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Editorial

Drugs That Improve Cardiovascular Prognosis in Diabetes and Are Not Yet Used by Cardiologists

Fármacos que mejoran el pronóstico cardiovascular en diabetes y los cardiólogos aún no usamos

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Type 2 diabetes mellitus (T2DM) is currently one of the most prevalent health problems worldwide. According to estimated data, 246 million people have T2DM globally, and this figure may double by 2025. If we concentrate on the population with cardiovascular (CV) disease, the registries give figures close to 35% of patients with established CV disease who also have T2DM.[1]

Recently, a multidisciplinary team of cardiologists, endocrinologists, and nephrologists published the monograph "*Diabetes tipo 2 en prevención secundaria. Recomendaciones de tratamiento*" (in English, Type 2 diabetes in secondary prevention. Treatment recommendations).[2] This document contains an extensive review of the CV safety of antidiabetic (AD) drugs and points out that a reduction in CV events and even in CV mortality has been demonstrated for 2 groups of these drugs: sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.

It is remarkable that these results have not had an impact in the world of cardiology, despite, as already mentioned, approximately 35% of the patients we treat in secondary prevention (2P) having T2DM[1] and their mortality risk being at least 3 times higher than that patients in 2P without T2DM.[3] Moreover, around 40% of patients with heart failure (HF)[4] have T2DM, which confers a significantly increased risk of hospitalization for HF, CV mortality, and all-cause mortality.[4] This so far lukewarm reaction from cardiologists must be stepped up given that T2DM confers a worse prognosis for our patients and we now have therapeutic tools to improve this situation.[5,6]

The reality is that, until recently, only multifactorial control, particularly of low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP), was demonstrated to reduce CV morbidity and mortality in patients with T2DM and high CV risk.[7] The paradigm shift in the treatment of patients with T2DM in 2P began in September 2015. For the first time, an AD, empagliflozin, was shown in a randomized clinical trial to reduce CV mortality and all-cause mortality, reduce major CV events,[8] hospitalization due to HF, and slow progression of and even reverse kidney disease.[9] The most surprising finding was that these benefits were independent of the glycated hemoglobin concentration (HbA_{1c}) achieved by patients during the study.

Six months later, another study was published reporting that liraglutide treatment significantly reduced CV mortality and major vascular events in the same population of patients with T2DM in 2P, and again that these benefits were independent of the HbA_{1c} levels reached.[10] Semaglutide, months later, and canagliflozin, in 2017, also showed a reduction in the composite outcome of death, nonfatal myocardial infarction and nonfatal stroke, this benefit being unrelated to HbA_{1c} levels.[11,12]

This is the paradigm shift: the reduction in CV complications and mortality in patients with T2DM and CV disease goes beyond glycemic control and appears to be more closely related to the specific benefit provided by these drugs on the heart, hemodynamic status, nephroprotection, and reversal of atherosclerosis. The glucocentric approach for patients with T2DM has been sidelined and the multifactorial approach is gaining ground, particularly the evidence on the CV benefit provided by these 4 drugs: empagliflozin, liraglutide, semaglutide, and canagliflozin.

The consequence of this transition in the approach to diabetes goes beyond the points mentioned here. From now on, there will be an unavoidable obligation to be aware of the drugs that can reduce these patients' CV risk–more drastically than the other drugs currently used in 2P with less evidence of benefit–and not deny patients this treatment.

It is necessary, therefore, to raise awareness among the different specialists about the need to incorporate these drugs into the therapeutic arsenal of 2P rather than simply considering them AD drugs. Even more importantly, we must embrace the idea that between us all we need to take control and ensure these patients are treated holistically, with cardiologists, endocrinologists, nephrologists and internists working hand-in-hand and, most importantly, with the involvement of the family doctor to achieve the continuity of care that is so necessary for this patient population.

The mechanism of action by which these drugs produce a CV benefit is yet to be elucidated. A period of tremendous research

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is beginning, which will address many of the currently unanswered questions. Besides establishing the mechanism of action of these drugs, several effects will need to be demonstrated. First, whether the reduction in CV risk occurs only in patients with T2DM or whether it extends to the nondiabetic population and whether the reduction in CV risk applies only to patients in 2P or also to those in primary prevention. Second, whether the cardioprotective effect produced by SGLT2 inhibitors in HF occurs in HF with reduced ejection fraction, with preserved ejection fraction, or in both. Last, it is important to determine whether the potentially antiatherosclerotic effect of GLP-1 receptor antagonists can be added to the cardioprotective effect of SGLT2 inhibitors in reducing HF. Essentially, times are changing for 2P and for cardiologists. This is a new era, and there are new drugs that improve our patients' CV prognosis. We cannot ignore this and limit their access to drugs that will undeniably improve their prognosis.

CONFLICTS OF INTEREST

A. Castro declares fees for presentations and consultancy from Boehringer Ingelheim, Janssen, Novo Nordisk, Amgem, Sanofi, Novartis, MSD, and Menarini. D. Marzal declares no conflicts of interest.

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