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Review

Effect of glucagon-like peptide-1 on major cardiovascular outcomes in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials

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ABSTRACT

The effect of glucagon-like peptide-1 (GLP-1) treatment in patients with type 2 diabetes mellitus (T2DM) remains controversial. The purpose of this study was to compare the effect of GLP-1 and placebo/conventional antidiabetic agents on cardiovascular risk in T2DM patients. PubMed, EmBase and the Cochrane Library were searched to identify its eligible studies as well as manual searches for the reliability of this study. All eligible trials were performed in T2DM patients who received GLP-1 therapy or placebo/conventional antidiabetic agents. The reported outcomes included major cardiovascular events (MACE), and total mortality. Of 490 identified studies, we included 13 trials reporting data on 11,943 T2DM patients. Overall, the pooled results suggested that GLP-1 therapy has no or little effect on MACE (RR: 0.99; 95% CI: 0.88–1.12; P = 0.872) and total mortality (RR: 0.90; 95% CI: 0.70–1.15; P = 0.399). Furthermore, sensitivity analysis indicated that GLP-1 was associated with lower incidence of total mortality (RR: 0.28; 95% CI: 0.08–0.93; P = 0.037). We concluded that GLP-1 therapy was not associated with MACE and total mortality compared with placebo or antidiabetic agents.

1. Introduction

It is estimated that 35% of children born in United States will develop type 2 diabetes mellitus (T2DM) through the year 2050 [1]. Subsequently, the development of cardiovascular disease (CVD) becomes one of the most serious consequences of T2DM and a leading cause of death. Compared with nondiabetic patients, patients with T2DM have a higher risk of developing CVD [2]. According to Haffner S.J. and Cassells H., people living with diabetes had 2 to 4 folds CVD death rates higher than the rates for people without diabetes [3].

Although there are advances in the treatment of T2DM, it is difficult to achieve full control of blood glucose. Many epidemiologic studies demonstrated that glucose levels had a positive association with microvascular (kidney, eye, nervous system) and macrovascular (heart, aorta, brain) complications [4–8]. However, three randomized control trials interpreted that glucose reduction has a modest effect on reducing CVD in T2DM for longer duration, namely, glucose lowering alone is deficient for CVD reduction [9–11].

An approach involving the use of incretin agents becomes a new area of research and therapeutics in treating not only T2DM but also CVD morbidity and mortality related to T2DM. An increasing number of evidence pointed out that incretin hormone glucagon-like peptide-1 (GLP-1) may improve endothelial function and may have direct vascular-protective effects [12]. Previous meta-analysis did not suggest any detrimental effect of GLP-1 on CVD events at least in the short term and in low-risk individuals [13,14]. Currently, few meta-analyses focus on the efficacy of GLP-1 on all vascular-related events in patients with T2DM. Meanwhile, it remains to be seen whether GLP-1 can lead to lasting beneficial effects on glucose, CVD risk factors and vascular function. Therefore, we performed a meta-analysis and systemic review of randomized clinical trials to investigate the effect of GLP-1 on cardiovascular complication in adults with T2DM.

2. Materials and methods

2.1. Data sources, search strategy, and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 [15]. Randomized controlled trials (RCTs) evaluated that the effect of GLP-1 on the cardiovascular risk was eligible for

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inclusion, with no restrictions on language and publication status. Relevant trials were identified by searched electronic databases, which include PubMed, EmBase, and the Cochrane Library through Feb 2016. The core search terms are listed as follows: "incretin" OR "glp-1" OR "Liraglutide" OR "glucagon like peptide-1 analogue" OR "exenatide" OR "Byetta" OR "Bydureon" OR "liraglutide" OR "Victoza" OR "Saxenda" OR "lixisenatide" OR "Lyxumia" OR "albiglutide" OR "Tanzeum" OR "dulaglutide" OR "Trulicity" OR "Taspoglutide" AND "type 2 diabetes mellitus" OR "type 2 DM" AND "randomized controlled trials". Manual searches were also conducted for reference lists to identify additional eligible trials. The medical subject heading and abstract were used as initial screened, study design, disease status, interventions, control and reported outcomes were used as screened in detail to determine included trials. The literature search was independently undertaken by 2 authors, and any inconsistencies were settled by the group discussion until a consensus was reached. The criteria for eligible of the studies were as follows: (1) RCTs were evaluating GLP-1 versus placebo or conventional antidiabetic agents; (2) comparison of cardiovascular risk between GLP-1 and placebo/conventional antidiabetic agents treatment in T2DM patients; (3) articles had to describe the cases and controls in the diagnoses and the sources; (4) risk ratio (RR) with corresponding 95% confidence intervals (CIs) or data that can be calculated were reported. Concerning the exclusion criteria, we applied the following criteria: (1) the type of study was non-RCT; (2) the controls including patients with other disease; (3) the publications were duplicated studies, abstracts, reviews, or the reported data from an abstract or from a meeting.

2.2. Data extraction and quality assessment

The following data were extracted from included RCTs by two authors independently: first author or study group name, country, sample size, mean age, percentage male, glycated hemoglobin, intervention, control, BMI, median duration of diabetes, SBP, DBP, and the duration of the follow-up periods. The quality of the eligible studies was assessed using the Jadad guidelines [16]. Randomization, blinding, withdrawals, generation of random numbers, and concealment of allocation as the essential parts to a RCT, were scored ranged 0 to 5. A threshold of ≥4 points was regarded as a high-quality study. Any discrepancies were solved by group discussion for a consensus.

2.3. Statistical analysis

This meta-analysis was carried out with the software STATA Version 10.0. The primary outcomes of our study were major cardiovascular events (MACEs). The risk ratio (RR) with 95% confidence intervals (CIs) was performed and reported for the statistical analysis. We combined the RRs for MACEs by using a random-effect model [17,18]. The significance of the pooled RR was determined by the Z-test with a statistically significant $P < 0.05$. Heterogeneity was determined using a Q-test [19,20]. Sensitivity analysis was conducted by excluding any studies which had obvious outlier in terms of results [21]. Subgroup analyses were conducted on the basis of mean age, percentage male, glycated hemoglobin, BMI, median duration of diabetes, SBP, DBP, and the duration

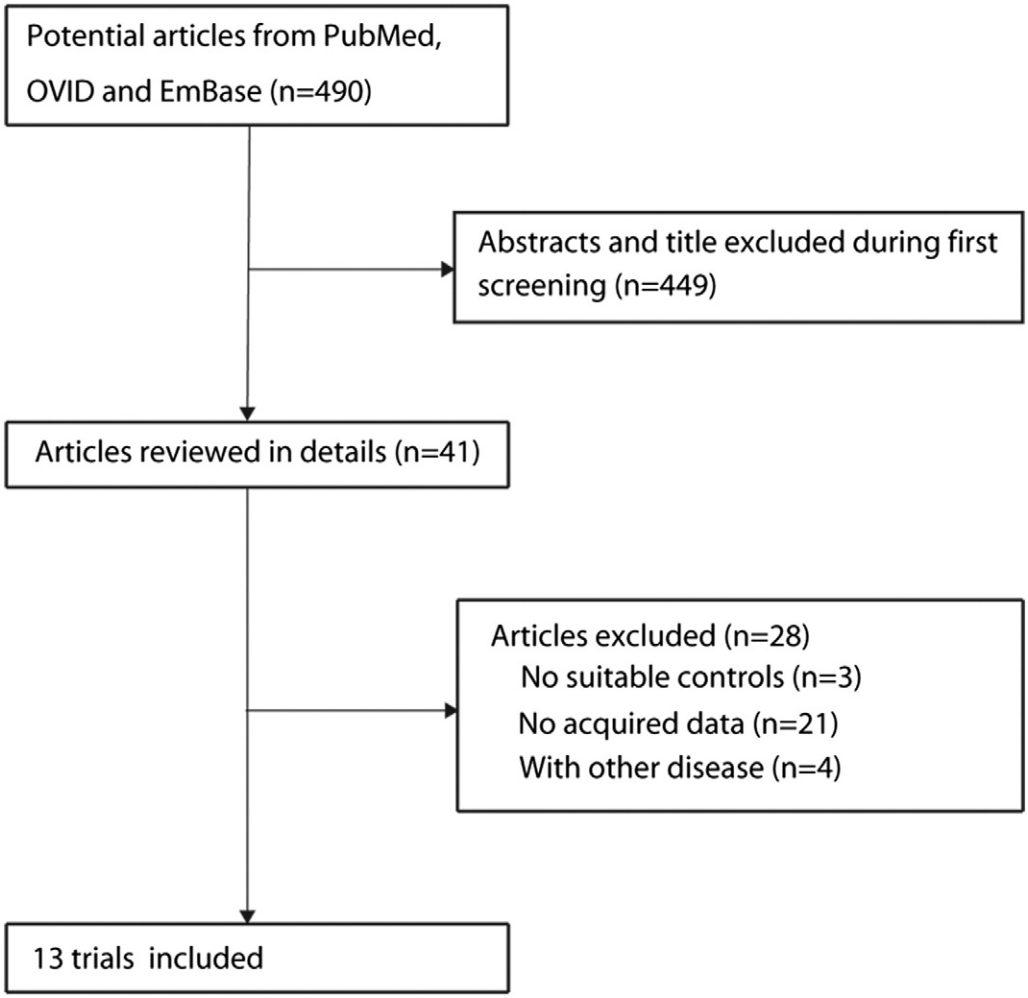

Fig. 1. Process of study selection.