Editorial

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Caution on the broad prescription of new antidiabetics with favorable cardiovascular effects

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It is well-kwon that individuals with type 2 diabetes (T2D) have two-to threefold greater risk of cardiovascular events compared with non-diabetic people. Furthermore, cardiovascular disease (CVD) is responsible for up to 75% of mortality in T2D.[1] We also know that hyperglycaemia is a weak risk factor for CVD.[2] Thus interventions focused on reducing plasma glucose have failed to significantly reduce CV risk and mortality, particularly in secondary prevention trials,[3–5] while multifactorial interventions that improves CV risk factors has been shown reduce CV events and mortality,[6] for this reason it is not surprising that lowering blood pressure and improving lipid profile lead to greater reductions in CVD risk than lowering glycemia in T2D.

According with to this, anti-diabetes agents such as insulin, sulfonylureas and dipeptidyl peptidase 4 (DPP-4) inhibitors, which lower plasma glucose without affecting insulin resistance or other metabolic effects, do not lower CVD risk and mortality in T2D patients. However, the anti-diabetes agents that besides the lowering blood glucose have other effects such as decrease blood pressure, improve the lipid profile, weight loss, increase insulin sensitivity and/or correct endothelial dysfunction can improve significantly macrovascular outcome in these patients.

The LEADER study examined the effect of once-daily Liraglutide a Glucagon-like-peptide 1 analogue (GLP-1) in comparison with placebo for a mean of 3.8 years.[7] This study included patients with high CV risk. The primary outcome was 3-point MACE (included cardiovascular death, non-fatal myocardial infarction and non-fatal stroke). Liraglutide-treated patients experienced a 13% reduction in MACE, which was driven by a 22% reduction CV mortality (P=0.007), nonfatal myocardial infarction (MI) was decreased by 12%, while nonfatal stroke was not significantly reduced. The gastrointestinal symptoms, such as nausea, vomiting and diarrhea, led withdrawal to 36 patients from Liraglutide group. One patient was withdrawal for acute pancreatitis. The SUSTAIN-6 study,[8] included T2D patients at high risk for CVD and compared treatment with subcutaneous Semagutide, another GLP-1 analogue, administered once-weekly with placebo for 104 weeks. The study was designed to demonstrate no-inferiority, being the primary outcome 3-point MACE. The primary outcome was reduced by 26%, being a 39% (P=0.04) and a 26% (P=0.12) in nonfatal stroke and nonfatal MI respectively. CV mortality was not decreased. Regarding to side effects, more patients in the Semaglutide group than the control group discontinued treatment because adverse events, mainly gastrointestinal.

The PIONEER 6 trial assesses the cardiovascular outcome of once-daily oral Semaglutide vs. placebo, involving T2D patients at high cardiovascular risk and follows a non-inferiority design. The primary outcome was the first occurred 3-point MACE. Concluded that cardiovascular risk profile of oral Semaglutide was not inferior to that of placebo. Safety outcome revealed that adverse events leading to discontinuation of treatment were more common in the Semaglutide group. Other side effects of GLP-1 analogues include, risk of thyroid C-cell tumors, pancreatitis, and cholelithiasis.[9] Empagliflozin is an inhibitor of sodium-glucose cotransporter 2 (SGLT2), in the EMPA-REG OUTCOME,[10] this antidiabetes agent caused in comparison with placebo, 14% reduction (P=0.04 for superiority) in 3-point MACE in patients with T2D with established CVD over 3.1 years. The primary outcome was driven by a robust 38% reduction in CV mortality, while nonfatal MI decreased slightly, but no significantly (HR 0.87, P= 0.22), and nonfatal stroke increased slightly but not significantly (HR 1.24, P= 0.22). Notably, reductions in the risks of death from CV causes and from any cause occurred at 3 months after starting treatment. Safety evaluation showed that genital infection was reported in a higher percentage in the pooled Empagliflozin group. Urosepstis was reported in 0.4% of patients in the Empagliflozin group and 0.1% in the placebo group.

The CANVAS and CANVAS-R,[11] clinical trials examine the efficacy and safety of Canagliflozin another SGLT2 compared with placebo in T2D patients followed-up a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular death causes, non-fatal MI and non-fatal stroke, tested with a non-inferiority design and the intention-to-treat approach. The rate of the primary outcome was lower with Cangliflozin than with placebo, 26.9vs. 31.5, P<0.001 for non-inferiority and P=0.02 for superiority. Patients treated with Canagliflozin has a high risk of amputation, mainly at the level of the toe or metatarsal.

Finally, DECLARE-TIMI 58 study,[12] evaluated the efficacy and safety of Dapagliflozin other selective inhibitor of the SGLT2. This study includes 17,160 patients with T2D, including 10,186 without atherosclerotic cardiovascular disease. The primary outcome was a composite of major adverse cardiovascular events (MACE), with a no-inferiority design versus placebo. In the primary efficacy analysis, Daplagliflozin did not result in a lower rate of MACE, 8.8% vs. 9.4% for the active substance and placebo, respectively (P=0.17), but did result in a lower rate of cardiovascular death or hospitalization for heart failure. The authors concluded that in T2D patients who had or were at risk for atherosclerotic cardiovascular disease, treatment with Daplagliflozin did not result in a higher or lower rate of MACE than placebo, but did result in a lower rate of cardiovascular death or hospitalization for heart failure. Respect to safety profile, diabetic ketoacidosis was more common with Dapagliflozin than with placebo (0.3% vs. 0.1%, P=0.02).

Another side effect reported in SGLT2 inhibitor is bone fractures.[9]

Also on August 9, 2018 the U.S. Food and Drug Administration (FDA) is warning that cases of a rare, but serious infection of the genitals and the area around the genitals have been reported to the class of Type 2 diabetes medicines called sodium-glucose-cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. They are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patients.

Conclusion

When prescribing antidiabetics with a favorable cardiovascular effect, we must bear in mind

a. The balance between the efficacy and safety of such drugs.

b. The results of the clinical trials do not easily extrapolate to the general population.

c. The drugs described have only shown their beneficial effect in patients with high cardiovascular risk, and may be useful only for secondary prevention.

d. And the high cost of these antidiabetic drugs.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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