta-analyses have demonstrated that GLP-1 RA treatment is associated with significant weight loss[129-132] and beneficial effects on lipid profile, decreasing LDL-c and TG.[131,133] These drugs are able to reduce systolic BP (SBP), but not diastolic BP (DBP);[132,134] nonetheless, they also seem to be associated with a small increase in heart rate.[132] Monotherapy with GLP-1 RA does not increase the risk of hypoglycemia in comparison with placebo, although is associated with higher frequencies of hypoglycemia when in combination with SU.[129,130] It has also been reported that β-cell function was improved with GLP-1 RA (HOMA-B, proinsulin-to-insulin ratio).[131]

Several studies have supported a cardioprotective effect of native GLP-1 and GLP-1 RA on the vascular endothelium and myocardium, including vasodilation and anti-inflammatory effects.[135-137] Evidence from clinical trials has shown that GLP-1 and GLP-1 RA can improve both left ventricular and endothelial functions and reduce arrhythmias in patients with or without diabetes and with coronary artery bypass graft, chronic HF and CAD.[138-140]

CARDIOVASCULAR SAFETY OF GLP-1: EVIDENCE FROM STUDIES

Although pinpointing that drug or those drugs that will provide CV protection remains elusive, the available data confirm the CV safety of GLP-1 RA. Ongoing randomized large-scale trials will be important to consolidate the results obtained so far. Indeed, several GLP-1 RA are undergoing long-term randomized trials to assess their CV safety – ELIXA (lixisenatide),[141] LEADER (liraglutide),[142] SUSTAIN 6 (semaglutide),[143] REWIND (dulaglutide),[144] and EXSCEL (exenatide extended release).[145]

At present, only the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study is complete.[141] Preliminary results were recently announced and have confirmed that the CV-safety profile of lixisenatide is non-inferior, although not superior, to placebo.[146] Despite the limitations, meta-analyses performed to ascertain CV outcomes are also a source of evidence concerning CV safety. The results exclude, at least in the short term, any increase in CV morbidity and mortality in comparison with placebo or other active drugs.[134,147,148] Besides, placebo-controlled trials have demonstrated that patients treated with GLP-1 RA have a lower incidence of MACE, CV mortality and all-cause mortality.[134,148]

SODIUM-GLUCOSE TRANSPORTER-2 INHIBITORS

The sodium-glucose transporter-2 (SGLT-2) inhibitors (SGLT-2i) are a new class of antidiabetic agents that inhibit glucose reabsorption from the kidney increasing urinary glucose excretion.[149] The FDA and EMA have approved three inhibitors, canagliflozin, dapagliflozin and empagliflozin, with several others being under late-stage clinical development.[150] Ipragliflozin, tofogliflozin and luseogliflozin have been approved for the treatment of T2DM in Japan.[151] Other compounds remain in development,[152] as well as Lx4211, a dual sodium-glucose transporter 1 and 2 inhibitor,[153] and ISIS – 388626, an antisense oligonucleotide (ASO) designed to block the expression of the SGLT2 gene in vivo.[152] SGLT-2i protect the proximal tubular cells, most likely by blocking glucose entry into the cell,[54] and indirectly reduce insulin secretion, improve insulin sensitivity and increase the peripheral glucose uptake.[155] This drug acts independently of the severity of insulin resistance and β-cell failure;[149] nonetheless, as the glomerular filtration

rate declines, its efficacy decreases.[156] Recent reports have suggested that SGLT2i may increase the risk of developing diabetic ketoacidosis (DKA),[157] although the pathophysiological mechanisms involved are not well defined. Selection of patients for this drug should therefore be carefully made.

In addition to lowering blood glucose, SGLT-2i may benefit such CV parameters as BP, weight and lipid profile.[149,151] In many studies, SGLT-2i have shown a consistent reduction in SBP,[158] with a less consistent reduction in DBP,[159] and without a compensatory increase in heart rate.[149] These drugs also seem to improve endothelial function[160] and to reduce arterial stiffness.[161] SGLT2i promote glucose excretion in the urine, corresponding to a caloric loss of 200 to 300 kilocalories per day and leading to weight loss.[162] SGLT-2i reduce total body weight, predominantly by reducing fat mass, visceral adipose tissue and subcutaneous adipose tissue.[163] Plasma lipids are affected by SGLT-2i, which cause an increase in HDL-c and in LDL-c and a reduction in TG levels.[149] To what extent these lipid changes translate into potential CV effects remains to be clarified, although they seem not to increase CV risk given the balanced effect of reduced hyperglycemia, BP and weight. Several studies have reported a reduction in urinary albumin excretion[164] and also in uric acid serum levels.[162] Whether these effects contribute to a beneficial CV outcome is a question that will hopefully be answered through further studies.

This class of drugs has a low potential to induce hypoglycemia,[158] unless used with SU or insulin.[151] SGLT-2i can also have a role in nephroprotection by preventing glomerular hyperfiltration;[154] nevertheless, to what extent these effects may contribute to a renal or CV beneficial outcome is yet to be established.

CARDIOVASCULAR SAFETY OF SGLT-2I: EVIDENCE FROM STUDIES

The recently published EMPA-REG OUTCOME study presented exciting CV results with empagliflozin.[165] In fact, empagliflozin was shown to significantly reduce deaths among patients with T2DM and established CVD when compared with placebo. These patients exhibited a 14% reduction in the three-point MACE primary endpoint. This effect was mainly due to the benefits related to CV death, since empagliflozin did not reduce the rate of nonfatal MI or nonfatal strokes. Overall, this drug displayed a 38% reduction in CV death and a 32% reduction in all-cause mortality. A significant reduction in the key secondary endpoint, which was the primary composite endpoint plus hospitalization for unstable angina, was also apparent, as well as a 35% reduction in HF hospitalization. Interestingly, these effects occurred early in the trial.[165] The diuretic effect is possibly the main factor responsible for these results, although in the long term the effect upon glycemia, BP and weight may also contribute to it. Recently, one study used the Archimedes Model to predict 20-year outcomes and found significant reductions in the risk of MI, stroke, CV death and all causes of death with SGLT-2i treatment versus standard care.[166] Nevertheless, to confirm these results, several trials are now in progress in order to evaluate the CV safety of the other SGLT-2i.[150] The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58), expected to be finished in 2019, was designed to evaluate the effect of dapagliflozin on the incidence of CV events.[167] The Canagliflozin Cardiovascular Assessment Study (CANVAS), expected to complete data collection in 2017, was also designed to evaluate the effects of canagliflozin on MACE.[168] The cardiovascular outcomes following treatment with ertugliflozin in participants with T2DM and established vascular disease trial was designed to assess the CV safety of ertugliflozin and it is expected to be completed in 2021.[169]

CONCLUSION AND CLINICAL IMPLICATIONS

This review analyzes the CV effects of antidiabetic drugs while outlining the evidence available and enumerating the ongoing trials. Several drugs are now available to treat T2DM. Metformin, with solid evidence of having beneficial CV effects, is the first-line therapy for these patients. The direct heart benefits of metformin, under study in several trials, if confirmed, will reinforce the position of this drug as first-line therapy. Nonetheless, when metformin alone is not enough, other drugs are needed. According to the ADA/EASD algorithm, all drugs herein discussed are valid as second- and third-line therapy. The choice will also be based on the characteristics

of the patient. As diabetic patients are at high risk for CV morbidity and mortality, taking into account the CV safety of these drugs certainly constitutes knowledge of crucial importance to all clinicians dealing with this condition.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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