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LARGE CLINICAL TRIALS THAT DEMONSTRATED A DECREASE IN CARDIOVASCULAR RISK THROUGH THE USE OF ANTIDIABETICS

GRANDES ESTUDOS CLÍNICOS QUE DEMONSTRARAM REDUÇÃO DE RISCO CARDIOVASCULAR ATRAVÉS DO USO DE ANTIDIABÉTICOS

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ABSTRACT

In recent years, breakthroughs in therapeutic findings for DM2 have encouraged physicians and specialists with regards to the reduction of cardiovascular events, hospitalization and mortality. Other studies are underway, and promise to strengthen the prospects of change in cardiovascular outcomes for this population. The goal of this review is to bring together the most important clinical trials that have demonstrated safety and/or a decrease in cardiovascular events with the use of antihyperglycemic drugs.

Keywords: Diabetes mellitus type 2; Cardiovascular risk; Insulin.

RESUMO

Nos últimos anos, os avanços nas descobertas da terapêutica para o DM2 entusiasmaram os clínicos e especialistas no que diz respeito à redução dos eventos cardiovasculares, internações e mortalidade. Outros estudos ainda estão em andamento e prometem fortalecer a expectativa de mudança nos desfechos cardiovasculares dessa população. O objetivo dessa revisão consiste em reunir os principais estudos clínicos que demonstraram a segurança e/ou redução na ocorrência de eventos cardiovasculares com uso de fármacos anti-hiperglicemiantes.

Descritores: *Diabetes mellitus tipo 2; Doenças cardiovasculares; Insulina.*

INTRODUCTION

Since the discovery of insulin over a century ago, whose therapeutic use has significantly increased the survival rate of carriers of diabetes mellitus, the association of this disease with cardiovascular diseases (CVDs) is known. This association has been strongly evidenced over the last decades because the presence of diabetes classifies the individual as high risk for cardiovascular mortality.[1] The prevalence of type 2 diabetes mellitus (DM2) has increased worldwide in recent years alongside CVDs, including coronary artery disease, encephalic vascular accidents, and peripheral artery disease, which constitute the main causes of death in this population[2]. Compared with the general population, diabetic individuals have an increased risk of cardiovascular events by three to four times and twice the risk of death due to cardiovascular causes.

Over the years, appropriate glycemic control in the diabetic population has shown more-significant benefits in reducing microvascular events than in reducing macrovascular outcomes. Metformin, regardless of whether associated with other classes of antihyperglycemic agents, was administered in most studies on cardiovascular efficacy and protection.[4-13]

The development of new drugs, sustained by increased physiopathological knowledge of DM2, enlivens the outlook that antihyperglycemic agents can go beyond glycemic control and provide even greater cardiovascular protection. Despite all the initial enthusiasm, problems were observed concerning the cardiovascular safety of these drugs. In 2007, a meta-analysis that focused on the use of rosiglitazone in >14,000 patients with DM2 generated controversy in demonstrating a 43% increase in the risk of myocardial infarction in diabetic patients taking this medication.[14] Another meta-analysis, which included other thiazolidinediones, unveiled increased aggravation to the clinical condition of patients with heart failure.[15,16] With regard to sulfonylureas, different meta-analyses and reviews questioned the cardiovascular safety of its use in clinical practice. It is important to highlight that many of these publications involved retrospective analyses and the use of several formulations, thus limiting the definitive interpretation based on these findings. Before this scenario, in 2008, the American regulatory authority, the Food and Drug Administration (FDA), determined that the new antidiabetics had been appropriately evaluated concerning their cardiovascular safety, especially in DM2 patients with elevated cardiovascular risk. In 2012, the European Medicines Agency also adhered to the same recommendation.

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MAIN TRIALS IN DIABETES AND CVDS

Metformin

Produced in the mid-1950s, metformin is a significant discovery for the treatment of DM2 and became the first-rate drug in DM2 therapy and continues to be so to the present day.

Even though studies on safety have not been required for metformin, vast clinical experience, and pharmacovigilance with this drug points to the potential protective benefits of the drug in the long term.

The UK Prospective Diabetes Study from the 1990s showed that early introduction of metformin in patients with DM2 reduced the incidence of vascular complications related to DM by 32%, myocardial infarction by 39%, diabetes-related death by 42%, and mortality by all causes at 36%. Subsequent studies also demonstrated similar effects, proving that metformin offers a protective effect against cardiovascular outcomes in DM2 patients.[6] The probable mechanism for this effect may be explained by the improved profile of lipoproteins, decreased plasma-free fatty acid concentration, and total and LDL cholesterol levels, in addition to increased HDL cholesterol levels. Furthermore, metformin was shown to reduce hypercoagulation and increase fibrinolysis in states of insulin resistance. Moreover, metformin may reduce plaque buildup, inflammation in atheromatous plaques, and the oxidative stress of endothelial cells.

DDP-4 Inhibitors

The clinical studies that assessed cardiovascular events using DDP-4 inhibitors were as follows: SAVOR-TIMI (*Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction*) in 2013, EXAMINE (*Examination of CV Outcomes with Alogliptin versus Standard of Care*) in 2013, and TECOS (*Trial Evaluating CV Outcomes with Sitagliptin*) in 2015, which examined saxagliptin, alogliptin, and sitagliptin, respectively, in diabetic patients with high cardiovascular risk. Seventy-eight percent of the patients in the SAVOR-TIMI study and 100% of the patients in the EXAMINE and TECOS studies presented with preexisting CVD.

The SAVOR-TIMI study randomized 16,492 patients with DM2 with a history or increased risk of CVD to receive saxagliptin or placebo for a mean period of 2.1 years. No significant reduction was observed for the primary outcome (cardiovascular death, myocardial infarction, or ischemic encephalic vascular accident) in the saxagliptin group in comparison with the placebo group (7.3% vs. 7.2%; relative risk [RR] with saxagliptin, 1.00; 95% confidence interval [CI], 0.89–1.12; $p = 0.99$ for superiority and $p < 0.001$ for non-inferiority). The secondary composite outcome (cardiovascular death, myocardial infarction, encephalic vascular accident, hospitalizations for unstable angina, coronary revascularization, or heart failure) occurred in greater numbers in the saxagliptin group than in the placebo group (12.8% vs. 12.4%; RR, 1.02; 95% CI, 0.94–1.11; $p = 0.66$). The number of hospitalizations for heart failure was greater in the saxagliptin group than in the placebo group (3.5% vs. 2.8%; RR, 1.27; 95% CI, 1.07–1.51; $p = 0.007$).[17,18]

A total of 5,380 DM2 patients with a recent history of acute myocardial infarction or unstable angina were randomized in the EXAMINE study for the use of alogliptin or placebo associated with conventional treatment. It was a noninferiority study with a primary composite outcome of death by cardiovascular causes, nonfatal myocardial infarction, or nonfatal encephalic vascular accident. The primary outcome occurred in 11.3% of the alogliptin group and 11.8% of the placebo group (RR, 0.96; maximum CI limit of 1.16; $p < 0.001$ for non-inferiority and $p = 0.32$ for superiority).[19]

The TECOS study evaluated 14,671 patients with DM2 with established CVD and allocated them to use sitagliptin or placebo, and demonstrated the non-inferiority in the primary composite outcome of cardiovascular mortality, nonfatal myocardial infarction, nonfatal encephalic vascular accident, or hospitalization for unstable angina (RR, 0.98; 95% CI, 0.88–1.09; $p < 0.001$). Unlike the two previous studies, the TECOS study presented greater cardiovascular safety with the use of sitagliptin to treat the DM2 patient in preventing the increased risk of cardiac arrest.[20]

All these clinical studies with DPP-4 inhibitors reached noninferiority as compared with placebo regarding major cardiovascular events, suggesting that saxagliptin, alogliptin, and sitagliptin are neutral drugs from a cardiovascular standpoint. Superiority in protection from major cardiovascular events was not achieved with any of these drugs, which led to questions as to whether a study with a longer duration (>3 years) may evidence some benefit. In 2016, the FDA alerted to eventual risks of heart failure from the use of alogliptin and saxagliptin.

GLP-1 Agonists

As for GLP-1 agonists, for at least two decades, the potential beneficial effects of this class of drugs on the cardiovascular system have been studied. Recent studies evaluated the drugs lixisenatide, exenatide, liraglutide, and semaglutide.

The ELIXA (*Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome*) study in 2015 compared the effect of lixisenatide to that of placebo in 6,068 patients with DM2 with acute coronary syndrome. The primary composite outcome was death due to cardiovascular causes, nonfatal myocardial infarction, nonfatal encephalic vascular accident, or hospitalization for unstable angina, which had an incidence of 13.4% in the lixisenatide group and 13.2% in the placebo group (RR, 1.02; 95% CI, 0.89–1.17; $p < 0.001$ for noninferiority and $p = 0.81$ for superiority). These data indicate that in DM2 patients with prior acute coronary syndrome, the use of lixisenatide was not inferior to that of placebo. While this medication failed to present superiority compared with placebo, in this study, cardiovascular safety was achieved, with a neutral effect on hospitalizations for heart failure.[22]

The EXSCEL (*Exenatide Study of Cardiovascular Event Lowering trial*) study in 2017 compared the effects of weekly administrations of exenatide (2 mg subcutaneously) associated with the usual treatment in isolation. The study considered the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal encephalic vascular accident in adult DM2 patients with potential cardiovascular risk. The use of exenatide did not increase the incidence of major cardiovascular events or the composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal encephalic vascular accident compared with the use of placebo (RR, 0.91; 95% CI, 0.83–1,0; $p < 0.001$ for noninferiority). Nonetheless, the EXSCEL study failed to illustrate any cardiovascular benefits in the placebo group.[24]

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

(SUSTAIN 6) assessed cardiovascular safety in 3,297 DM2 patients randomized for the use of semaglutide and placebo. Eighty-three percent (n = 2,735) of the patients presented with established CVD and/or chronic kidney disease. Semaglutide exhibited both noninferiority and superiority with primary composite outcomes of cardiovascular death, nonfatal AMI, and nonfatal CVA (6.6% vs. 8.9%; RR, 0.74; 95% CI, 0.58–0.95; p < 0.001 for non-inferiority and p = 0.02 for superiority), with the decrease supported by the lower rate of nonfatal CVA (1.6% in the semaglutide group vs. 2.7% in the placebo group; RR, 0.61; CI 95%, 0.38–0.99; p = 0.04). The risk of cardiovascular death was similar between the treated and placebo groups (2.7% vs. 2.8%; RR, 0.98; 95% CI, 0.65–1.48). In the second composite outcome of cardiovascular death, nonfatal AMI, EVA, revascularization (coronary or peripheral), or hospitalization due to unstable angina or heart failure, semaglutide was superior to placebo (RR, 0.74; 95% CI, 0.62–0.89). No significant difference was found between the groups in relation to mortality by all or cardiovascular causes (RR, 1.05; 95% CI, 0.74–1.50 and RR, 0.98; 95% CI, 0.65–1.48, respectively), and for hospitalizations for heart failure (RR, 1.11; 95% CI, 0.77–1.61). Nephropathy occurred in 3.8% of the group receiving semaglutide and in 6.1% in the placebo group (RR, 0.64; 95% CI, 0.46–0.88; p = 0.005).[28]

The LEADER (*Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes)* study in 2016 was designed to examine the cardiovascular safety of liraglutide in a diabetic population with elevated cardiovascular risk. It was a long-term, multicentered, randomized, double-blind study controlled by placebo. The primary composite outcome was death by CVD, nonfatal myocardial infarction, or nonfatal cerebrovascular accident. Hierarchical noninferiority was first determined for the superiority hypothesis between liraglutide and placebo. For the study, 9,340 patients were randomized, of which >10% (approximately 900 individuals) received medical follow-up for 3.8 years. The results show a considerable reduction of 13% (95% CI, 0.78–0.97; p < 0.001 for non-inferiority and p = 0.01 for superiority) in the risks of the primary outcome in the liraglutide group as compared with the placebo group. Moreover, a decrease of 22% in deaths due to cardiovascular causes was observed in the group of patients who received liraglutide as compared with the placebo group (95% CI, 0.73–0.97; p = 0.02). A significant reduction of 16% was also observed in microvascular events (95% CI, 0.73–0.97; p = 0.02). This decrease was due mainly to the expense of the first renal event where there was a 22% decrease (95% CI, 0.67–0.92; p = 0.003). Recently, data were published on subgroups of patients from the LEADER study with chronic kidney failure and individuals aged >75 years. In both subgroups, there was consistency in maintaining the safety and reduction of cardiovascular outcomes. The difference in the observed reduction in cardiovascular events in the LEADER and SUSTAIN studies could be related to the homology that these molecules have with human GLP-1 (>90%).[23]

Sodium-Glucose Cotransporter-2 Inhibitors

In 2015, the use of a new class of antidiabetics, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, in the renal tubule brought exciting results. The Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study compared the effects of empagliflozin in doses of 10 to 25 mg with those of placebo on cardiovascular and overall mortality in 7,020 DM2 patients with a heightened risk of cardiovascular events and a glomerular filtration rate of at least 30 mL/min, as estimated by the MDRD equation, who had been receiving standard antihyperglycemic treatment. The EMPA-REG OUTCOME study compared the effects of empagliflozin in doses of 10 to 25 mg to placebo on cardiovascular and overall mortality in 7,020 DM2 patients with a heightened risk of cardiovascular events and a glomerular filtration rate of at least 30 mL/min, as estimated by the MDRD equation, and who had been receiving standard antihyperglycemic treatment. The primary composite outcomes were cardiovascular death, nonfatal myocardial infarction, and nonfatal CVA. The mean period for observation was 3.1 years. The results of EMPA-REG revealed a 14% decrease in primary outcomes in the group of patients who received empagliflozin as compared with the placebo group (95% CI, 0.74–0.99; p = 0.04 for superiority). In addition, the group that received empagliflozin had a considerably lower cardiovascular mortality rate (3.7% vs. 5.9% in the placebo group; 38% reduction in RR) and a 32% reduction in mortality by all causes. In relation to heart failure, the use of empagliflozin compared with placebo was associated with reduced hospitalization for heart failure (2.7% vs 4.1%; 35% reduction in RR) and reduced mortality by all causes (5.7% vs 8.3%; 32% decrease in RR). No significant differences in myocardial infarction and cerebrovascular accident rates were found between the groups. The incidence rate of genital infection increased, but that of other adverse events did not.[25]

It is important to emphasize that these benefits were observed in a population with established CVD, most of which were receiving appropriate treatment to control the risk factors of CVDs, where controlling blood pressure and dyslipidemia came close to the objectives established by the guidelines.

Two years later, in August 2017, the CANVAS (*Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes)* study was published, which compared the use of canagliflozin with placebo in 10,142 DM2 patients with heightened cardiovascular risk. The primary outcome was death by cardiovascular causes, nonfatal myocardial infarction, and nonfatal encephalic vascular accident. Nearly 65% of the patients presented with a history of CVD and 14% presented with heart failure. The rate for the primary outcome was lower in the canagliflozin group than in the placebo group (26.9 vs. 31.5 participants for 1,000 patient-years; RR, 0.86; 95% CI, 0.75–0.97; p < 0.001 for non-inferiority and p = 0.02 for superiority). The drug also had potential benefits in the progression of albuminuria (RR, 0.73; 95% CI, 0.67–0.79) and the composite outcome with reductions in the glomerular filtration rate, need for renal substitution therapy, or death by renal causes (RR, 0.60; 95% CI, 0.47–0.77), and hospitalization for heart failure (RR, 0.67; 95% CI, 0.52–0.87). Notwithstanding, the CANVAS study presented nearly twice the number of amputations, most of which went as high as the metatarsus (6.3 *vs.* 3.4 cases for 1,000 patient-years; RR, 1.97).[26]

It is interesting enough that the decrease in HbA1c level with the use of empagliflozin and canagliflozin was modest, approximately 0.5% and 0.58%, respectively. Many other clinical studies were not capable of showing a reduction in major cardiovascular events with intense glycemic control. Therefore, the real mechanism that brought the cardiovascular benefits with the use of SGLT-2 inhibitors remains unclear.

On the basis of the results of the observed patients in the EMPAREG and LEADER studies, the guidelines of several international societies and even the Combined Guidelines of the Brazilian Societies for Endocrinology, Diabetes, and Cardiology recommend the utilization of empagliflozin and liraglutide in high-risk diabetic patients to lower cardiovascular mortality.[27]

CONCLUSION

The decision over which class of antihyperglycemics to use must be grounded on several aspects such as contraindications, adverse effects, dosage, and costs. Since the controversy with rosiglitazone in 2008, which unveiled an increase in the risk for heart failure, the scientific medical community turned their attention to the cardiovascular safety of antihyperglycemic agents. Thus, for DM2 patient with CVD, the choice in medication must prioritize factors associated with the prevention of outcomes of clinical interest, such as death, myocardial infarction, and heart failure. The current scientific evidence assures the safety of new classes of antihyperglycemic agents in patients with CVDs. Among the medications examined, empagliflozin, canagliflozin, liraglutide, and semaglutide were shown not only to be safe but also to reduce cardiovascular risks and death. This evidence changed paradigms in diabetes treatment in patients with CVDs, thus offering prospects to increase survival rates in this population.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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