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ORIGINAL RESEARCH ARTICLE

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

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those enrolled in randomized trials so far. These findings were unchanged after additional multivariable adjustment, and in multiple sensitivity analyses. Specifically, the results were unchanged after sequential removal of several oGLD classes from the comparator group, suggesting that the differential outcomes observed are unlikely to reflect adverse effects of comparator drugs, but are rather associated with benefit from SGLT-2i. Furthermore, results were consistent across countries, regardless of variability in healthcare systems and use of specific SGLT-2i (predominantly canagliflozin in the United States; dapagliflozin in Europe), suggesting an association with the class rather than any single agent. Importantly, initiation of SGLT-2i versus oGLDs was also associated with a 51% lower rate of all-cause death, and a 46% lower rate of the combined end point of HHF or all-cause death.

Although intensive glucose lowering has, in randomized trials, failed to reduce what are arguably some of the most important outcomes in patients with T2D (all-cause death and incident HF), results from the EMPA-REG OUTCOME trial demonstrated that such benefits are achievable within a short time frame with an SGLT-2i, likely via nonglycemic mechanisms. Ultimately, the main goals of treating patients with T2D are to prolong life and improve quality of life. Given that CVD (including HF) is a leading cause of mortality/morbidity in T2D, the results of the recent cardiovascular outcomes trials suggest that the time has come to shift from the narrow focus on hemoglobin A1c to a more comprehensive focus in which treatments proven to improve important outcomes (especially mortality) are prioritized.

Our findings address several key unanswered questions with regard to the potential role of SGLT-2i in the management of T2D, with important clinical implications. First, our results demonstrate that the effects associated with the use of SGLT-2i in regard to HHF and all-