The Cardiovascular Effects of Glucagon-like Peptide-1 Receptor Agonists: A Trial Sequential Analysis of Randomized Controlled Trials

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Background and Objective: Glucagon-like peptide-1 (GLP-1) receptor agonists are a new class of anti-diabetic drugs. Their wider use for the treatment of patients with type 2 diabetes mellitus has led to concerns about its cardiovascular effects. However, the robustness of data leading to those concerns is unclear. The purpose of this study is to systematically assess the robustness of the available evidence on the adverse cardiovascular effects of GLP-1 receptor agonists in patients with type 2 diabetes.

Methods: The Cochrane library, MEDLINE, EMBASE and www.clinicaltrials.gov were searched from inception through to 25 January 2013. Randomized controlled trials (RCTs) were selected if they compared GLP-1 receptor agonists with placebo or other drugs with a duration?12 weeks. Mantel-Haenszel odds ratio (MH-OR) of cardiovascular events with 95% confidence interval (CI) was estimated using a random effects model. Trial sequential analysis based on required information size with an assumption of plausible reductions in relative risk in the low bias trials, 5% risk of a type I error and 20% risk of a type II error was used to explore the robustness of available evidence.

Results: Fifty-eight trials were included in the analysis (10 466 patients receiving GLP-1 receptor agonists and 7138 patients receiving comparators, respectively). Overall, the OR for cardiovascular events with GLP-1 receptor agonists was 0.52 (95% CI: 0.27V0.99) compared with placebo and 0.84 (95% CI: 0.52V1.36) with active controls. Trial sequential analyses showed that the actual accumulated sample size was only 11% (7445 of 65 212) and 13% (10 157 of 79 198) of the required information size for placebo-controlled trials and active-controlled trials, respectively. These results indicate that there is still insufficient evidence on cardiovascular events.
Conclusion: GLP-1 receptor agonists do not seem to show any increased risk of cardiovascular events. However, the available data from RCTs remain insufficient to confirm an absence of detrimental effect. More long-term trials and population-based studies are required to provide the necessary reassurance on the cardiovascular safety of GLP-1 receptor agonists.