Reviewer’s report

Title: SGLT2 inhibitors in T2D and associated comorbidities — differentiating within the class

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Reviewer: Gabriel Chodick

Reviewer's report:

1) This is a very timely summary of a group of medical experts from the Central and Eastern European Region on the class effects of SGLT2 inhibitors. I applaud the authors for their review and conclusion that despite the encouraging CV and renal data from the EMPA-REG OUTCOME® and CANVAS Program, the class effect in all-cause mortality, CV death and safety, require further investigation.

2) Their conclusion is fully support by the recently published results of DECLARE-TIMI RCT. While Dapagliflozin was found to reduce the risk of cardiovascular death or HHF (HR= 0.83; 95% CI, 0.73 to 0.95), most of this effect was due to a lower rate of HHF (HR= 0.73; 95% CI, 0.61 to 0.88). Dapagliflozin had no or little effect in reducing the risk of cardiovascular death (HR= 0.98; 95% CI, 0.82 to 1.17) or MACE (HR= 0.93; 95% CI, 0.84 to 1.03; P=0.17), irrespective to CVD status at baseline. In addition, it had no effect in reducing all-cause mortality. The results of this important study should be incorporated into the summary.

3) The authors have rightfully addressed real-world evidence in their summary. These studies add to the confusion regarding the class effect of SGLT2-I in reducing CVD and all-cause mortality. Some important studies should be mentioned including the EASEL cohort study. With less than two years of median follow-up, the authors concluded that SGLT2i was associated with 43% reduction in all-cause mortality and HHF and 33% reduction in major adverse cardiovascular events. Importantly, SGLT2i initiation was also associated with a 2-fold higher risk of below-knee lower extremity amputation. Similar results have been shown in an additional observational study- CVD REAL2- an international study of patients with T2D from the Asia Pacific, the Middle East, and North America. These observational studies should be discussed in the summary.

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