Cardiovascular Safety: Which Antidiabetic Agent Will Be Your Choice in Patients, Who Have Coexisting Cardiovascular Disease?

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Background:
In 2008, FDA began requiring companies to carry out long-term cardiovascular outcome studies as part of post-approval commitments. The FDA does not require that the companies show that the new drug improves heart function, but rather that it does not significantly increase the risk of heart disease since it is accepted that a new drug, by virtue of its blood sugar lowering action, will reduce the risk of diabetic complications.

TECOS:
Previous cardiovascular safety studies with saxagliptin in diabetic patients with high cardiovascular risk or existing cardiovascular disease and alogliptin in diabetic patients following acute coronary syndromes had demonstrated cardiovascular safety for these drugs, with no increase in major adverse coronary events (noninferiority), but neither had they demonstrated any benefit (superiority). TECOS was a longer study comparing sitagliptin and placebo in 14 671 patients with type 2 diabetes and existing cardiovascular disease for a median of 3.0 years. sitagliptin was non-inferior to placebo and did not increase the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for unstable angina, and on a secondary analysis sitagliptin was not superior to placebo Figure, 1.

EMPA-REG OUTCOME
This was a large cardiovascular safety study in 7020 people with type 2 diabetes and existing cardiovascular disease. It compared empagliflozin 10mg, empagliflozin 25mg, and placebo in addition to usual standards of care, and nearly half of the participants were on insulin. The first patient was enrolled in 2010 and the study was completed in 2015. Empagliflozin was superior to placebo in reducing major adverse coronary events and reduced total mortality by 32%. The effects were the same for both doses of empagliflozin Table, 2.

ELIXA:
Lixisenatide is a short-acting GLP-1 receptor agonist, and like exenatide it is a synthetic version of exendin-4. was a large, randomised, controlled trial comparing lixisenatide with placebo in 6068 patients with type 2 diabetes who had suffered an acute coronary syndrome within the previous 180 days. There was no significant difference in the primary endpoint of cardiovascular death Figure, 3.

Conclusion and recommendations:
The impressive reduction in total mortality that was seen with empagliflozin in the EMPA-REG OUTCOME trial will lead to a change in the management of this challenging group of patients, who have existing cardiovascular disease and may be uncontrolled on insulin therapy, and initially the increased use of empagliflozin should be focused on this group. As there are currently no data to support a similar benefit with dapagliflozin or canagliflozin it is likely that empagliflozin will quickly become the most prescribed drug in this class.

References:
1. Miles Fisher, Recent cardiovascular safety trials with antidiabetic drugs: time to change the guidelines!, PRACTICAL DIABETES VOL. 32 NO. 9.

Acknowledgement
I thank Dr.Rezvan in Azadi Hospital in Dohuk, Iraq who helps me to design this poster.