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The Easy and Prompt Access to Research Results for Patients vs. the Premature Incorporation of New Drugs

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Editorial

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Editorial

Type 2 diabetes mellitus (T2DM) is a common and increasingly prevalent disease and represent a major public health worldwide. People with diabetes have increased risk of serious health complications including vision loss, kidney failure, vascular complications such as myocardial infarction and stroke, and premature death [1,2].

Good glycemic control remains the main foundation of T2DM treatment, this approach play a role in preventing or delaying the onset and progression of diabetic complications.

Among diabetes-related complications, cardiovascular disease (CVD) is a leading cause of mortality and adverse outcomes in people with T2DM [1]. However, despite the clear correlation between diabetes and negative CV outcomes, it is still not clear whether glycemic control per se would have any effect on reducing CVD in T2DM patients [3-5]. Before 2008 US Food and Drug Administration (FDA) and 2012 European Medicines Agency (EMA) regulations, few trials of glucose-lowering drugs or strategies in people with type 2 diabetes have investigated cardiovascular outcomes, even though most patients die from cardiovascular causes despite the beneficial effects of lipid-reducing and blood pressure-lowering treatments. Since these dates FDA and EMA requirement that all new therapies for diabetes undergo a rigorous assessment of CV safety through large-scale cardiovascular outcome trials (CVOT).

FAD guidelines include, among others: 1. Patient selection should focus on high risk populations, including those with advanced disease, elderly and those with renal impairment. 2. Trials must include at least 2 years of CV safety data, and 3. A prospective independent adjudication of CV events in phase 2 and 3 studies must also be performed (CV events include, CV mortality, myocardial infarction, stroke and possibly hospitalization for acute coronary syndrome).

After FDA and EMA guidance request for the CV safety for new anti-diabetic drugs, 18 CVOT have been initiated. From those, results for seven are already available: SAVOR-TIMI53, EXAMINE, TECOS, ELIXA, EMPA-REG OUTCOME, LEADER, and SUSTAIN-6. To resume, DPP-4 inhibitors Saxagliptin, Alogliptin and Sitagliptin and the GLP-1 receptor agonist Lixisenatide are safe with respect to CV outcomes in high CV risk patient populations with long T2DM duration. LEADER study has shown that Liraglutide, a GLP-1 receptor agonist, is not only safe, but that is also capable of reducing the incidence of CV-related death [6]. SUSTAIN-6 shows that another GLP-1 receptor agonist, Semaglutide is superior to placebo in reducing the risk of a cardiovascular disease and significant reduction of stroke risk [7]. Finally, SGLT-2 inhibitor Empagliflozin was not only non-inferior to placebo, but also significantly reduced CV risk, as shown by the composite primary and secondary outcomes, and a composite outcome of heart failure hospitalization and CV death [8]. Following these optimistic results, ADA mention in its last guidelines [9] "that in patients with long-standing sub optimally controlled T2DM and established atherosclerotic cardiovascular disease, Empagliflozin or Liraglutide should be considered as they have been shown to reduce CV and all-cause mortality when added to standard care". Given the great prestige of the ADA, it is expected an early incorporation of the mentioned drugs in our clinical practice.

The results of the those seven CVOTs may be useful for treatment-decision and for diabetes patients safety, however, the real safety profile of aforementioned new drugs remains to be completely established, due to limitations of the CVTO studies: The comparison among

CVTOs is overall difficult for: 1. The definition of CVD risk and/or CVD is different for each trial, 2. Variable trial duration, 3. Diverse definitions of the primary endpoints. Other obstacles to the rapid incorporation of these drugs into clinical practice are: The majority of the CVOTs was designed as no-inferiority vs. placebo designs; trial duration is too short (less than 4 years of follow-up) to evaluate real-life long-term outcomes, lack of head to head comparisons among the different new drugs and despite the focus on high risk patients in CVOTs design, problems for extrapolation of results to the general population exist, because the criteria for patient selection varied from trial to trial.

All of this leads to clinicians face with an ethical dilemma, the easy and prompt availability of research results, which is a people right, vs. the premature incorporation of therapeutic novelties into daily practice.

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