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Meta-analysis of dipeptidyl peptidase-4 inhibitors use and cardiovascular risk in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Some meta-analyses have shown that dipeptidyl peptidase-4 (DPP-4) inhibitors decrease the risk of major adverse cardiovascular events (MACE) compared to placebo. However, this association has not been confirmed in large placebo-controlled clinical trials with cardiovascular events as a primary endpoint. The aim of the present meta-analysis is to assess the association between DPP-4 inhibitors use and cardiovascular risk using uniform definition of MACE.

Methods: Relevant studies through 31 December 2014 were searched in the electronic databases, and we identified all eligible trials comparing DPP-4 inhibitors with active drugs or placebo. Summary odds ratio (OR) with 95% confidence interval (CI) for MACE was calculated using random-effects model.

Results: In 69 trials included in our study, 36,488 patients were treated with DPP-4 inhibitors and 31,290 with other comparators. Treatment with DPP-4 inhibitors was associated with a lower risk of MACE (OR [95% CI] = 0.52 [0.36,0.76]) compared to sulfonylureas, while showed a trend toward increased risk (OR [95% CI] = 1.89 [0.60,5.93]) compared to sodium-glucose cotransporter 2 (SGLT2) inhibitors. The difference was not statistically significant when compared to placebo (OR [95% CI] = 1.04 [0.92,1.18]), and this tendency was similar in both subgroup analyses conducted with a general type 2 diabetes population as well as the population at high cardiovascular risk.

Conclusions: There is no significant difference in the risk of MACE between DPP-4 inhibitors and placebo groups. DPP-4 inhibitors show significantly lower risk of MACE when compared to sulfonylureas, while SGLT2 inhibitors might have lower risk compared to DPP-4 inhibitors.

1. Introduction

Diabetes is known as one of the risk factors for the incidence of cardiovascular events [1,2]. In addition to the condition itself, it has been reported that some drugs used for the treatment of diabetes such as rosiglitazone increase the risk of cardiovascular events [3]. There are growing concerns about the association between the use of hypoglycemic drugs and cardiovascular events, and therefore the US Food and Drug Administration (FDA) requires

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pharmaceutical companies to evaluate this association through clinical trials [4].

Drugs for type 2 diabetes include metformin, sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors and basal insulin [5]. DPP-4 inhibitors are relatively new medications for type 2 diabetes, and there are some clinical trials that have been initiated by request from the FDA, with the aim to reveal the association between the use of DPP-4 inhibitors and cardiovascular events [6–9]. Although it is necessary to wait for the completion of these clinical trials to obtain conclusive evidence, several meta-analyses designed to assess the risk of incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes receiving DPP-4 inhibitors have been previously performed [10–12]. These results suggest that DPP-4 inhibitors decrease the risk of MACE compared not only to active drugs for type 2 diabetes but also to placebo [10,12]. On the other hand, results of some large prospective clinical trials conducted on DPP-4 inhibitors observing cardiovascular events as a primary endpoint have also been reported, in which cardiovascular events occurred at similar rates in the patient groups treated with DPP-4 inhibitors and placebo [6–8]. The results of these large clinical trials did not present evidence that DPP4 inhibitors statistically significantly reduce the risk of MACE compared to placebo. However, it is also important to note that the study population in these large clinical trials comprised patients not only with type 2 diabetes but also at high cardiovascular risk, such as having an acute coronary syndrome within a certain period before randomization. Thus the population represents only a part of the general population with type 2 diabetes.

The aim of the present meta-analysis is to assess the association between DPP-4 inhibitors and cardiovascular risk using uniform definition of MACE when recently-implemented clinical trials are included.

2. Methods

This meta-analysis aimed to evaluate the cardiovascular risk of DPP-4 inhibitors in patients with type 2 diabetes. We used incidence of MACE reported as serious adverse events as the measure of cardiovascular risk, and to standardize the definition of MACE, we referred to the list provided by the FDA as the definition of MACE [13].

A literature search was performed in Medline, Embase and Cochrane Central Register of Controlled Trials up to 31 December 2014. In addition, through a search in www.clinicaltrials.gov website, we identified unpublished trials that had already had results posted in the ClinicalTrials.gov results database. The search terms were 'vildagliptin', 'sitagliptin', 'saxagliptin', 'alogliptin', 'linagliptin', 'dutogliptin', 'anagliptin' and 'teneligliptin'. In this meta-analysis, we included all clinical trials if they were randomized controlled trials in patients with type 2 diabetes, comparing DPP-4 inhibitors with other agents (other than DPP-4 inhibitors) or placebo, with a study duration of at least 24 weeks. Trials were excluded if there was insufficient information on MACE. Data extraction was performed by two independent authors (M.K. and M.N.). No review protocol was published. We used the Cochrane risk of bias assessment tool to assess the risk of methodological quality within the included studies [14].

Heterogeneity was assessed by using the I^2 statistic [15], where a value of 50% or greater indicated substantial heterogeneity. Moreover, considering the potential heterogeneity among the studies for the overall analysis such as the differences in study population and study design, subgroup analyses were performed by study duration (<52 weeks or ⩾52 weeks), type of comparators (placebo or active) and type of study population (general type 2 diabetes population, population at high cardiovascular risk or other special populations such as patients with renal failure or the elderly). Publication bias was assessed by the funnel plot and the rank correlation test [16]. We calculated odds ratio (OR) with 95% confidence interval (CI) for MACE defined above foreach individual study, and we used the random-effects model to calculate the summary OR with 95% CI, which accounts for heterogeneity among studies. Analyses were performed on an intention-to-treat basis, and trials with zero events were excluded from the analyses.

This present meta-analysis was reported following the PRISMA checklist [17]. A $p < 0.05$ (two-sided) was considered statistically significant. All analyses were performed using SAS software, version 9.2 (SAS Institute), and R software, version 3.2.0 [18].

3. Results

The trial flow is summarized in Fig. 1. Out of the included 84 trials, 15 trials were excluded because they did not report any events, resulting in 69 trials available for inclusion in this meta-analysis (Table 1, Appendix A). The analysis included 67,778 patients, and 36,488 and 31,290 patients were treated with DPP-4 inhibitors and other comparators (placebo or active drugs for type 2 diabetes other than DPP-4 inhibitors), respectively. Total exposure was 126,453 patient-years (66,099 and 60,355 patient-years for DPP-4 inhibitors and other comparators, respectively). Out of the 69 trials, 33 were placebo-controlled and 19 were active-controlled trials; 12 trials included both placebo and active comparator arms and five trials included switching from placebo to active drugs in the middle of the trials. The number of reported MACE was 631 in patients who received DPP-4 inhibitors and 612 in patients who received other comparators. We thought that the risk of bias in the included studies was low (Appendix B). The value of I^2 was low within the group of pooled studies ($I^2 = 9.9\%$), and the further potential heterogeneity was assessed by subgroup analysis. The funnel plot is shown in Fig. 2. The rank correlation test suggested no major publication bias (Kendall's tau rank correlation coefficient = −0.03, $p = 0.68$).

Analysis comparing DPP-4 inhibitors with other comparators showed non-significant trends toward decreased risk of MACE (OR [95% CI] = 0.88 [0.73,1.05], Fig. 3). Subgroup analysis by study duration (<52 weeks or ⩾52 weeks) also showed a similar tendency (OR [95% CI] = 0.85 [0.57,1.28], 0.86 [0.69,1.07], respectively, Fig. 4). The OR [95% CI] for MACE in DPP-4 inhibitors monotherapy trials was 1.00 [0.62,1.62].