Case Study

THE IMPACT OF ANTI-DIABETIC DRUGS IN CARDIOVASCULAR OUTCOMES

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Introduction:

In most developed countries, Cardiovascular diseases (CVD) remain the main cause of morbidity and mortality in the general population, especially among the elderly.[1] People with Diabetes mellitus (DM) are on average at double the risk of CVD.[2] Cardiovascular disease (CVD) prevention includes all the actions intended to eliminate or reduce the impact of these disorders and their disabilities in the population or even targeted at individuals. The goal of this editorial is to review the pharmacological strategies aimed to control blood glucose that was proven to be useful in preventing death related to CVD or other important cardiovascular outcomes (i.e. myocardial infarction, stroke or renal impairment).

Keywords: Cardiovascular mortality, Cardiovascular prevention, Diabetes mellitus.

Discussion:

The results from the UKPDS 34 Trial supports the systematic and current use of metformin as a first-line drug therapy for patients with DM. This study established the great importance of intensive glucose lowering with this drug in order to promote CVD risk reduction in patients with DM. In this important and historical trial, 1.704 overweight patients with newly diagnosed T2DM were randomized to one of three arms: conventional therapy with diet alone, intensive therapy with metformin, or intensive therapy with early-generation antiglycemic agents (chlorpropamide, glibenclamide, or insulin). The primary analysis compared metformin to diet alone, with a secondary analysis comparing metformin to intensive therapy with the other agents. With a median follow-up of 10.7 years, metformin was associated with a reduction in DM-related complications and all-cause mortality when compared to the other two arms of therapy.[3] These benefits persisted for an additional 10 years of follow-up.[4] The benefits of metformin monotherapy in overweight patients with T2DM was further solidified by a 2005 Cochrane review of 29 randomized trials comparing metformin to conventional therapy with diet or other modern antiglycemic agents. This meta-analysis demonstrated a benefit for metformin monotherapy throughout a diverse range of outcomes including glycemic control, weight loss, lipid and blood pressure control, diabetes-related mortality, all-cause mortality, and incidence of myocardial infarction.[5]

Since the publication of UKPDS 34, several generations of antiglycemic agents have been developed, and direct comparisons with metformin have been made both prospectively and retrospectively. The large multicenter Spread-Dimcad trial (2013) randomized patients with T2DM and CAD to either metformin or glipizide for 3 years. At a median follow-up of 5 years, both groups achieved goal HbA1c levels (7.1% vs. 7.0%) but metformin was associated with a 12% absolute risk reduction in the composite primary outcome of nonfatal MI, nonfatal stroke, revascularization, CV mortality, or all-cause mortality, when compared to the other.[6]

Biguanides have many theoretical benefits over other agents in the treatment of T2DM including a reduction of hepatic gluconeogenesis, decreasing plasma insulin levels, and facilitating weight loss. However, the biguanide phenformin was associated with increased CV and all-cause mortality in UGDP (1975).[7]

Recent trials using newer therapies such such as dipeptidyl peptidase-4 demonstrated safety in cardiovascular outcomes among patients with T2DM and existing CVD or at higher risk of events. The use of sitagliptin, for example, in more than 7.000 patients - in the TECOS trial - was not associated with an increased risk

of heart failure or related to adverse outcomes after Sitagliptin therapy.[8] There was, however, an increase in the rate of hospitalization for HF with the use of saxagliptin (SAVOR-TIMI 53) trial.[9]

The use of Liraglutide, a glucagon-like peptide 1 analogue, had controversial outcomes among diabetic patients in recent trials. The use of this drug in patients with high-risk heart failure and in patients with reduced ejection fraction was associated with an almost 30% increase in the rates of death or heart failure hospitalization within 6 months (FIGHT study).[10] Very recently, the use of the same GLP1 analogue in type 2 diabetic patients without heart failure was associated with lower rates of the development and progression of diabetic kidney disease than placebo.[11]

Another type of anti diabetic drug has recently demonstrated incredibly good results for secondary prevention of new cardiovascular events in diabetic patients: the Sodium-glucose co-transporter-2 inhibitors (SGLT2i). Empaglifozin, one of these SGLT2i, was the first to demonstrate unequivocal benefit in the cardiovascular outcome of diabetic patients with a history of a prior cardiovascular event (heart attack, stroke or others). In the EMPAREG OUTCOME trial, 7020 patients were randomized for the use Empaglifozin added to standard anti-diabetic treatment or standard treatment alone. Patients using this SGLT2i presented a 38% reduction in CVD death, all-cause mortality (32%) and also in the hospitalization for heart failure (35%). However, the rates of non-fatal myocardial infarction and stroke were not reduced.[12]

The use of Canagliflozin (another type of SGLT2i) was also related to the reduction of cardiovascular and renal events in type 2 diabetic patients. In this trial, Canaglifozin was used for primary prevention of cardiovascular events. The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive Canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Patients treated with Canaglifozin, had a significantly lower risk (14%) of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than those who received placebo. However, this treatment led to a greater risk of peripheral amputation (primarily at the level of the toe or metatarsal (1,97 times more events) and infection of male genitalia (3,2 times more events).[13] Another recently published meta-analyses (The CVD-Real study) also showed lower rates of hospitalization for heart failure (39%) and all cause mortality (51%) in new users of three different SGLT2i (predominantly Canaglifozin and Dapaglifozin and a lower proportion of Empaglifozin) when compared with standard glucose treatment with the use of other types of medication for diabetes mellitus.[14]

Another anti diabetic drug that also demonstrated some impact in the reduction of new cardiovascular events and which we must highlight in this summary was Pioglitazone. In the IRIS Trial (a multicenter, double-blind trial), 3876 patients who had had a recent ischemic stroke or transient ischemic attack (TIA) were randomly assigned to receive either pioglitazone (target dose of 45 mg daily) or placebo. At the time of randomization, eligible patients did not yet have the diagnosis of diabetes but were found to have insulin resistance (a high HOMA-IR index). The primary outcome was fatal or nonfatal stroke or myocardial infarction. By 4.8 years, the incidence of the primary outcome was 24% lower in the Pioglitazone treated group. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture.[15]

The Diabetes Control and Complications Trial (DCCT) established the importance of tight glucose control to lessen the risks of both micro vascular and macro vascular disease in type 1 DM patients. A 27 year follow-up of this trial showed that 6.5 years of initial intensive DM therapy in type 1 DM was associated with a modestly lower all-cause mortality rate when compared with conventional therapy.[16] A glycemic target for HbA1c of 6.5-7.5% (48-58 mmol/mol) appears to be a balanced approach for long-term care of patients with type 1 DM. In patients with type 1 Diabetes, there is still insufficient data to affirm that there is any benefit with the use of other oral agents (e.g. metformin, GLP-1 agonists), commonly used in type 2 DM.

Conclusion:

Effective control of blood glucose levels has been proven to prevent the development of cardiovascular disease. In patients with type 2 diabetes mellitus, several studies have established the importance of glucose lowering to prevent CVD, with the best evidence supporting metformin, leading to its position as first-line therapy in the treatment of this disease, especially because of its good cardiovascular safety. New anti diabetic drugs can also be used to reduce the incidence of future cardiovascular events. Two SGLT2

inhibitors (Empaglifozin and Canaglifozin) have lessened CV mortality and HF in high risks patients with prior CVD or with a high cardiovascular risk. More research on the benefits of glucagon-like peptide 1 (GLP-1) receptor agonists on CVD risk is needed and trials are due to be reported in subsequent years. Early evidence suggests no CVD benefit with short-term use of dipeptidyl peptidase 4 (DPP-4) inhibitors in people at high risk for CVD (no harm only with the use of Sitagliptin). Pioglitazone can also be useful to reduce the incidence of myocardial infarctions and stroke, but did not have an impact on total mortality in patients without established DM. There is no doubt about the importance of intensive glucose lowering (only reached with the use of Insulin) in patients with type 1 DM. Further studies are needed on metformin and GLP-1 receptor agonists in patients with type 1 DM to determine whether they improve glycemic control, help in weight reduction or improve clinical outcomes.

Conflicts of interests: The authors state that they have no conflicts of interests.

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