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Effect of dipeptidyl peptidase-4 inhibitors on heart failure: A meta-analysis of randomized clinical trials

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ABSTRACT

Background: Recent studies have suggested that dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) may be associated with increased risk of heart failure (HF), but evidence was inconclusive. We aimed to determine the effects of DPP-4 inhibitors on risk of HF.
Methods: An extensive search in PubMed, EMBASE, CINAHL, IPA, Cochrane, ClinicalTrial.gov and the manufacturers' websites for randomized controlled trials (RCT) of all DPP-4 inhibitors was performed up to June 2015. All RCTs comparing DPP-4 inhibitors to any comparators with minimum follow-up of 12 weeks were included. The primary outcome was the occurrence of HF.
Results: A total of 54 studies with 74,737 participants were included for analysis. Overall, DPP-4 inhibitors were not associated with an increased risk of HF compared to comparators (relative risk (RR) 1.106; 95% CI 0.995–1.228; $p = 0.062$). When analyzed individually, saxagliptin was significantly associated with the increased risk of HF (RR 1.215; 95% CI, 1.028–1.437; $p = 0.022$), while others were not. Age ≥ 65 years, diabetes duration of ≥10 years and BMI ≥ 30 kg/m^2 were associated with an increased risk of HF among patients using saxagliptin.
Conclusions: Our meta-analysis suggested a differential effect of each DPP-4 inhibitor on the risk of HF. Use of saxagliptin significantly increases the risk of HF by 21% especially among patients with high CV risk while no signals were detected with other agents. This information should be taken into consideration when prescribing DDP-4 inhibitors.

1. Introduction

In recent years, numerous advancements have been made in the discovery and introduction of new anti-diabetes medications which have helped to expand options for the management of diabetes mellitus. While the ability of anti-diabetic drugs to provide glycemic control is essential, their effects on cardiovascular disease (CVD) may be of equal importance since CVD is the major cause of morbidity and mortality among patients with diabetes [1,2]. Based on this principle along with recent concern raised by previous drugs [3], the US Food and Drug Administration (FDA) requires the assessment of cardiovascular (CV) safety for new anti-diabetes agents [4]. Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are new anti-diabetic drugs that reduce blood glucose mainly by suppressing glucagon release through the enhancement of glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) [5]. Presently, members in this drug class include sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin. These agents have recently been introduced into clinical practice with wide acceptance and are currently recommended by international and national guidelines worldwide.

In response to FDA guidance, two large international multicenter randomized controlled phase III-IV studies; Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) [6] and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) [7] were recently conducted to assess the CV safety of saxagliptin and alogliptin, respectively. The SAVOR-TIMI 53 study reported a small, but significant 27% increase in rate of HF related hospitalization in patients treated with saxagliptin compared to placebo [6], while the EXAMINE study showed a numerical excess that did not achieve statistical significance in the risk of HF related hospitalization [7]. These reports were followed by two meta-analyses of randomized, controlled trials evaluating the effects

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of DPP-4 inhibitors and HF [8,9]. Both meta-analyses showed that DPP-4 inhibitors significantly increased the risk of HF [8,9]. However, those two meta-analyses were conducted with key limitations including restrictive inclusion criteria, failure to assess the effect of important patient characteristics on risk and small sample size in some members of the DPP-4 inhibitors. A recent meta-analysis published in February 2015 by Savarese G. et al. [10] aimed at evaluating the effects of DPP-4 inhibitors on various cardiovascular outcomes with heart failure as a part of such analysis. The heart failure results of the study were in line with two previous meta-analyses [8,9]. However, a new large multicenter randomized controlled trial study; Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) [11] reported the rate of hospitalization of HF did not differ between the two groups (3.1% in both groups). We therefore aimed to conduct an updated and more comprehensive meta-analysis with the focus on 3 key issues; 1) broadening inclusion criteria to include studies with ≥12 weeks of exposure, 2) assessing the effect of important patient characteristics on risk, and 3) including newer studies published after previous meta-analyses, especially from the newer agents which may be under-represented in previous meta-analyses [8,9] and the results from the TECOS study [11]. This may help improve the understanding on the effect of DPP-4 inhibitors on risk of HF.

2. Methods

2.1. Search strategy

An electronic literature search of PubMed, EMBASE, the Cochrane Library, CINAHL, IPA, and www.ClinicalTrial.gov were conducted using keywords including alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin, dipeptidyl peptidase 4 inhibitors, DPP-4 inhibitors, DPPIs and gliptin. The results of unpublished studies were identified through searching of www.clinicaltrials.gov, www.clinicaltrialresults.org and the manufacturers' websites. The FDA (www.fda.gov) and European Medicines Agency (EMA; www.ema.europa.eu) reviews of approved drugs, as well as published information provided to FDA in response to queries during the approval process, were also searched for retrieval of unpublished studies. The literature search was conducted from the inception of each database through June 2015.

2.2. Study selection

Studies were included if they met the following inclusion criteria 1) were randomized controlled clinical trials (RCTs), 2) were conducted in adults (18 years of age or older) using any DPP-4 inhibitors, 3) were conducted with any comparisons of DPP-4 inhibitor and placebo or active comparators (oral/injectable anti-diabetes agents), 4) were conducted with at least 12 weeks of follow-up time, and 5) reported any occurrence of HF and HF related hospitalizations.

2.3. Data extraction and quality assessment

Title and abstract of all articles were primarily retrieved and screened. The studies which met our inclusion criteria were reviewed in detail. Information of each included study was extracted using a standardized data extraction form. The information included treatment arms; DPP-4 inhibitor dose; patients per arm; study duration; disease type; age; hemoglobin A1c (HbA1c); body weight and body mass index (BMI); history of hypertension, dyslipidemia, coronary artery disease (CAD), smoking, metabolic syndrome, HF; medication at baseline; and number of HFs, hospitalization of HFs, events per treatment arm.

For multiple arm studies, any DPP-4 inhibitor arms were combined into "DPP-4 inhibitor group" and comparators were collapsed as an overall control group. The control groups were also analyzed separately against DPP-4 inhibitor groups. For studies reporting outcome at various time points, the results in longer observational time period were used.

Jadad scale was used to assess studies' methodological quality [12]. The Cochrane Collaboration risk of bias tool was also used to assess risk of bias [13]. The literature search, data extraction, and quality assessment were independently undertaken by two reviewers (JK, PD). Any disagreements in literature search, data extraction, and quality assessment were solved by all researchers' discussion.

2.4. Outcomes of interest

Primary outcome was an occurrence of HF. The occurrence of HF outcomes were defined as a clinically significant HF episode and/or a HF related hospitalization. Because the definition of a clinically significant HF episode or a HF related hospitalization were different among included RCTs, we used the data reported in the studies without any modification in the definition of HF related events.

2.5. Data synthesis and analysis

This meta-analysis was reported following the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) guidelines [14]. We pooled the risk ratios (RRs) and 95% CIs across studies using the DerSimonian and Laird random effects model [15]. The results were stratified by each individual DPP-4 inhibitor.

Subgroup analyses were conducted by several parameters including individual DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin, or vildagliptin), dose, duration of treatment baseline characteristics of subjects including age (<65 or ≥65 years), diabetes duration (<10 or ≥10 years), HbA1c at baseline (<8.0% or ≥8.0%), and BMI (<30 or ≥30 kg/m^2). In addition, we also stratified included studies into low CV-risk and high CV-risk groups. This was performed by comparison of annualized CV mortality rate in the placebo group of each study with the annualized CV mortality rate derived from diabetes subset of the Heart Outcomes Prevention Evaluation (HOPE) study [16], which was 2.16%. If a study had the control event rate (CER) that was equal or higher than 2.16%, it was considered as "high CV-risk" study. If a study had the CER lower than 2.16%, it was considered as "low CV-risk" study. After applying this criteria, we found that only EXAMINE [7], SAVOR-TIMI 53 [6] and TECOS [11] studies were stratified as "high CV-risk", while the other studies were stratified as "low CV-risk".

We conducted sensitivity analysis by including the studies that 1) had Jadad score ≥3, 2) met the Cochrane criteria risk of bias for unclear and low risk of bias, 3) met the Cochrane criteria risk of bias for low risk of bias, 4) had adjudicating cardiovascular (CV) committee and 5) assess the influence of individual studies on the results. Statistical heterogeneity was evaluated using the I^2 statistical test [17]. We generated funnel plots to examine possible publication bias [18], and these were supplemented by formal statistical testing using the Begg test [19] and the Eggers test [20]. All analyses were conducted using Stata version 10.1 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Study selection

Through our extensive search 4152 studies were identified. However, only 54 studies were included into the data analysis while 4098 studies were excluded. Reasons for exclusion were irrelevance or failure to meet inclusion/exclusion criteria (4080), post-hoc analysis in nature (8) and data duplication (10). As a result, a total of 54 studies with 74,737 patients were included in the final analysis (9 with alogliptin [7,21–26], 7 with linagliptin [24,27–30], 9 with saxagliptin [6,31–37], 19 with sitagliptin [11,24,38–48] and 10 with vildagliptin [24,49–56]) [Fig. 1]. There were a total of 133,771 patient-years of follow-up