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Comparative effectiveness of oral antidiabetic drugs in preventing cardiovascular mortality and morbidity: A network meta-analysis

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In the Guidance for Industry from the Food and Drug Administration in 2008, excess cardiovascular risk should be ruled out in trials of all new antidiabetic drugs; however, relatively few studies have focused on cardiovascular safety with antidiabetic drug use. We aimed to examine mortality and cardiovascular risk using a network meta-analysis. We searched the Medline, Embase, Cochrane, and ClinicalTrials.gov registry databases in March, 2016 to identify randomized controlled trials reporting cardiovascular risk with the following oral antidiabetic drugs: metformin, sulfonylureas, thiazolidinedione (TZD), dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose co-transporter-2 (SGLT2) inhibitors. We assessed the differences in the risks of all-cause mortality, cardiovascular-related mortality, acute coronary syndrome (ACS), and myocardial infarction (MI) among antidiabetic drugs with fixed effect models for direct pairwise comparisons and Bayesian network meta-analyses to integrate direct and indirect comparisons. Of the 101,183 patients in 73 randomized controlled trials, 3,434 (3.4%) died. The relative risks of all-cause mortality with SGLT2 inhibitor use were 0.68 (95% credible interval: 0.57-0.80), 0.74 (0.49-1.10), 0.63 (0.46-0.87), 0.71 (0.55-0.90), and 0.65 (0.54-0.78), compared with placebo, metformin, sulfonylurea, TZD, and DPP4 inhibitor, respectively. The relative risks of cardiovascular-related mortality with SGLT2 inhibitor use were 0.61 (0.50–0.76), 0.81(0.36-1.90), 0.52(0.31–0.88), 0.66(0.49–0.91), and 0.61(0.48–0.77), compared with placebo, metformin, sulfonylurea, TZD, and DPP4 inhibitor, respectively. The relative risks of ACS with SGLT2 inhibitor use was consistent with that of all-cause mortality. SGLT2 inhibitor use was associated with a lower risk of ACS than the other OADs and placebo. The relative risks of MI with SGLT2 inhibitor use were 0.77 (0.63-0.93) and 0.75 (0.60-0.94), compared with placebo and DPP4 inhibitor, respectively. In network meta-analyses, SGLT2 inhibitor use was associated with significantly lower risks of all-cause and cardiovascular-related mortality, MI, and ACS compared with other oral antidiabetic drugs.

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