Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials

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Summary

Background In our 2015 systematic review and meta-analysis of cardiovascular outcome trials for glucose-lowering drugs or strategies in people with or at risk of type 2 diabetes, we reported a modest reduction in atherosclerotic cardiovascular events and an increased risk of heart failure, but with heterogeneous effects by drug or intervention type. In view of the completion of many large cardiovascular outcome trials since our previous analysis, including trials of novel drugs that have shown beneficial effects on cardiovascular outcomes, we aimed to update our analysis

adverse cardiovascular events (MACE) as an outcome of interest and have had a follow-up of at least 12 months. We excluded trials with fewer than 1000 participants and those that enrolled patients with an acute cardiovascular event. Additionally, trials were excluded if a multifactorial risk-factor intervention or non-glycaemic drug were tested or if the intervention resulted in a mean difference of 0·01% or less in HbA_{1c} between treatment groups. Trials with fewer than 20 cardiovascular events were excluded.

We did an updated literature search of Ovid MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials databases for trials published from Nov 15, 2013, to Nov 20, 2019, with no language restrictions. Key search terms were "hyperglycemic agents", "glucose control", "type 2 diabetes", "adults", "cardiovascular disease", "heart failure", and "risk" (appendix p 2). To ensure accurate identification of relevant published and unpublished studies, we reviewed reference lists, appendices, and supplementary material of eligible publications and conference abstracts between Nov 15, 2013, and Nov 20, 2019, and we used ClinicalTrials.gov to find updated data or the primary or secondary report over the same time period. If study data

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was done in accordance with the recommendations of the Cochrane Collaboration and PRISMA guidelines.

Data analysis

The primary outcomes of interest were heart failure and MACE (defined as a composite of cardiovascular death, myocardial infarction, or stroke). If trials did not report MACE as an outcome according to this definition, the following alternative definitions were used in preferential order: cardiovascular death, myocardial infarction, or ischaemic stroke; all-cause death, myocardial infarction, or stroke; an expanded MACE endpoint that included other atherothrombotic events (excluding heart failure), fatal and non-fatal myocardial infarction, or stroke; or fatal and non-fatal myocardial infarction. Secondary outcomes included all-cause mortality, individual components of MACE, and occurrence of new or worsening heart failure. All cardiovascular endpoints were adjudicated and defined within the individual trials according to standard criteria (appendix p 9). The definition of cardiovascular endpoints was in accordance with standard diagnostic criteria across all trials, which allowed for trial comparisons.

A review of quality metrics was done, including rating