The Rate of Adverse Events of Sodium-Glucose Cotransporter 2 Inhibitors: A Meta-Analysis of Randomized Clinical Trials

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Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have proven cardiovascular benefits in diabetics and in patients with heart failure in the presence or absence of diabetes. We sought to assess the rate of adverse events with the use of SGLT2 inhibitors compared to placebo.

Methods: We included all randomized, double-blinded, placebo-controlled trials of SGLT2 inhibitors regardless of the indication. Data were pooled using the Mantel-Haenszel random-effects model to calculate the relative risk (RR) and 95% confidence interval (CI).

Results: We included a total of 62 trial comprising 95,594 patients (55,739 patients in the SGLT2 arm and 39,855 patients in the placebo arm). Compared to placebo, use of SGLT2 inhibitors was associated with a statistically significant increased rate of overall infections (9.6% vs. 5.7%, RR: 1.28, 95% CI: 1.18 - 1.40), and diabetic ketoacidosis (0.2% vs. 0.08%, RR: 2.7, 95% CI: 1.62 - 4.50). The increased rate of overall infections was primarily driven by higher rates of genital infections (3.6% vs. 0.7%, RR: 3.23, 95% CI: 2.73 - 3.82). The rates of hypoglycemia, bone fracture and amputation were not significantly different between both treatment arms (10.0% vs. 7.3%, RR: 1.06, 95% CI: 0.98 - 1.14), (3.6% vs. 3.6%, RR: 1.02, 95% CI: 0.94 - 1.10), and (1.5% vs. 1.3%, RR: 1.09, 95% CI: 0.94 - 1.27), respectively.

Conclusion: SGLT2 inhibitors increase the risk of diabetic ketoacidosis and genital infections. The overall rate of diabetic ketoacidosis was, however, low.

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