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Considerations on the cardiovascular effect of some oral antidiabetics

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Abbreviations
DM: diabetes mellitus
CVD: cerebrovascular disease
HbA1c: glycosylated hemoglobin
AMI: acute myocardial infarction
MACE: major adverse cardiovascular events

ABSTRACT
Type 2 diabetes mellitus is associated to high cardiovascular risk. Given the epidemic proportions it is reaching, treatment guidelines emphasize the need of preventing and reducing major adverse cardiovascular events as well as improving glycemic control, especially in the early stages of the disease. The drugs that decrease or regulate glucose have increased in recent years and, as a result, the treatment of type 2 diabetes mellitus has become increasingly changing and complex; therefore, it is important to know the different drugs that exist nowadays for the treatment of diabetes mellitus and their effects, both positive and negative, at a cardiovascular level. The current recommendations emphasize the individualization of glycemic targets.
Keywords: Diabetes mellitus, Antihyperglycemic agents, Cardiovascular risk

Consideraciones sobre el efecto cardiovascular de algunos antidiabéticos orales

RESUMEN
La diabetes mellitus tipo 2 se asocia a un elevado riesgo cardiovascular, dadas las proporciones epidémicas a las que está llegando; las guías de tratamiento ponen de relieve la necesidad de prevenir y reducir las complicaciones cardiovasculares y mejorar el control glucémico, especialmente en las etapas precoces de la enfermedad. Los fármacos que disminuyen o regulan la glucosa se han incrementado en los últimos años y, a consecuencia de ello, el tratamiento de la diabetes mellitus tipo 2 se ha vuelto cada vez más complejo y cambiante; por tanto, es importante conocer los diferentes medicamentos que existen hoy para el tratamiento de la diabetes mellitus y sus efectos, tanto positivos como negativos, a nivel cardiovascular. Las actuales recomendaciones hacen hincapié en la individualización de los objetivos glucémicos.
Palabras clave: Diabetes mellitus, antihiperglucemiantes, riesgo cardiovascular

Cardiovascular disease is the leading cause of death in the world. In 2010, according to the World Health Organization (WHO), cardiovascular disease accounted for 31% of all deaths worldwide. The main diseases associated with cardiovascular death are hypertension, coronary artery disease and cerebrovascular disease (CVD). Other cardiovascular risk factors are dyslipidemia, obesity, sedentary lifestyle, smoking, genetic factors[1], and diabetes mellitus (DM), which is associated with a higher risk of heart failure, hypertensive heart disease and a two-fold increase in mortality in men

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and three-fold increase in women compared to non-diabetics; hence, it is considered to be an equivalent of cardiovascular disease [2].

In 2015, the International Diabetes Federation recorded 415 million adults with DM and 317 with glucose intolerance, which was associated with 5 million deaths[3], which is why the WHO ranked it as the third risk factor for early mortality, after arterial hypertension and smoking.

Cardiovascular disease is the main cause of mortality and morbidity in patients with DM[4]. Therefore, it would be logical for an optimal glycemic control to reduce possible cardiovascular complications and cardiovascular mortality; however, the foregoing has only been shown to reduce morbidity with no impact on mortality[5]. This is precisely why effective therapies aimed not only at glycemic control but also at reducing cardiovascular complications have emerged as a necessity for patient management, something that has recently divided in two the history of DM treatment[4].

Knowledge of the different drugs available today for the treatment of diabetes mellitus −and their effects, both positive and negative on the heart− is crucial. For this reason, the different scientific societies and associations around the world have recommended that all drugs for the treatment of type 2 diabetes mellitus should be thoroughly evaluated and certified as heart-safe [4].

Metformin is the most widely used drug for the treatment of type 2 DM. It has a hypoglycemic effect by reducing hepatic glucose production and increasing its utilization, through induction of the enzyme adenosine monophosphate-activated protein kinase (AMPK)[4]. The benefits in glycemic control by reducing glycated hemoglobin (HbA1c) by approximately 1.5% compared to placebo have been documented[4,6]. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a lower risk of macrovascular and microvascular complications in overweight patients who underwent strict glycemic control on metformin therapy[7]. Long-term follow-up (10 years) of this population confirmed the benefits of the intensive strategy with this drug on glycemic control; mainly, in these patients, by achieving a decrease in the relative risk of acute myocardial infarction (AMI) (0.67; CI 0.51-0.89; p=0.005), DM-related death (0.70; CI 0.53-0.92; p=0.01) and death from any cause (0.73; CI 0.59-0.89; p=0.002). A Cochrane review in 2005 also concluded that metformin was superior in reducing outcomes associated with DM, −including all-cause mortality (p=0.03)[4]− and that this drug is safe in cardiac patients since it is even associated with a reduction in complications from this origin[4].

Thiazolidinediones are insulin-sensitizing drugs, since their mechanism of action is based on binding to the peroxisome proliferator-activated receptor (PPAR) expressed mainly in adipocytes, in the liver and, to a lesser extent, in the pancreas. Binding of thiazolidinediones (TZDs) to these receptors in the pancreas results in increased insulin synthesis and content in the pancreatic islets, increased expression of the glucose transporters GLUT-1 and GLUT-4 and increased glucose oxidation, which favors glucose utilization by reducing HbA1c by 0.5-1.4%[6]. These drugs has a neutral effect in terms of the risk of hypoglycemia and produces weight gain mainly due to fluid retention/edema, which is why they have also been associated with an increase in heart failure. Pioglitazone has been associated with a putative cardiovascular risk benefit, whereas rosiglitazone appears to be associated with major adverse cardiovascular events (MACE), with significant increases in the incidence of AMI and death from cardiovascular disease,[8-10] as well as heart failure and all-cause mortality[11]. On the other hand, the RECORD study found no significant differences in cardiovascular outcomes except for an increase in heart failure with the use of rosiglitazone (HR 2.24; 95% CI 1.27-3.97) and the Proactive study (pioglitazone), in patients at high cardiovascular risk, reduced all-cause mortality, non-fatal AMI and CVD (HR 0.84; CI 0.72-0.98; p=0.027), and has therefore been attributed a potential cardiovascular benefit[4].

Meglitinides are insulin secretagogues that act on adenosine triphosphate (ATP)-dependent potassium channels at the level of pancreatic beta cells. They decrease dose-dependent postprandial glycemia[6] and cause less late postprandial hypoglycemia[6]. This group achieves a decrease in HbA1c of 1.5%, although it is lower with nateglinide[4]; its most important adverse effect is hypoglycemia, especially in patients with compromised renal function[12]. Its use −in terms of cardiovascular effect− reported a higher incidence of MACE (including ischemia) when compared to glibenclamide; however, it should be clarified that the patients studied in the repaglinide group had more severe underlying coronary artery disease than those in the glibenclamide group[4]. When compared to metformin, meglitinide was found to be less effective in reducing endothelial dysfunction in type 2 DM non-obese patients despite having the same glycemic control[13]. The Left Ven-

tricular Dysfunction in Type 2 Diabetes (DYDA) study[14] showed that repaglinide is an independent predictor of left ventricular dysfunction after two years follow-up in patients without underlying heart disease, although its role in left ventricular dysfunction remains unknown. The evidence presented is insufficient to conclude that meglitinides have any negative cardiovascular effects on patients with type 2 DM; nevertheless, this group of drugs remains a pharmacological option as combined or triple therapy for the treatment of type 2 DM[15].

Sulfonylureas act mainly by stimulating insulin secretion by pancreatic beta cells, achieving HbA1c reductions of 1.5 to 2% as long as there is a functioning pancreas[4]. Strict control with sulfonylureas has been shown to reduce the risk of microvascular complications, but does not have an impact on DM-related mortality or the occurrence of AMI at 10 years[16]. Compared to metformin, its use for the initial treatment of diabetes has been associated with an increase in MACE, a higher incidence of AMI, CVD or death, and with a number of cardiovascular events of 18.2 and 10.4 per 1000 persons annually in sulfonylurea and metformin users, respectively (HR 1.21; 95% CI 1.13-1.30)[16]. This is due to inhibition of myocardial ATP-dependent potassium channels or sulfonylurea 2A receptors, which decreases myocardial response to ischemia[16], which is associated with arrhythmias and increased cardiovascular mortality[4]. Meanwhile, the Nationwide study found that glimeperide, glibenclamide and glipizide monotherapy appears to be associated with an increase in cardiovascular mortality compared to metformin; however, gliclazide was associated with a lower risk[17]. Furthermore, the increased risk of hypoglycemia with the use of this pharmacological group limits its use in the treatment of diabetes. Although the evidence is not conclusive, certain societies recommend avoiding them in patients at high cardiovascular risk; even recent Colombian guidelines do not consider their use, especially that of glibenclamide as monotherapy[4]. GLP-1 agonists belong to the group of incretins, endogenous hormones secreted by the L cells of the small intestine after food intake, which bind to GLP-1 receptors on the beta cells of the pancreas and stimulate insulin secretion[18]. This pharmacological group is key in the treatment of DM as its benefit against MACE has been demonstrated[19,20]. The LEADER study (liraglutide), in which 81% of the population had known cardiovascular disease, demonstrated a significant reduction in MACE (HR 0.87; 95% CI: 0.78-0.97; p< 0.001; p=0.01 for superiority), cardiovascular death (HR 0.78; 95% CI: 0.66-0.93; p=0.007) and death from any cause (HR 0.85; 95% CI: 0.74-0.97; p<0.001), with no significant difference for non-fatal AMI, CVD and heart failure[21].

Meanwhile, semaglutide demonstrated reduction in MACE (HR 0.74; 95% CI: 0.58-0.95; p<0.001 for non-inferiority; p=0.02 for superiority) and non-fatal CVD (HR 0.61; 95% CI: 0.38-0.99; p=0.004), with no significant reduction for cardiovascular death, non-fatal AMI and heart failure, with significant increase in retinopathy (HR 1.76; 95% CI: 1.11-2.78; p=0.02)[22]. Other drugs such as lisixenatide failed to show a reduction in MACE (HR 1.02; 95% CI 0.89-1.17)[20], while exenatide (Exenatide Study of Cardiovascular Event Lowering Trial - EXSCEL) did not achieve a reduction in cardiovascular mortality[23]. The above suggests that MACE reduction does not belong to the treatment class and that liraglutide is considered the drug with the best safety profile in this group[4].

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a group of drugs with a glucosuric effect, which results in a 0.5-0.7% decrease in HbA1c[24]. Their cardiometabolic profile with a decrease in triglycerides, increase in HDL (high density lipoprotein), improvement in insulin resistance and, therefore, in atherosclerosis and hemodynamic profile, plus a decrease in blood pressure, give this group a high expectation in the reduction of MACE[24], which was confirmed by the study with empagliflozin (EMPA-REG OUTCOME) in patients with type 2 DM and existing cardiovascular disease, where a 14% reduction in AMI, CVD and cardiovascular death was observed, and a 38% reduction in cardiovascular death alone. Canagliflozin in the CANVAS study reduced the incidence of cardiovascular death, AMI and non-fatal CVD (HR 1.27; 95% CI: 0.75-0.97; p<0.001 for non-inferiority, p=0.02 for superiority), without achieving individual reductions in cardiovascular death, CVD and AMI. Furthermore, an increase in amputations (6.3 vs. 3.4%; p<0.001) and fractures (15.4 vs. 11.9%; p=0.02)[25] was observed. In addition to the favorable cardiometabolic and hemodynamic profile of these drugs, there are other theories associated with their favorable cardiovascular effects, such as the theory of mild ketogenesis, since SGLT2 inhibitors derive glucose metabolism to fatty acid oxidation and generate an increase in ketones. The heart eagerly extracts ketone bodies to generate ATP, so that their oxidation increases cardiac muscular efficiency and this is reflected in the reduction of cardiovascular mortality and morbidity[24]. This seems to be a proba-

ble treatment class effect; however, each drug shows a different safety profile in clinical studies and additional cardiovascular safety studies including the remaining molecules are needed[4].

Dipeptidyl-peptidase 4 inhibitors are drugs that increase the incretin effect, which triggers pancreatic insulin secretion, an effect that is dependent on glucose levels (a great clinical advantage, as they do not produce hypoglycemia) and also inhibit postprandial increase in glucagon. These are effective drugs, with neutral effect on weight, which provide some improvement in beta-cell function and various markers of cardiovascular risk[26]. Until now, non-inferiority studies (aimed at assessing safety) had appeared, such as Savor Timi and Examine, which did not show an increase in MACE, although there was an increase in admissions for heart failure in the former; but the TECOS study[27] has been published, in this case with sitagliptin, and in this study no differences were observed in any of the defined cardiovascular objectives, nor in admissions for heart failure. The sitagliptin group required fewer requirements for other antihyperglycemic drugs, a longer time until new drugs were added, and a lower rate of insulinization. Neither were significant differences reported in cases of pancreatitis, nor a relationship with pancreatic and thyroid cancer[27], as had been previously suggested.

A study published in 2012 on the cardiovascular effects and safety of hypoglycemic drugs stated: "Considering that the primary objective of DM treatment is not to normalize glycemia but to prevent its complications, it is striking that the data available to date on the cardiovascular effect of the different hypoglycemic drugs are scarce and inconsistent, especially for what we could call "hard" endpoints. This fact, together with the publication of the data that led to the withdrawal of rosiglitazone, led to a change in the conditions required for approval of the different drugs by the regulatory agencies. Since then, the designs of phase III clinical trials have been modified to allow more consistent meta-analyses to be carried out and post-marketing cardiovascular safety mega-trials have been launched. This "policy" change has and will generate new data that may change the treatment paradigm for diabetes mellitus in the future[28].

In view of the above, it has been shown that adequate glycemic control is associated with favorable repercussions in terms of the prevention of microvascular complications. However, with regard to macrovascular involvement, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Control Evaluation (ADVANCE) studies failed to demonstrate a decrease in the incidence of macrovascular events despite intensified treatment, even with significant reduction in HbA1c levels. In addition, some hypoglycemic therapies have been shown to be associated with an increase in cardiovascular risk. Therefore, the need for new therapeutic strategies to attenuate the vascular risk that characterizes diabetic patients is recognized[29].

The different characteristics of the participants in the clinical studies should be taken into account for an accurate comparison of the results. In this regard, when analyzing those studies in which patients had experienced previous coronary events, the incidence of this combined endpoint varies between 9% (PROVE-IT-TIMI 22 study) and 14% (TIMI 38 study)[29].

In contrast, in those protocols in which individuals with diabetes and a high risk of coronary events, —without a history of established cardiovascular disease—, participated, this rate was 4%.

In addition to the history of coronary artery disease, follow-up time is another important variable for results interpretation. In this regard, exposure to a drug with a potential cardioprotective action may require a prolonged period of exposure to achieve reversal of the atherosclerosis process. In the United Kingdom Prospective Diabetes Study, 10 years follow-up from the initial intervention was necessary to demonstrate the benefits of intensified glycemic control on cardiovascular risk in subjects with recently diagnosed diabetes and low initial cardiovascular risk.

In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)[30] trial, the effect of a DPP-4 inhibitor (dipeptidyl peptidase 4 [alogliptin]) was analyzed in diabetic patients with an early coronary event. The EXAMINE study was designed to evaluate the non-inferiority of this drug (n=2701) to placebo (n=2 679), in terms of MACE (cardiovascular mortality, non-fatal AMI, non-fatal stroke).

Patients –with type 2 diabetes and a recent history of unstable angina or AMI, requiring hospitalization in the 15 to 90 days prior to the beginning of the study– participated. Alogliptin or placebo was added to the usual treatment of diabetes. After a median 18-month follow-up, MACE were described in 11.3% of individuals treated with alogliptin and 11.8% of participants receiving placebo (hazard ratio [HR] 0.96;

upper limit of confidence interval: 1.16; p<0.001 for non-inferiority).

HbA1c values were significantly lower for the intervention group compared to placebo (mean difference: -0.36%; p<0.001). In contrast, no differences were demonstrated between the two groups in terms of the incidence of hypoglycemia, cancer, pancreatitis or dialysis initiation. The EXAMINE study, therefore, proved that in patients with type 2 diabetes at high vascular risk, the administration of DPP-4 inhibitors did not increase the incidence of MACE, compared to placebo[30].

In the last two decades, an increasing number of drugs with a proven antihyperglycemic effect have been incorporated. None of them, with the exception of metformin, had achieved a relevant impact on the reduction of these macrovascular events[31].

During periods when individuals with non-diabetic dysglycemia (prediabetes) are detected, the use of new drugs such as glinides (NAVIGATOR study)[31] or long-acting insulin analogs (ORIGIN study) has not been shown to have an impact on reducing cardiovascular risk[32]. In the BARI 2D study, no benefit in overall or MACE-free survival was demonstrated when comparing the use of insulin or drugs that improve insulin sensitivity[31]. Data from the United Kingdom Prospective Diabetes Study demonstrated the impact of satisfactory glycemic control on vascular complications. An analysis of these data estimated that a 1% decrease in HbA1c correlated with a 21% reduction in the risk of diabetes-related deaths (p<0.0001), a 37% reduction in the risk of microvascular complications (p<0.0001), and a 14% reduction in the risk of AMI (p<0.0001). These risk-impacting reductions form the basis of diabetes therapeutic principles that recommend aggressive targets for HbA1c control in individuals with type 2 DM[31].

Follow-up of the cohort included in this study has shown that intensive glycemic control with combinations of drugs, such as insulin and sulfonylureas, can be associated with a 15% reduction in the incidence of new AMI, and in all causes of mortality by another 13%, which reinforces the concept that glycemic control, from the onset of the disease, leaves a metabolic benefit that is expressed as memory in the vascular territory. This same team of researchers was one of the first to demonstrate that patients treated with metformin had a greater reduction in the relative risk of AMI (33%) compared to those who received insulin or sulfonylureas (15%)[33].

At present, there are several oral antidiabetic drugs, so when choosing pharmacotherapy, each patient should be individualized and specific characteristics such as body weight, renal function, age and cardiovascular risk should be taken into account, knowing that the latter accounts for a large number of deaths in diabetic patients. It is now known that liraglutide (GLP-1 agonist) and empagliflozin (SGLT2 inhibitor) are associated with a decrease in MI, non-fatal MI and cardiovascular death, so that patients at high cardiovascular risk should ideally receive either of these drugs in combination with metformin, provided there is no contraindication for either of them, since the latter continues to be the mainstay in the treatment of type 2 DM, not only because of its efficacy but also because of its cardiovascular safety profile and low cost[4].

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