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Can a Diabetic Medication offer Cardiovascular benefits?

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Editorial

Within the past 20 years, the number of available classes of medications for treatment of Type 2 diabetes mellitus (T2DM) has drastically increased. In the evaluation of these anti-hyperglycemic agents, the long-term effects on cardiovascular safety have become as important as the glucose lowering effects themselves. Novel therapies are required to prove their safety, without clinically meaningful increases in the rates of major adverse cardiovascular events (MACE).

While SGLT-2 inhibitors are among these new classes in the treatment of T2DM, their benefits in regards to HbA1c reduction and weight loss have already been lauded. SGLT-2 inhibitors address a path physiologic defect in the kidney of patients with T2D. By decreasing the renal threshold of glucose reabsorption they improve hyperglycemia in patients with T2DM. The increased urinary glucose excretion lowers serum glucose levels and provides an approximate 200-300 kCal deficit, resulting in modest weight loss.

The release of EMPA-REG [1] in 2015, initially done to demonstrate no increased risk of MACE, took the world by surprise when its results showed significant decreases in CV death, all-cause mortality, and heart failure hospitalizations compared to placebo (38%, 32%, and 35%, respectively). In addition, patients also saw an initial reduction in HbA1c without increases in hypoglycemic events, weight loss, and decreases in both systolic and diastolic blood pressure. While the exact mechanism behind the CV benefit has yet to be elucidated, proposed mechanisms include improved glucose control, reduced arterial stiffness, decreased uric acid levels, and a decreased blood pressure without a compensatory increase in heart rate [2]. Of these potential mechanisms, improved glucose control appears to be the least likely. The initial HbA1c reduction was not sustained and at the conclusion of the study levels were similar to the placebo group. EMPA-REG is unique, as no other studies have demonstrated improved CV mortality with improved glucose control.

In light of this study, further questions have arisen. Of particular interest, can the results of EMPA-REG be applied to other drugs in the same class? Are the cardiovascular benefits only in patients with pre-existing CV disease or is there a preventative effect in those without cardiovascular disease? All of these questions have major treatment implications and are currently being investigated. Both the ongoing CANVAS - Canagliflozin Cardiovascular Assessment Study [3], and DECLARE - TIMI 58-Dapagliflozin Effect on Cardiovascular Events [4], will assess SGLT2 effects in patients with preexisting cardiovascular disease and those that are high-risk for cardiovascular events. Results for these trials should be expected in 2017 and 2019, respectively.

While awaiting the results of these studies, how do clinical endocrinologists proceed with the currently available information? It is unlikely that the results of the EMPA-REG trial should be limited to empagliflozin. More than likely, this is a class effect, therefore, should not preclude the use of the other drugs in this class in favor of empagliflozin. However, should the SGLT-2 inhibitors become first line therapy over other T2DM medications? To date, metformin (MFM) has been the first line agent in the diabetes treatment algorithm. Should this algorithm be modified to make empagliflozin first line therapy in patients with cardiovascular disease? In our opinion, the benefits of emagliflozin in CV disease are impressive; however, MFM should remain as first line therapy. MFM is a relatively safe medication with significant benefits in patients with T2DM and many years of safety data to support it. However, since empagliflozin is the first anti-hyperglycemic agent to show CV benefit, we believe SGLT-2 inhibitors should be considered second line therapy after metformin, or started in combination with metformin initially.

As a class, SGLT-2 inhibitors are still relatively new. More information regarding the mechanism behind its cardiovascular benefits as well as long-term safety is needed. Despite a decent adverse reaction profile seen among empagliflozin users in EMPA-REG, clinically significant complications have been brought to attention in relation to SGLT-2 inhibitor use. The risk of diabetic ketoacidosis, especially among Type 1 diabetics and insulin dependent Type 2 diabetics, has emerged as a serious complication [5,6]. Presently, we await the results of formal studies evaluating the true risk of this complication and must consider this potential adverse effect when starting patients on this medication. Additionally, there have been rare cases of clinically significant pyelonephritis requiring hospitalization related to SGLT-2 inhibitor use [7]. SGLT-2 inhibitors are known to increase the risk for urinary tract infections and genital mycotic infections, however, most are treatable and do not necessitate the discontinuation of medication.

As the use of SGLT-2 inhibitors increases, more safety data will emerge and will help to guide future recommendations regarding the use of this class and its position in the diabetes treatment algorithm. Until this information becomes available, we will continue to recommend MFM (assuming no contraindications) as a first line treatment and strongly consider the use of SGLT-2 inhibitors as second line therapy, especially in those with established CV disease. Until then, we anxiously await the results of ongoing studies and remain optimistic there will soon be diabetic medications which are cardioprotective.

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