

SGLT2 inhibitors (including EMPA-REG OUTCOME)

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Cardiovascular (CV) disease is the leading cause of mortality and morbidity in patients with T2D and reducing CV risk is the critical part in the management of diabetes. Therefore, it is important to consider therapies that address not only blood glucose control but also other CV risk reduction. EMPA-REG OUTCOME® is the first study of a glucose-lowering agent that has shown a reduction in CV events in patients with T2D especially with high CV risk. While the primary composite outcome of myocardial infarction, stroke or CV death was reduced by empagliflozin (HR 0.86 [95 CI 0.74, 0.99], the reductions in heart failure hospitalization (by 35%), CV death (by 38%) and all-cause deaths (by 32%) in patients with empagliflozin were highly striking and unexpected. The separation of CV death curve between the empagliflozin and placebo groups became apparent from 3~6 months and continued throughout the study and it has been arguing what could make this rapid emergence of these benefits. The potential mechanisms that could explain the CV benefits are likely multifactorial and probably non-glycemic and non-atherothrombotic mechanisms, perhaps hemodynamic benefits of SGLT2 inhibitors are suggested. However, there are still uncertainties and unanswered questions including the mechanisms for the reduction in CV outcomes, generalization of the results to other patients with different characteristics, and whether the benefits are a class effect. Additional information from other ongoing trials for canagliflozin (CANVAS) and dapagliflozin (DECLARE-TIMI 58) will help to understand the relevant mechanisms and prove these questions.