The impact of glucose-lowering medications on cardiovascular disease

Angelo Avogaro, Saula Vigili De Kreutzenberg and Gian Paolo Fadini

Patients with type 2 diabetes mellitus die most frequently from cardiovascular disease. Metabolic control is mandatory both for preventing long-term complications and for reducing the negative effects of the exposure of the other risk factors. In this article, we will describe the most commonly used glucose-lowering agents, the pathophysiological mechanisms underlying their cardiovascular protection, the available evidence-based data for this protection, and the contraindications and potential adverse effects. *Cardiovasc Endocrinol Metab* 7:13–17 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Department of Medicine, Division of Metabolic Diseases, University of Padova, Padova, Italy

Correspondence to Angelo Avogaro, MD, Department of Medicine, Division of Metabolic Diseases, University of Padova, Via Giustiniani 2, 35128 Padova, Italy
Tel: +39 049 821 2178; fax: +39 049 821 7878;
e-mail: angelo.avogaro@unipd.it

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Introduction

Patients with type 2 diabetes mellitus (T2DM) die most frequently from cardiovascular disease (CVD) [1]. Modifications of life-style, blood pressure, and lipid control are, along with optimal glucose control, the main cornerstones of the treatment of these patients. Metabolic control is mandatory both for preventing long-term complications and for reducing the negative effects of the exposure of the other risk factors. To gain early, durable, and personalized glucose control, it is relevant, for each antidiabetic drug: (a) to understand the mechanisms underlying cardiovascular (CV) protection; (b) to recognize the evidence-based data for their CV protection; and (c) to appreciate contraindications and potential adverse effects.

Older drugs

Metformin

Metformin is the first-line agent for the cure of T2DM: nonetheless, it should be kept in mind that up to 30% of the patients are intolerant, and in as many as 21% of patients, metformin treatment fail to maintain metabolic control [2]. Its use is contraindicated when estimated glomerular filtration rate (eGFR) falls below 30 ml/min/1.73 m² [3]. Metformin activates the cellular energy sensor AMP-activated protein kinase, with consequent beneficial effects on endothelium [4]. Metformin gained popularity from the UKPDS-34: in 268 nonoverweight and overweight patients, this drug, compared with the conventional group, induced a risk reduction of 36% for all-cause mortality and of 39% for myocardial infarction (MI) [5]. A recent meta-analysis underlies a certain degree of uncertainty as to whether the drug reduced the risk of CVD [6]. Metformin also appears to be safe in patients with T2DM and heart failure (HF) [7], and, is

possibly linked to a better outcome [8]. Among patients initiating sulfonylureas (SU) for diabetes treatment versus metformin, the latter had a lower risk for HF and CV death [9]. In conclusion, in patients with T2DM and eGFR above 30 ml/min/1.73 m², with or without CVD and/or HF, metformin appears to be safe; it is debatable whether it might exert any direct CV protection [10].

Sulfonylureas and metiglinides

These classes of drugs stimulate insulin secretion by closing the ATP-sensitive potassium channels (KATP-channels) in the pancreatic β -cells [11]. However, the CV system also shares these KATP-channels: during ischemia, they open because of a decrease in the cytosolic ATP levels. SU block the opening of KATP-channels in myocardial and vascular smooth muscle cells, thus interfering with this cardioprotective mechanism, which is called ischemic preconditioning. However, in the UKPDS and the ADVANCE trials, there was no evidence for a direct detrimental effect of SU on the CV system [12,13]. More evidence is available from observational studies in which patients on SU treatment were more susceptible to CVD and hospitalization for heart failure (hHF) [9,14,15] although this is not consistently observed for all SU [16,17]. Inappropriate use of SU can be highly dangerous because of their ability to induce hypoglycemia [18,19], especially when added in addition to other secretagogues [20]. Repaglinides, a metiglinide, may interfere with ischemic preconditioning [21,22], although an excess of CV events was not observed in the NAVIGATOR trial in patients randomized to nateglinide [23]. In conclusion, SU and metiglinides may have direct detrimental effects during ischemia, but their adverse consequences on CV are probably mostly linked to their propensity to cause hypoglycemia.

Acarbose

Acarbose decreases glucose absorption by the gut by exerting a competitive inhibition of α -glycosidase, thus interfering with the intestinal hydrolysis of oligosaccharides. Its alleged positive action on CV is mainly mediated by a decreased postprandial glucose peak [24,25]. The 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 has been assessed in Chinese patients with impaired glucose tolerance and established CVD [30]. This study showed that acarbose did not reduce the risk of major adverse CV events, but did reduce the incidence of diabetes. In conclusion, there are not enough data to conclude that decreasing postprandial hyperglycemia with acarbose might prevent CVD in patients with T2DM.

Thiazolidinediones

Thiazolidinediones are activators of the nuclear receptors peroxisome proliferator-activated receptors (PPARs): they activate several genes, which increases the storage of fatty acids in adipocytes, thereby decreasing their levels in blood. PPAR γ modulate inflammation, especially in the context of the atherosclerotic process [31], and they stimulate cholesterol efflux transporter ABCA1 [32]. Among thiazolidinediones, pioglitazone is the most widely used since the negative reports on the others of the same class [33,34]. Pioglitazone has been shown to exert a direct anti-atherosclerotic effect in the arterial wall in humans [35,36]. In the PROactive study, involving 5238 patients with T2DM and 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 [37]. This protective effect has also been observed in insulin-resistant, non-diabetic patients [38]. Pioglitazone as the other PPAR γ induces fluid retention, edema, and sometimes precipitates or exacerbates HF in patients at risk for this condition [39]. 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 [40]. In conclusion, the most widely used PPAR γ , pioglitazone, exerts a direct, widespread, and protective vascular effect, which is, however, counterbalanced by an increased incidence of HF.

Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 inhibitors decrease plasma glucose in a glucose-dependent manner by increasing the circulating glucagon-like peptide 1 (GLP-1) by preventing its enzymatic degradation. These agents do not

significantly affect blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. However, they may improve endothelial dysfunction [41], increase the levels of circulating endothelial progenitor cells, and exert an anti-inflammatory effect by reduction of high-sensitivity C-reactive protein and modulation of monocyte-macrophage polarization toward an anti-inflammatory phenotype [42]. Three large prospective cardiovascular outcome trials (CVOTs) confirmed their CV safety [43–45]. Only in the SAVOR a significant 27% increase in hHF was observed in patients randomized to the saxagliptin group: this was not confirmed in real-world surveys [15,46].

Insulin

Insulin is the most powerful antidiabetic agent, with important effects also on the CV system [47,48]. The physiologic and positive effects of insulin on the CV system must not be equated with the negative effects of insulin resistance, a maladaptive condition, this, resulting from the progressive increase in insulin levels because of increased fat mass and sedentary life-style [49]. Insulin therapy may be needed in diabetic patients failing to secrete enough insulin in response to other glucose-lowering agents (β -cell failure). Although it worsens hyperinsulinemia, insulin therapy becomes essential to fully exert the metabolic effects of the hormone also in patients with insulin resistance. The only randomized-controlled trial, which explored the potential CV benefits of insulin, has been the ORIGIN trial [50], in which high-risk individuals with impaired fasting glucose, impaired glucose tolerance, or early diabetes were randomized to receive either glargine or placebo. The coprimary endpoint, CV death, or MI, or stroke was neutral (adjusted hazard ratio = 1.02; 95% confidence interval: 0.94–1.11) as was all-cause death. Recently, the DEVOTE trial has also shown that newer insulin with more protracted effects appears to be CV safe [51]. In conclusion, insulin exerts important CV effects, which are observed when the hormone is acutely administered. Its chronic administration appears to be CV neutral and is overall safe, except for an excess and expected incidence of hypoglycemic reactions.

Newer drugs

Glucagon-like 1 receptor agonist

GLP-1 is mainly secreted by the intestine in response to eating, but it is rapidly cleaved by dipeptidyl peptidase 4: to overcome this problem, either a mimetic or an analog of GLP-1 receptor agonist (RA) should be administered. They stimulate insulin secretion and decrease glucagon secretion without hypoglycemia.

These drugs significantly reduce, beyond glucose, several risk factors for CVD [52]. Trials have reported a mild increase in heart rate [53]. Four CVOTs (Table 1) are now available in which GLP-1 RA have been tested

Table 1 Antidiabetic drugs and major adverse cardiovascular end-points

	Drugs	Death because of any cause	CV death	Nonfatal MI	Nonfatal stroke	hHF	Renal outcome	Eye outcome
Efficacy trials	Metformin/pioglitazone/ sulfonylurea/insulin	Neutral	Neutral	↓17%	Neutral	Neutral	↓20%	↓13%
SAVOR	Saxagliptin	Neutral	Neutral	Neutral	Neutral	↑27%	Improved ^a	ND
EXAMINE	Alogliptin	Neutral	Neutral	Neutral	Neutral	Neutral	ND	ND
TECOS	Sitagliptin	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
ELIXA	Lixisenatide	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
LEADER	Liraglutide	↓15%	↓22%	Neutral	Neutral	Neutral	↓22%	Neutral
SUSTAIN-6	Semaglutide	Neutral	Neutral	Neutral	↓39%	Neutral	↓36%	↑76%
EMPAREG	Empagliflozin	↓32%	↓38%	Neutral	Neutral	↓35%	↓39%	Neutral
CANVAS	Canagliflozin	Neutral	Neutral	Neutral	Neutral	↓33%	↓40%	ND
EXSCEL	QW exenatide	↓14%	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

CV, cardiovascular; hHF, hospitalization for heart failure; MI, myocardial infarction; QW, once-weekly.

^aOn the basis of changes of microalbuminuria.

ND, not determined.

in high-risk and very high-risk patients with T2DM: the ELIXA, the LEADER, the SUSTAIN-6, and the EXSCEL trials [54–57]. Although in ELIXA, lixisenatide was neutral compared with placebo in terms of the primary endpoint (CV death, nonfatal MI, and nonfatal stroke), in the LEADER and SUSTAIN-6, both liraglutide and its weekly analog semaglutide were superior to placebo in the prevention of the primary endpoint. Liraglutide reduced the primary endpoint by 13%, CV death by 22%, and all-cause death by 15%. In the SUSTAIN-6, the primary endpoint was observed in 6.6% of patients randomized to semaglutide and in 8.9% in those randomized to placebo; CV and all-cause death were similar in the two groups, whereas nonfatal stroke was significantly lower in patients randomized to semaglutide. Remarkably, in both LEADER and SUSTAIN-6, the renal endpoint was also significantly lower in patients randomized to active drug [58]. In the EXSCEL trial, once-weekly exenatide marginally failed the primary endpoint in patients treated in both primary and secondary prevention, but could reduce all-cause mortality. Overall, GLP-1 RA are beneficial for CV protection, although possible differences within class needs deserve further scrutiny [59].

Sodium–glucose cotransporter-2 inhibitors

Sodium–glucose cotransporter-2 inhibitors (SGLT2) are present predominantly at the apical membrane of the renal proximal convoluted tubule, and are required for the 90% of glucose reabsorption. Their inhibition (30–50%) decreases the renal glucose threshold, thus favoring glycosuria and osmotic diuresis; SGLT2-I induces a decrease in the blood pressure by ≈ 5 mmHg especially in hypertensive patients, and increases the urine output (100–400 ml), whereas a natriuretic effect is limited and transient [60]. Glycosuria dissipates calories (200–300 kcal/day) through urine so that a loss in body weight also occurs. SGLT2-I not only improves several risk factors for CVD but also decreases the blood volume, with a parallel improvement in cardiac afterload and preload [61]. By increasing the availability of Na^+ and Cl^-

at the macula densa level, they favor the normalization of the tubular glomerular feedback, with the consequent afferent arteriolar vasoconstriction and reduction of intraglomerular pressure. Meta-analysis and real-world surveys have shown that SGLT2-I reduce all-cause mortality, major adverse CV events, and hHF [62–65]. The two available randomized-controlled trials with SGLT2-I, the EMPAREG-OUTCOME and the CANVAS studies, have shown a reduction in the primary combined endpoint and a reduction in hHF [66,67]. They have also reported renal protection, which may partly account for the CV protection [68,69], whereas they do not exert any protection within the cerebral circulation despite their ability to decrease blood pressure [70]. Their mechanism of action restricts their use for eGFR above 45 ml/min/1.73 m², but some preliminary reports indicate that their functional targets may not be restricted to SGLT2 [71]. In conclusion, SGLT2-I is a new class of drugs with important, and positive effects, both direct and indirect, on the CV system: it will be relevant to explore the possibility to extend their use in the early phase of atherosclerotic CVD.

Conclusion

The recently introduced new classes of drugs, GLP-1 RA and SGLT2-I, confer a CV protection in high-risk patients with T2DM: this may be intrinsic not only to their mechanism of action but it may also be linked to their ability to decrease HbA1c without inducing hypoglycemia. 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.

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Conflicts of interest

A.A. received honoraria for research grants, advisory boards and lectures from Novo Nordisk, Amgen, AstraZeneca, Boehringer-Ingelheim, Servier, Lilly, Sanofi, Takeda, Mediolanum, Merck Sharp & Dohme, Janssen, Menarini Diagnostics, Novartis, Bruno Farmaceutici. G.P.F. received honoraria for research grants, advisory boards and lectures

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