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EDITORIAL

Results from Cardiovascular Outcome Trials in Diabetes☆

Ensayos clínicos de resultados de enfermedad cardiovascular en diabetes

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Patients with type 2 diabetes mellitus (T2DM) have a high risk of cardiovascular disease (CVD) due to both hyperglycemia and other associated vascular risk factors, and also have a poorer prognosis of cardiovascular events. Diabetes increases the severity of all phases of atherosclerosis, its development and its complications.[1] Patients with diabetes have a higher mortality rate attributable to cardiovascular causes as compared to the non-diabetic population (HR: 2.32; 95% CI: 2.11–2.56), and myocardial infarction and stroke account for 80% of deaths in patients with T2M.[2,3] In this context, it has been estimated that patients with diabetes are at risk of experiencing a cardiovascular event some 15 years earlier than non-diabetic subjects.[4] Thus, a comprehensive intervention on the risk factors for CVD in this population is recommended to improve prognosis. The significance of blood glucose control for this comprehensive approach should be stressed. However, the impact of antidiabetic drugs on CVD development and progression is as yet insufficiently known. In recent years, a number of clinical trials (ADVANCE, ACCORD, VADT) have assessed the impact of strict blood glucose control on microvascular complications and CVD.[5–7] Microvascular disease results were satisfactory, but none of these studies showed in their active phase a decrease in CVD incidence, and one of them even reported increased mortality (ACCORD). However, a recent publication with 10-year follow-up data for patients in the VADT study reported a reduction of major cardiovascular events, but no differences in all-cause or cardiovascular mortality.[8] In these studies, rates of hypoglycemia and weight increase were greater in the intensive therapy group. The debate goes back to 2007 following the publication of a controversial meta-analysis reporting that treatment with rosiglitazone significantly increased the risk of myocardial infarction, which led to the drug being taken off the market in Europe.[9] A definition of the benefits or risks of antidiabetic drugs with regard to CVD is therefore very important. The Food and Drug Administration (FDA) in 2008 issued guidelines for assessing the risk of new drugs for the treatment of T2DM because of the uncertainty regarding the CV safety of some of these drugs, and other agencies subsequently proposed similar measures.[10] For new antidiabetic drugs, the FDA guidelines stipulate that an independent committee be established to assess the adverse events of CVD during all Phase 2 and 3 clinical trials. Classical major adverse CVD events (cMACE), including death from CVD, non-fatal myocardial infarction, and non-fatal stroke, should be assessed. Thus, before an application for approval of a new drug is submitted, a meta-analysis of data from Phase and 3 studies should be conducted to show that the drug is not associated with an unacceptable increase in the risk of CVD. The regulations state that if for the risk of cMACE the upper limit of the 95% confidence interval of the estimated risk

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is greater than 1.8, the drug cannot be approved. If values ranging from 1.3 to 1.8 are found, additional studies are required, and approval is only recommended when the value is less than 1.3. However, these studies are not designed as clinical trials of CVD outcomes, and only specific, randomized clinical trials will be able to determine the benefits or risks regarding CVD of an antidiabetic agent.

Several CVD outcome trials with different types of antidiabetics, such as dipeptidylpeptidase-4 inhibitors (DPP-4 inhibitors), GLP-1 receptor agonists (GLP-1 RAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors have been published recently. Their inclusion criteria were not consistent, which should be taken into consideration in their interpretation. Studies with three DPP-4 inhibitors have been reported: saxagliptin, alogliptin, and sitagliptin. In the SAVOR-TIMI study, 16,492 patients with T2DM and risk factors for CVD or prior cardiovascular events were randomized to saxagliptin or placebo and were followed up for a median of 2.1 years.[11] The primary endpoint (cMACE) occurred in 7.3% of the patients treated with saxagliptin and in 7.2% of those treated with placebo (HR: 1.00; 95% CI: 0.89–1.12). An unexpected finding in this study was that more patients were admitted to hospital for heart failure (HF) in the saxagliptin arm (3.5% and 2.8% respectively; HR: 1.27; 95% CI: 1.07–1.51), although this was not associated with increased mortality. In the EXAMINE study, 5380 patients with T2DM and a history of myocardial infarction or hospitalization for unstable angina were randomized to alogliptin or placebo added to prior antidiabetic treatment and followed up for a median of 18 months.[12] An event included in the primary endpoint (cMACE) occurred in 11.3% of the patients randomized to alogliptin and 11.8% of the placebo patients (HR: 0.96; upper limit of confidence interval 1.16; $p < 0.001$ for non inferiority). There was no difference in the hospitalization rates for HF (3.1% vs 2.9%). Finally, in the TECOS study, 14,671 patients with T2DM and established CVD were randomized to sitagliptin or placebo (added to their regular treatment) and followed up for a median of three years.[13] cMACE occurred in 11.4% of the patients treated with sitagliptin and in 11.6% of the placebo patients (HR: 0.98; 95% CI: 0.89–1.08). No difference was found either in the hospitalization rates for HF (3.1% vs 3.1%). The results of studies with DPP-4 inhibitors have promoted a greater attention to the relationship between T2DM and HF, whose pathophysiological mechanisms are poorly known.[14]

GLP-1 RAs were tested in the ELIXA study. In this study, 6608 patients with T2DM and a recent acute coronary event were randomized to lixisenatide or placebo and were followed up for a median of 25 months.[15] The primary endpoint (death for CVD, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina) occurred in 13.4% of patients treated with lixisenatide and in 13.2% of placebo patients (HR: 1.02; 95% CI: 0.89–1.17). There were also no differences in other secondary endpoints including hospitalization for HF (4.2% vs 4%).

The most recent of these studies is the so-called EMPA-REG OUTCOME trial. In this study, 7020 patients with T2DM and prior CVD were randomized to empagliflozin (10 or 25 mg/day) or placebo (added to their regular treatment) and followed up for a median of 3.1 years.[16] The primary endpoint (cMACE) was significantly reduced (RRR: 14%) in the group treated with empagliflozin when both empagliflozin doses were assessed together (10.5% vs 12.1%, HR: 0.86; 95% CI: 0.74–0.99). A significant reduction was also seen in cardiovascular mortality (3.7% vs 59%, RRR: 38%), hospitalization for HF (2.7% vs 4.1%, RRR: 35%), and all-cause mortality (5.7% vs 8.3%, RRR: 32%). However, there were no significant differences in the rates of non-fatal myocardial infarction and non-fatal stroke. This study has had a great impact due to the consistency of the results on cardiovascular and all-cause mortality. The benefits of empagliflozin were seen early in the EMPA-REG study and were maintained throughout follow-up in a population mostly treated with statins and antihypertensive medication. A debate as to whether empagliflozin is an effective drug for the secondary prevention of CVD in patients with T2DM is now underway. The lack of efficacy for the reduction of non-fatal myocardial infarction and stroke fans the flames of controversy. In this regard, the favorable effects of empagliflozin on the hospitalization rate for HF are of great interest and very different from the effects reported for other antidiabetic drugs. It may be interpreted that empagliflozin is effective as regards an improved prognosis in patients with T2DM who have experienced a cardiovascular event. The number of patients it was necessary to treat to prevent one death during a three year period was 39 with empagliflozin, much lower than that reported for other drugs such as ramipril or simvastatin. The results of the EMPA-REG study should however be interpreted with caution when assessing the impact of the drug on the management of patients with T2DM and its complications. The results discussed raise new questions related to the generalization of benefits to populations with a lower risk of CVD, or as to whether these findings represent a potential class effect of SGLT2 inhibitors.

The overall assessment of clinical trials on CVD outcomes in diabetes conducted under the new FDA regulations and reported to date leaves us with a reassuring message regarding the cardiovascular safety of these drug interventions. However, detailed analysis, including specific outcomes such as HF, undoubtedly raises significant unanswered questions. The results of additional ongoing studies that should provide relevant information about this problem will be reported in the coming years. The drugs being assessed include DDP4 inhibitors such as linagliptin, GLP-1 RAs such as liraglutide, exenatide, dulaglutide and semaglutide, and SGLT2 inhibitors such as dapagliflozin and canagliflozin. Thus, the final word as to the ability of antidiabetic drugs to prevent CVD and its consequences in patients with diabetes should await the results of long-term clinical trials in patients with different risk levels using treatment approaches that optimize blood glucose control, minimize the risk of hypoglycemia, and prevent weight gain.

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