МЕХАНИЗМЫ КАРДИОПРОТЕКЦИИ НЕИНСУЛИНОВЫХ САХАРОСНИЖАЮЩИХ ПРЕПАРАТОВ

© Angelo Avogaro

University of Padova, Dept. of Medicine, Падуя, Италия

Пациенты с сахарным диабетом 2 типа (СД2) чаще всего умирают от сердечно-сосудистых заболеваний (ССЗ). Метаболический контроль является краеугольным камнем как для первичной, так и для вторичной профилактики ССЗ: он вдвойне важен, поскольку нормализация гликированного гемоглобина (HbA_{1c}) позволяет не только отсрочить дебют и прогрессирование микрососудистого осложнения, но также помогает снизить риск серьезных нежелательных сердечно-сосудистых событий (MACE). Однако из доступных сахароснижающих препаратов некоторые оказывают прямое кардиопротективное действие, независимо от способности достигать целевых метаболических показателей. В этом обзоре я обращу внимание на патофизиологические механизмы, лежащие в основе кардиопротективных свойств различных сахароснижающих препаратов, существующие доказательно обоснованные данные касательно этих свойств, потенциальные побочные эффекты и различные фенотипы пациентов, подходящие под определенное лечение. Понимание патофизиологических механизмов кардиопротекции каждого препарата и ограничений их применения помогает врачам индивидуализировать лечение метаболических нарушений у пациентов с СД2.

КЛЮЧЕВЫЕ СЛОВА: сердечно-сосудистые заболевания; сахарный диабет 2 типа; осложнения сахарного диабета; ингибиторы дипептидилпептидазы-4; глюкагоноподобный пептид-1; натрий-глюкозный котранспортер-2

MECHANISMS OF CARDIOVASCULAR PROTECTION OF NON-INSULIN ANTIDIABETIC MEDICATIONS

© Angelo Avogaro

University of Padova, Dept. of Medicine. Padova, Italy

Patients with type 2 diabetes mellitus die most frequently from cardiovascular disease (CVD). Metabolic control is a cornerstone of both primary and secondary prevention of CVD: its important is two-fold since the normalization of HbA_{1c} not only counteracts the onset, and the progression of microvascular complication, but has also important and positive role in reducing the risk of major adverse cardiovascular events (MACE). However, among the available glucose-lowering medications, some exert a direct CV protection independently from their ability to normalize metabolic control. In this review I will highlight the pathophysiological mechanisms underlying the claimed cardiovascular protection of the different glucose-lowering drugs, the available evidence-based data for their protection, the potential adverse effects, and the different phenotypes of patients eligible for a specific treatment. The knowledge of pathophysiological mechanisms for CV protection of each glucose-lowering medication, and the constraints of their use supports the health care professionals to individualize the normalization of metabolic control in patients with type 2 diabetes mellitus.

KEYWORDS: cardiovascular disease; type 2 diabetes mellitus; complications of diabetes mellitus; dipeptidyl peptidase iv inhibitors; glucagon-like peptide 1; sodium glucose transporter 2

Patients with Type 2 diabetes (DMT2) have an increased risk of cardiovascular disease (CVD). Macrovascular disease in diabetes remains the leading cause of mortality: early studies suggested that, on average, patients with diabetes but without a previous history of myocardial infarction have a similar risk of experiencing a future cardiac event as subjects without diabetes but with a prior myocardial infarction(1). This high cardiovascular risk is attributed in part to the harmful effect of hyperglycaemia per se on vascular wall, and, in part, to the coexistence of other traditional CV risk factors in the cluster of metabolic syndromes, such as hypertension, atherogenic dyslipidemia, and central obesity(2). For this reason, the normalization of glucose, blood pressure, lipid profile, and body weight is considered a priority by all available. The pathophysiology of vascular damage in diabetes is complex and involves abnormalities in endothelial cells, vascular smooth muscle cells, and platelet function(3). Hyperglycaemia reduces endothelium-derived nitric oxide (NO) availability, and compromises vascular function through several mechanisms, mainly involving overproduction of reactive oxygen species (ROS) from mitochondria and cytoplasmic sources. As result of all these pathological changes, the development of atherosclerotic plaque in people with diabetes is a complex, progressive process, characterized by early vascular inflammation and endothelial dysfunction, leading to monocyte recruitment and subsequent formation of fatty streaks(4). In the light of this knowledge, and of the recent findings from cardiovascular outcome trials (CVOT), it is of great importance to understand the molecular mechanisms underlying the direct CV protection of each different class of glucose-lowering drugs (GLD), independently

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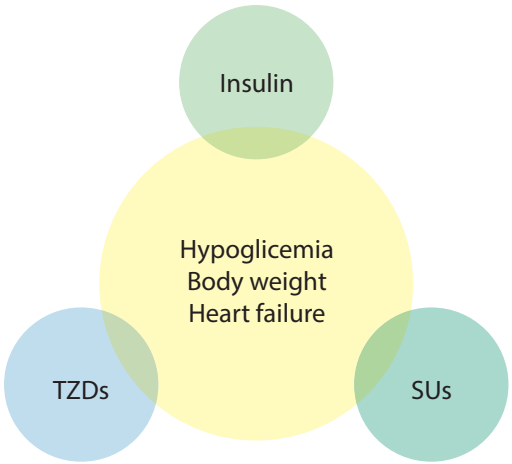

Fig. 1. The most prominent adverse effects observed in patients treated with insulin, thiazolidinediones (TZDs) and sulphonylureas (SUs): hypoglycemia, increase in body weight, and heart failure.

from their effectiveness in reducing HbA1c. It is also of importance to appreciate contraindications and potential adverse effects in order to assigned the optimal diabetes treatment to each patient suffering from this disease (Fig. 1).

METFORMIN

Metformin is considered the first-line agent by all guidelines for the treatment of T2DM: in patients tolerant to the drug, its use is contraindicated when estimated glomerular filtration rate (eGFR) falls below 30 ml/min/1.73m2. Its main action is to increase glucose uptake, while inhibiting intestinal glucose absorption, and hepatic gluconeogenesis. Metformin triggers an array of intracellular biochemical pathways, the most important being the activation the cellular energy sensor AMP-activated protein kinase (AMPK), which is known to positively affect the endothelial function(5). In isolated endothelial cells exposed to elevated glucose concentration, it restrains the production of ROS by inhibiting protein kinase C, a serine-threonine dependent kinase(6). In the United Kingdom Prospective diabetes Study (UKPDS)-34, in 268 overweight patients randomized to metformin, this drug, compared to placebo, induced a 36% and a 39% relative risk reduction for all-cause mortality and myocardial infarction, respectively(7). However, a recent meta-analysis questioned the potential of metformin to reduce the CVD risk(8). Metformin appears to be safe also in patients with T2DM and heart failure (HF), and, it is linked to a better outcome(9). Among patients initiating sulfonylureas (SUs) for diabetes treatment versus metformin, the latter had a lower risk for HF and CV death(10). It has been demonstrated that the risk for myocardial infarction in patients with metformin monotherapy is lower than in patients in whom sulfonylureas were added as second line drugs(11). In conclusion, in patients with T2DM, tolerant to the drug, and eGFR above 30 ml/min/1.73m2, with or without CVD and/or HF, metformin appears to be safe, and it may probably exert a direct CV protection (Table 1) (12).

SULPHONYLUREAS AND METIGLINIDES

These GLD stimulate insulin secretion by closing the ATP-sensitive potassium channels (KATP channels) in the pancreatic β-cells: however, KATP channels are also present in myocytes where they shorten action potential to reduce cardiac workload, and in vascular smooth muscle cells where they induce vasodilatation, thus providing a protective mechanism during episodes of ischaemia(13). The available SUs have different binding affinity for KATP channels, being highest for glibenclamide (and for repaglinide) and lowest for gliclazide. In a small trial we assessed the effects of treatment with glibenclamide or insulin on the extension of left ventricular myocardial dysfunction induced by acute ischemia: in 19 patients with type 2 diabetes and coronary artery disease randomly assigned to either insulin or glibenclamide treatment ischemic myocardial dysfunction induced by dipyridamole infusion was less severe during treatment with insulin than with glibenclamide(14). Does this effect of SUs have significant clinical read-out? Apparently not. In the UKPDS and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials, there was no evidence for a direct detrimental effect of SU on the CV system: more evidence is available from observational studies in which patients on SU treatment were more susceptible to CVD and hospitalization for heart failure (hHF) (15, 16) although this is not consistently observed for all SUs (17, 18). However, not all observational studies are unanimous in demonstrating such negative effect. In patients assessed within 30 days of acute coronary syndrome, there was no significantly increased risk of death or death/HF in those exposed to KATP channel inhibitors versus patients not exposed to KATP channel inhibitors prior to their acute coronary syndrome(19). The detrimental effect of SUs on CV system is rather indirect than direct, and mediated by their ability to induce hypoglycemia(20), especially when added in addition to other secretagogues (21). Repaglinides, a metiglinide, may also interfere with ischemic preconditioning(22): however, an excess of CV events was not observed in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial in patients randomized to nateglinide (23). In conclusion, SUs and metiglinides may have direct detrimental effects on CV system, although their adverse value is, probably, mostly linked to their propensity to induce hypoglycaemia (Table 1).

ACARBOSE

Acarbose decreases glucose absorption by the gut by inhibiting α-glycosidase: therefore, its alleged positive action on CV is mediated by decreased postprandial glucose peaks(24, 25). The Study to Prevent NIDDM (STOP-NIDDM) trial has shown that 300 mg of acarbose a day led to a 50% decrease in CV events, and a 34% decrease in new cases of hypertension compared with those receiving placebo (26). A subsequent meta-analysis confirmed these positive effects(27), although these results were disputed(28, 29). Recently, the role of acarbose in the frequency of CV events and, in the incidence of T2DM

Table 1. Phenotyping glucose-lowering drugs for patients with type 2 diabetes mellitus

Glocose-lowering Drug	Purse	Avoid
Metformin	Patients with type 2 diabetes irrespective of BW, history of CVD and/or HF	Before angiography eGFR < 30 ml/min Severe COPD Ongoing ischemic episode and HF GI intolerance Excessive alcohol intake
Sulphonylureas	Lean patients without target organ damage and normal (50-60% total daily caloric intake) carbohydrate intake	Risk for hypoglycemia Elderly patients eGFR < 60 ml/min Ongoing ischemic episode and HF Excessive alcohol intake Dementia
Acarbose	Lean/obese patients with or without CVD or/ and HF	GI intolerance Renal impairment
Thiazolidinediones	Overweight/Obese patients with evidence of subclinical or clinical CVD Overweight/Obese patients with prior history of stroke or TIA	Previous history of/or ongoing HF Proliferative retinopathy or macular edema End-stage kidney disease
DPP-4 inhibitors	Lean/Overweight patients with or without history of CVD and HF	Patients with history of HF only for saxagliptin History of pancreatitis or gallstone
GLP-1 receptor agonists	Overweight/obese patients with or without history of CVD	History of pancreatitis or gallstone eGFR < 15 ml/min Ongoing HF
SGLT2 inhibitors	Lean/overweight/obese patients with or without history of CVD and HF	eGFR < 45 ml/min Insufficient carbohydrate intake Excessive alcohol intake Ischemic peripheral artery disease Recurrent UTI or GI

Notes: GI: genital infection; UTI: urinary tract infections; eGFR: estimated glomerular filtration rate; HF: heart failure; BW: body weight; TIA: transitory ischemic attack

has been assessed in Chinese patients with impaired glucose tolerance and established CVD(30): this trial demonstrates that acarbose did not reduce the risk of major adverse CV events, but did reduce the incidence of diabetes. In conclusion, the data are too scanty to firmly conclude that decreasing postprandial hyperglycaemia with acarbose might prevent CVD in patients with T2DM.

THIAZOLIDINEDIONES

Thiazolidinediones (TZDs) activate the nuclear receptors peroxisome proliferator-activated receptors (PPARs), which, in turn, trigger several other genes affecting the storage of fatty acids in adipocytes: this action results in a significant decrease in circulating free fatty acids, and in a simultaneous decrease in blood glucose concentration(31). PPARγ modulate also inflammation, especially in the context of the atherosclerotic process, and stimulate cholesterol efflux transporter ABCA1(32). Among TZDs, pioglitazone is the most widely used after the adverse consequences observed by the others of the same class: it exerts a direct anti-atherosclerotic effect in the arterial wall in humans(33). In the prospective pioglitazone clinical trial in macrovascular events (PROactive) trial, involving 5238 patients with T2DM and established CVD, those who received pioglitazone had similar incidence of the primary composite endpoint, but in the subgroup of patients who had a previous MI, there was a significant 28% risk reduction for fatal and a significant 37% reduction for acute coronary syndrome(34). In the TOSCA.it trial the authors compared the long-term effects of pioglitazone versus sulfonylureas on metformin background on CV events in patients with type 2 diabetes: they showed, in the per protocol analysis, that in patients in primary prevention, pioglitazone could be beneficial compared to SUs in terms of durability of glycaemic control, frequency of hypoglycaemia, and reduction of events(35).

Pioglitazone also exerts a direct protective effect at the level of cerebral circulation: in nondiabetic, insulin-resistant patients with a history of recent stroke, this drug decreased by 26% the composite primary endpoint fatal or nonfatal stroke or MI(36). Pioglitazone, as the other PPARγ activators, induces fluid retention, edema, and sometimes precipitates or exacerbates HF in patients at risk for this condition [39]. In conclusion, the most

widely used PPARγ, pioglitazone, determines a direct, widespread, and protective vascular effect, which is, however, counterbalanced by an increased incidence of HF (Table 1).

DIPEPTIDYL PEPTIDASE 4 INHIBITORS

Dipeptidyl peptidase-4 inhibitors (DPP-4-I), also called gliptins, increase the concentration of glucagon-like peptide-1 by 2 to 4 folds. Fifty per cent of native GLP-1(7-36) is degraded in roughly 1 minute by the DPP-4 or CD26, a 110 kDa peptidase that belongs to a unique class of membrane associated peptidases(37). The net effects of DPP-4 inhibition, independently from GLP-1, on the potential beneficial actions of GLP-1 cleaved forms on the cardiovascular system are largely unknown. Beyond its effect on insulin and glucagon secretions, GLP-1 is known to positively affect CV system by decreasing vascular adhesion molecules, increasing endothelial nitric oxide (NO), decreasing pro-inflammation, decreasing endothelin synthesis, platelet activation, and smooth muscle cell proliferation(38). Beside incretin hormones, there are several proteins that have a penultimate alanine, proline, or serine in the N-terminus start site, the most important for the CV system being the stromal cell-derived factor-1α (SDF-1α), and brain natriuretic peptide (BNP). SDF-1α and its receptor CXCR4 play a prominent role in the trafficking and homing of hematopoietic stem cells: SDF-1α levels increase in both plasma and ischemic tissue shortly after ischemic injury, in response to hypoxia which upregulates HIF-1α(39). In this context, it has been shown that DPP-4 contributes to SDF-1α degradation after myocardial infarction: DPP-4 inhibition blocks the degradation of SDF-1α, which, in turn, allows a much more efficient recruitment of progenitor cell in the site of ischemia (40). The hypothesis that DPP-4 inhibition prevents the degradation of SDF-1α, thus favoring the homing of progenitor cells with a consequent amelioration of ulcer healing, has been tested in humans in the context of peripheral artery disease and its complication. We have shown that diabetes delayed wound healing, with reduced granulation tissue thickness and vascularity, and increased apoptosis as a consequence of an increased apoptosis, and decreased proliferation of bone marrow-derived progenitor cell (41). Marfella and associates reported that in patients with Type 2 diabetes and at least one full-thickness wound below the ankle, the treatment with the DPP-4-I vildagliptin leads to a more rapid wound closure rate at week 12 than in controls, and the doubling in complete healing of the index ulcer (42). In a retrospective analysis conducted in 82,169 propensity score-matched pairs of DPP-4 inhibitor users and nonusers with Type 2 Diabetes, DPP-4 inhibitor users were associated with a lower risk of both peripheral arterial disease and risk of lower-extremity amputation than nonusers(43). More recently, Long and colleagues have recently tested the hypothesis that DPP-4 inhibitors can improve diabetic wound healing, independently from their beneficial effects on glycaemic control: the DPP-4 inhibition, in patients with DMT2, seems to restore the ability of the bone marrow to release progenitor cells(44). The importance of this observation is two-fold. First, diabetes is characterized by a "diabetic stem cell mobilopathy" determined, at least in part, by the presence of a bone marrow microangiopathy and by the maladaptive regulation of CXCR4/SDF-1α(45). DPP-4 inhibition may affect natriuresis in both animals and humans: one month of sitagliptin treatment increases circulating levels SDF-1α 1-67, and induces natriuresis by blocking distal tubular sodium reabsorption, distal to the macula densa, without affecting renal haemodynamic, and blood pressure(46). Another DPP-4 sensitive substrate relevant to CV homeostasis is BNP, which is synthesized as a 134-amino acid precursor protein (preproBNP) and is subsequently processed during secretion to form the 108-aa peptide, proBNP(47). On the extracellular surface of cardiomiocytes, proBNP interacts with corin to form the active BNP 1–32 and NT-proBNP 1-76; there is also a circulating proBNP 1-108. All these forms of BNP are substrates for DPP-4 since they all have a proline in the second N-terminal position. BNP concentrations are reduced in people with obesity, insulin resistance, and diabetes, and this deficiency may contribute to their CV risk(48). Theoretically, DPP-4 inhibition could exert beneficial effects on cardiac function, by increasing the proportion of circulating BNP 1–32, and NT-proBNP 1-76. Thus, one can speculate that the administration of DPP-4 inhibitors should, supposedly, positively affect the CV system beyond their ability to decrease plasma glucose. However, we have shown that the acute treatment with a DPP-4 inhibitor, at least in patients without a history of HF, exerts no clinically-meaningful effects on BNP and NT-proBNP(49). Meta-analysis of phase 2 and 3 clinical trials and observational studies have shown a substantial neutrality of this class of drug on CV safety(50, 51). In all CVOT, the DPP-4 inhibitors saxagliptin, alogliptin, and sitagliptin met the primary endpoint of non-inferiority vs. placebo with respect to MACE (CV mortality, non-fatal myocardial infarction, and non-fatal stroke)(52-54). No significant differences were reported in those parameters such as heart rate, and blood pressure, potentially modifiable by the DPP-4 inhibition, and linked to its pleiotropic activity. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) randomized 16,492 patients with Type 2 Diabetes, with a history of or at high risk for CVD, to saxagliptin or placebo in addition to usual care. At the end of follow-up period (median of 2.1 years), the rate of primary end-point (a composite of cardiovascular death, non-fatal MI or ischemic stroke) was similar in the two groups. Interestingly, in those patients randomized to saxagliptin, the risk for hospitalization for heart failure was significantly higher(55). Several speculations, yet unproven, have been proposed for this increased risk of heart failure, which was observed only for this drug of the class but not with the others. Notably, in both SAVOR and in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trials, heart failure was not included among the pre-specified end-points. Recently, a RCT specifically assessing the effect of vildagliptin on heart function in patients with DMT2 and heart failure, has been completed, and showed that 52

weeks treatment with vildagliptin 50 mg twice daily was neutral vs. placebo in left ventricular ejection fraction and geometry(56). Following the results of the SAVOR trials, numerous observational studies have conducted either to confirm or rule-out the association between DPP-4 inhibitors treatment and heart failure: most of them have excluded this link except for saxagliptin(57, 58). There is an ongoing CVOT testing the safety of linagliptin against glimepiride: the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA)(59). It will be interesting to assess the risk of a DPP-4 inhibitor vs. a sulphonylurea (glimepiride) on heart failure. In conclusion, DPP-4-I play an important role in the management of patients with DMT2; beyond their ability to improve glucose control, they also exert numerous pleiotropic actions, which have been proven in several experimental conditions but their evidence in humans are flimsy, and at best not harmful in patients with type 2 diabetes treated with these drugs.

GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS

Glucagon-like peptide 1 (GLP1) is mainly secreted by the intestine in response to eating but it is rapidly cleaved by DPP4: to overcome this problem, either mimetic or analogues of GLP-1 receptor agonists (GLP-1RA) should be administered. They stimulate insulin secretion and decrease glucagon secretion with a significant reduction of plasma glucose concentrations. Multiple GLP-1R agonists have been developed for the treatment of patients with type 2 diabetes(60). The first clinically approved agent, exenatide, is delivered as a twice-daily injection or via a once-weekly microsphere-coupled formulation; lixisenatide, structurally related, is a DPP-4–resistant GLP-1RA agonist for once-daily administration. Liraglutide is a long-acting, acylated, DPP-4–resistant human GLP-1 analog administered once daily, which noncovalently associates with albumin, while dulaglutide is a DPP-4–resistant GLP-1R agonist with a modified immunoglobulin G fragment crystallizable region enabling extended pharmacokinetics. GLP-1R activation may influence the CV system: treatment of human umbilical vein endothelial cells (HUVEC) with liraglutide increased endothelial NO synthase phosphorylation and NO production in a 5'AMP-activated protein kinase (AMPK)–dependent manner(61). Treatment with GLP-1 reduced reactive oxygen species (ROS) and vascular cell adhesion molecule-1 mRNA expression in HUVEC after exposure to advanced glycation end products; furthermore, the activation of GLP-1R reduced tumor necrosis factor (TNF)-α, and decreased the expression of inflammatory genes. Sprague–Dawley rats treated with either GLP-1 or albiglutide exhibited a marked reduction in infarct size after temporary occlusion of the left anterior descending (LAD) coronary artery(62). The cardioprotective actions of GLP-1R agonists have also been demonstrated in large animal, where exenatide decreased infarct size, increased insulin levels, and improved LV systolic function in pigs subjected to 75 minutes of LAD coronary artery occlusion followed by 72 hours of reperfusion(63). In humans, GLP-1 infusion enhanced acetylcholine-induced forearm blood flow, while GLP-1 do not affect sodium nitroprusside–regulated blood flow(64). In humans, in subjects with diabetes on background metformin therapy, exenatide treatment for 16 weeks improves flow-mediated vasodilation of the brachial artery after 5 minutes of forearm ischemia compared with patients treated with glimepiride(65). In the context of left ventricular function, a 72-hour infusion of GLP-1 initiated 3.5 hours after coronary angioplasty within 6.5 hours from symptom onset in patients undergoing acute myocardial infarction (MI), improved LV ejection fraction (LVEF; 29±2% versus 39±2%), and regional myocardial wall motion(66). Acute infusion of GLP-1 30 minutes before dobutamine stress echocardiography and continuing for 30 minutes into recovery in 14 patients with stable coronary artery disease and normal resting LV function prevented the development of post-ischaemic myocardial dysfunction(67). Finally, the infusion of GLP-1 after completion of the first balloon occlusion reduced LV dysfunction during dual-inflation balloon angioplasty in 20 nondiabetic patients with single-vessel coronary artery disease(68). In patients undergoing percutaneous coronary intervention to treat ST-segment elevation MI, exenatide reduced infarct size relative to the ischemic area at risk and increased the myocardial salvage index assessed via cardiac magnetic resonance at ≈90 days postinfusion(69). Exenatide did not reduce mortality or improve LV contractility(70). In a study of 58 patients with ST-segment elevation MI and thrombolysis in MI flow grade 0, exenatide enhanced LVEF at 6 months post–percutaneous coronary intervention, and reduced infarct size at 1 month post–percutaneous coronary intervention(71). GLP-1RA exert favorable effect also on myocardial performance, although the findings are not consistent: 5-week infusion of GLP-1 in 12 patients (8 with T2DM) with New York Heart Association class III/IV heart failure improved LVEF, oxygen consumption, and 6-minute walk distance times(72). At variance, in a phase 2, double-blind, placebo-controlled randomized clinical trial of patients with established heart failure and reduced LVEF, liraglutide (1.8 mg/d) had no significant effect on the primary end point (time to death, time to rehospitalization for heart failure, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days)(73). A meta-analysis of 33 RCTs assessed the role of GLP-1RA on CV risk: no significant difference was found in terms of outcome as compared either to comparators or placebo, although this class of drugs is able to significantly reduce several risk factors for CVD such as body weight, blood pressure, total and HDL cholesterol(74). Notably, in all trials an increase in heart rate (1 to 4 bpm) was reported. Four CVOT are now available in which GLP-1 RA have been tested in high and very high-risk patients with T2DM: the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial, and the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial,

respectively(75-78). In the ELIXA, lixisenatide, and in the EXSCEL, exenatide qw, were neutral compared to placebo regarding the primary end-point (CV death, non-fatal MI and non-fatal stroke); on the contrary, in both LEADER and SUSTAIN-6, liraglutide and its weekly analogue semaglutide, were superior to placebo in reducing the risk for primary end-point. Liraglutide reduced the primary end-point by 13% , CV death by 22%, and by 15% all-cause death. In the SUSTAIN-6 the primary end-point was observed in 6.6% of patients randomized to semaglutide and in the 8.9% in those to placebo; CV and all-cause death were similar in the 2 groups while non-fatal stroke was significantly lower in patients randomized to semaglutide (HR, 0.61; 95% CI, 0.38 a 0.99; P=0.04). In the LEADER trial a was also observed significant reduction of nephropathy end-point in those randomized to liraglutide as compared to those on placebo (HR 0.78; 95% C.I. 0.67-0.92; p=0.003). Similarly, semaglutide was able to significantly decrease the risk of new or worsening nephropathy as compared to placebo (HR 0.64 95% C.I. 0.46-0.88; p=0.005). Thus, their CV effects appear more consistent with beneficial actions counteracting the mechanisms of plaque formation and progression rather than interfering with volume overload. In conclusion, GLP-1RA are beneficial for CV disease, although their effects appear not class-related: the differences in terms of CV protection within the class deserves further scrutiny, although the use of this class of drug overall is associated with lower mortality as compared to DPP-4 users or placebo or no treatment(79).

SODIUM GLUCOSE COTRASPORTER 2 INHIBITORS

High-capacity, low-affinity sodium glucose co-transporters (SGLT) 2 are located in the renal proximal tubular epithelium, and reabsorb filtered glucose. SGLT2 inhibition leads to glycosuria, and to a parallel insulin-independent reduction of HbA1c from 0.7% to 1.0% depending on the initial HbA1c value(80). The glucose loss links to a caloric loss, which accounts for a body weight loss ranging from 2 to 3 kg. SGLT2 inhibition induces a modest uricosuric effect. SGLT2s are responsible for roughly 5% of sodium reabsorption at the proximal tubule: their inhibition produces a natriuretic effect with a simultaneous decrease in plasma volume, blood pressure, and a contraction of circulating volume, thus reducing cardiac pre-load(81). SGLT2 inhibition increases sodium/chloride delivery to the macula densa, which activates tubule-glomerular feedback followed by afferent arteriolar vasoconstriction, and reduced intra-glomerular pressure. These intraglomerular effects may account for the reduction in albuminuria. In the presence of a reduction in eGFR (<45 ml/min/1.73 m2), the glucose-lowering effect observed with SGLT2 is blunted, although the natriuretic effect may persist: this effect probably accounts for most of the protective CV effects of these drugs, although several hypotheses have been proposed(82). Certainly, the combined sustained glucose-lowering effect, the osmotic diuresis, and the weight loss, all these concur to the CV protection, which has been shown by the two CVOT trials available for the SGLT2 inhibitors, the EMPA-REG and the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, respectively(83, 84). They demonstrate a significant reduction vs. placebo of the primary combined end-point (0.86; 95% C.I. 0.74-0.99 p=0.04 for EMPA-REG; 0.86; 95% C.I. 0.75-0.97 p=0.02 for CANVAS), and a reduction of hospitalization for heart failure (0.65 95% C.I. 0.500.85 p=0.002 for EMPA-REG and 0.67 95% C.I. 0.52-0.87 for CANVAS). Both studies were neutral for MI, fatal and non-fatal, and stroke, fatal and not fatal. Anticipated by their effects on renal physiology, both trials reported a consistent renal protection, while they do not exert any protection within the cerebral circulation despite their ability to decrease blood pressure. In a post-hoc analysis of the EMPA-REG study, after 12 week, the placebo-adjusted geometric mean ratio of UACR change from baseline with empagliflozin was -7% in patients with normoalbuminuria, -25% in patients with microalbuminuria, and -32% in patients with macroalbuminuria, thus suggesting that their positive effects on this condition parallel the severity of albuminuria(85). Their mechanism of action restricts their use for eGFR above 45 ml.min-1.1.73 m-2 but some preliminary reports indicate that their functional targets may not be restricted to normal eGFR. Similarly, in a prespecified exploratory analysis, canagliflozin treatment was also associated with a reduced risk of sustained loss of kidney function, attenuated eGFR decline, and a reduction in albuminuria (HR 0.53, 95% C.I. 0•33-0•84)(86). In the primary analysis of the EMPA-REG study, a non-statistical significant increase in stroke was noticed among patients randomized to empagliflozin; this issue has been further investigated, and in a sensitivity analysis based on events during treatment or ≤90 days after last dose of drug, the HR for stroke with empagliflozin versus placebo was 1.08 (95% C.I. 0.81-1.45; p=0.60). The comparative effects of canagliflozin among participants with and without a history of cardiovascular disease (secondary versus primary prevention) were assessed(87): this analysis shows that canagliflozin reduced cardiovascular and renal outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups. Further studies are needed to corroborate the efficacy of this class of drugs on CV risk reduction, independently of prevention stage. Based on the results of both EMPA-REG and CANVAS trials, beside the preeminent action on volume, their anti-atherosclerotic effect differs in different regions, and it appears to follow a U-shape curve: it is presently unknown whether this is determined either by a specific organ response to their action or by specific vascular regulation or by a different hierarchy in the negative influence of each different risk factor.

Interested has been upturned by the finding that SGLT2 inhibitors are capable to inhibit Na/H counter-transport in cardiomyocites with a consequent improvement in contractility(88): the clinical read-out for this observation needs further studies. In conclusion SGLT2-I is a new class of drugs with important, and positive effects, both direct and indirect, both on micro- and microcirculation, on CV system: it will be relevant to explore the possibility to

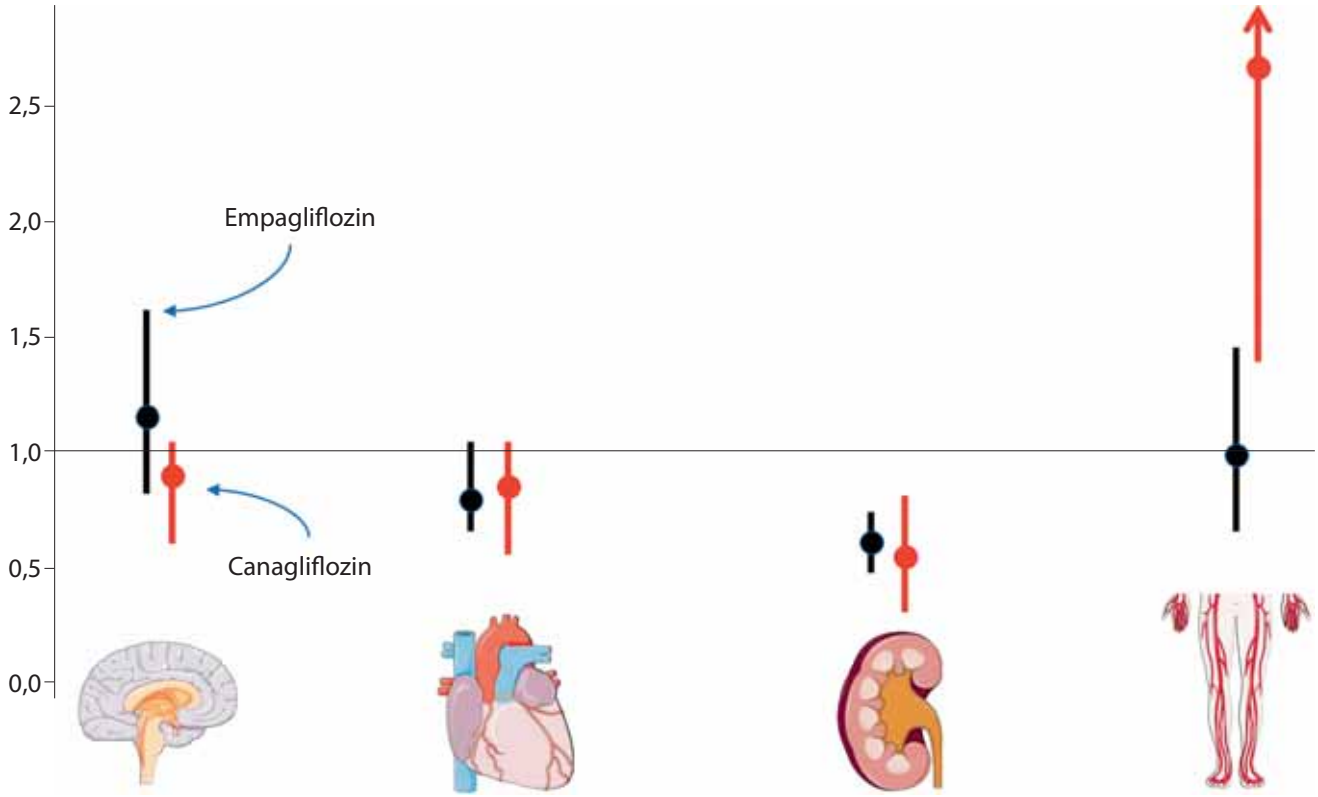

Fig. 2. The U-shaped Hazard ratio for stroke, myocardial infarction, kidney end-points, and amputation in EMPA-REG and CANVAS.

extend their use in the early phase of atherosclerotic of the CV continuum.

CONCLUSION

The recently introduced new classes of drugs, incretins and SGLT2-I, confer an increased CV protection on top of all other cardioprotective therapies. Importantly, this protection has been observed despite the presence of a consistent amount of older medications, since their safety has been assessed in patients with long-standing duration of diabetes: therefore, it is still matter of speculation whether they would show an even enhanced protection if they were used as a second drug therapy add-on to metformin or whether they would have been used earlier during the natural course of vascular disease. In the CVOT trials their protection has been observed in the presence of relatively limited glucose-lowering effect: therefore, one might speculate that other mechanisms account for their protection. Another hypothesis would be that the significant reduction in hypoglycemic episodes may also partly explained these findings. Without doubts both CVOT and real-world data should drive diabetologists toward a more tailored and safety approach to the prevention of CVD in patients with type 2 diabetes(89).

ADDITIONAL INFORMATION

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ИНФОРМАЦИЯ ОБ АВТОРАХ [AUTHORS INFO]

*__Angelo Avogaro__, MD, PhD, Professor of Endocrinology & Metabolism, Head Unit of Metabolic Diseases [address: 2, Via Giustiniani, 35128 Padova, Italy]; ORCID: http://orcid.org/0000-0002-1177-0516; e-mail: angelo.avogaro@unipd.it

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