Effect of Dipeptidyl Peptidase-4 Inhibitors on Heart Failure: A Network Meta-Analysis

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ABSTRACT

Background: Previous meta-analyses evaluating the effectiveness of individual dipeptidyl peptidase-4 (DPP-4) inhibitors on the risk of heart failure (HF) were limited because of the small number of trials with direct comparisons between two treatments. Methods: A Bayesian network meta-analysis was performed to investigate the relationship between DPP-4 inhibitors and the risk of HF in patients with type-2 diabetes mellitus. The primary outcome was the occurrence of HF or hospital admission for HF. Results: Fifty randomized controlled trials were identified. Relative to placebo, no increased risk of HF events was seen for vildagliptin (risk ratio [RR] 0.71; 95% confidence interval [CI] 0.25–1.68), sitagliptin (RR 0.86; CI 0.43–1.57), or saxagliptin (RR 0.84; 95% CI 0.33–1.61), but alogliptin was associated with a higher risk of HF (RR 2.13; 95% CI 1.06–6.26). Vildagliptin and sitagliptin were associated with a significantly decreased risk of HF compared with alogliptin. Vildagliptin had the highest probability to be the safest option with regard to the risk of HF (49.18%), followed by saxagliptin (26.56%), sitagliptin (20.76%), linagliptin (0.25%), and alogliptin (0.12%). A statistically significant inconsistency was noted in some comparisons. Conclusions: The risk of HF needs to be taken into account when prescribing DPP-4 inhibitors. Evidence suggests that vildagliptin may be the least harmful agent with regard to the risk of HF. However, a statistically significant inconsistency was identified in the Bayesian network meta-analysis. Therefore, further studies are warranted to evaluate the cardiovascular safety of DPP-4 inhibitors.

Keywords: dipeptidyl peptidase-4 inhibitor, heart failure, network meta-analysis, type 2 diabetes mellitus.

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"randomized controlled trial," “dipeptidyl peptidase-4 inhibitors (including alogliptin, linagliptin, sitagliptin, saxagliptin, and vildagliptin)."

We included studies if 1) the recruited population comprised patients with type 2 DM; 2) the intervention was with DPP-4 inhibitors, including alogliptin, linagliptin, sitagliptin, saxagliptin, and vildagliptin; 3) comparators were DPP-4 inhibitors, other hypoglycemic agents, and placebo; 4) the studies reported any occurrence of HF or hospital admission for HF; 5) the studies were randomized controlled trials (RCTs); 6) the studies were published in English. We excluded studies with zero events in both groups because these comparisons provide no information on treatment effect. To reach a consensus, a divergence of views was resolved by joint review of the literature.

Two independent investigators (W.G., Q.S.) reviewed the full text of eligible studies and extracted the relevant information. If different results were noted in the same trial, we extracted the most recent data for analysis. In some trials, if the DPP-4 inhibitors were sequentially used with another drug, we collected the data about the treatment before the switching occurred. The primary outcome was the occurrence of HF or hospital admission for HF, which was defined according to the individual trials. Intention-to-treat sample sizes were used when they were available. The Cochrane risk-of-bias tool was used to assess the risk of bias for RCTs [6].

We used the random effects model for the Bayesian network meta-analysis because it assumes and accounts for unexplained heterogeneity [7,8]. We used vague priors with uniform prior (0–2) distributions for parameters, such as means and standard deviations. All outcomes were expressed as risk ratios (RRs) and its corresponding 95% confidence intervals (CIs). Additionally, the analysis was done using the Markov chain Monte Carlo methods [7]. Four chains were suitable, yielding 400,000 iterations (100,000 per chain) generating the posterior distributions of the model parameters. Convergence was checked using the Brooks-Gelman-Rubin diagnostic [9]. The goodness of fit of the model was assessed by calculating residual deviance [10]. The I² statistic was used to investigate the possibility of statistical heterogeneity [11,12]. To assess inconsistency, we carried out the “node splitting” approach to calculate the Bayesian F value [11]. In addition, we evaluated rank probabilities to determine the probability of each treatment being the best in terms of safety outcome [13].

To explore the association between log-risk of HF and the length of study follow-up, we performed a meta-regression analysis, wherein treatment effects relative to placebo were allowed to depend on the study follow-up through a single interaction term [14]. Sensitivity analysis was performed by excluding the trials in which the outcome was hospital admission for HF. Additionally, we created a comparison-adjusted funnel plot to detect the presence of any publication bias [13,15]. The Bayesian framework meta-analysis was conducted by using R software (version 3.2.0), and further analysis was conducted by STATA 12.0. (The R code is shown in the Supplementary Appendix).

Results

Finally, 50 trials were included in the network meta-analysis (Supplementary Table 1). The PRIMA flow chart is shown in Supplementary Figure 1. The characteristics of the included studies and their quality assessment are shown in Supplementary Table 2. The following options were tested in the network: saxagliptin, sitagliptin, alogliptin, vildagliptin, linagliptin, placebo, and active comparison. Active comparators included metformin, gliptide, glipizide, gliclazide, glimepiride, canagliflozin, empagliflozin, pioglitazone, albigitide, and liraglutide. We regarded these agents as active comparators rather than the type of the hypoglycemic agents (e.g., sodium glucose cotransporter 2) because they were not therapy options that we focused on in our network meta-analysis. Therefore, we combined all these hypoglycemic agents into one active comparator, which was important for making a connected network. The network plot is given in Figure 1.

The results are shown in Table 1. Relative to placebo, a significant increased risk of HF was seen for alogliptin (RR 2.13; 95% CI 1.06–6.26), whereas sitagliptin (RR 0.86; 95% CI 0.43–1.57), vildagliptin (RR 0.71; 95% CI 0.25–1.68), or saxagliptin (RR 0.84; 95% CI 0.33–1.61) were comparable. Linagliptin had a tendency to increase the risk of HF (RR 2.76; 95% CI 0.98–8.31), although the difference was not significant.

When compared with that with vildagliptin, HF risk was significantly higher for alogliptin (RR 3.05; 95% CI 1.01–14.19) and linagliptin (RR 3.95; 95% CI 1.07–17.45) and nonsignificantly higher for sitagliptin (RR 1.21; 95% CI 0.44–3.69) and saxagliptin (RR 1.18; 95% CI 0.36–3.57).

The pooled results favored vildagliptin (RR 0.33; 95% CI 0.07–0.99) and sitagliptin (RR 0.40; 95% CI 0.11–0.96) compared with alogliptin. Relative to linagliptin, the pooled results favored vildagliptin (RR 0.25; 95% CI 0.06–0.94), sitagliptin (RR 0.31; 95% CI 0.09–0.95), and saxagliptin (RR 0.30; 95% CI 0.07–0.97).

The probability ranking of each treatment is shown in Supplementary Table 3. Vildagliptin had the highest probability to be the safest option with regard to the risk of HF (49.18%), followed by saxagliptin (26.56%), sitagliptin (20.76%), linagliptin (0.25%), and alogliptin (0.12%).

The global heterogeneity parameter I² values were 0% (Supplementary Figure 2). A statistically significant inconsistency was identified in the Bayesian framework (Supplementary Figure 3).

Bayesian meta-regression analyses showed no significant effect of the study follow-up time (regression coefficient 0.35; CI -0.56 to 1.25). The results of the sensitivity analysis were mostly similar to the results of the main analysis (Supplementary Table 4). The comparison-adjusted funnel plots of the network meta-analysis were not suggestive of any publication bias (Supplementary Figure 4).

Discussion

To the best of our knowledge, this is the first network meta-analysis to review the safety of different DPP-4 inhibitors on HF...
outcomes in patients with diabetes. We found that alogliptin is the only agent with a significantly increased risk of HF compared with placebo, and no signals were detected with other therapy options. Relative to alogliptin, sitagliptin and vildagliptin were associated with a lower risk of HF. Therapy with alogliptin seemed the most harmful across all the DPP-4 inhibitors, and vildagliptin had the highest probability to be the safest option with regard to the risk of HF.

There is a well-established epidemiologic link between DM and HF. Compared with patients without diabetes, those with diabetes were much more likely to develop chronic HF [16]. Therefore, controlling the risk factors of HF was emphasized in the management of type 2 DM. In our network meta-analysis, alogliptin was the only therapy option to have a higher risk of HF compared with placebo and seemed the most harmful therapy across all the DPP-4 inhibitors, suggesting that the HF risk needs to be taken into account when prescribing any DPP-4 inhibitors, especially for patients with diabetes who have pre-existing HF.

Some studies were performed to evaluate the effect of individual DPP-4 inhibitors on HF [3,4,17,18]. Their results showed that vildagliptin was not associated with an increased risk of HF compared with placebo, which was consistent with the results of our network meta-analysis [17]. However, we were able to provide a formal rank order for treatment strategies with respect to the HF risk. Our results demonstrated that vildagliptin had a higher probability of being at a superior ranking position, suggesting that vildagliptin is the least harmful in terms of HF risk. An observational study, conducted by Fu et al., evaluated the risk of hospitalization for HF differed across DPP-4 inhibitors by diabetes status and HF. Compared with patients without diabetes, those with diabetes were much more likely to develop chronic HF [16].

Table 1 - Estimated relative treatment effects as risk ratios (RRs) and its corresponding 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Alogliptin</th>
<th>Active comparator</th>
<th>Linagliptin</th>
<th>Placebo</th>
<th>Sitagliptin</th>
<th>Vildagliptin</th>
<th>Saxagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>—</td>
<td>1.23 (0.45, 2.68)</td>
<td>—</td>
<td>0.47</td>
<td>0.40</td>
<td>0.33</td>
<td>0.38</td>
</tr>
<tr>
<td>Active comparator</td>
<td>0.82</td>
<td>—</td>
<td>0.31 (1.43)</td>
<td>0.16 (0.94)</td>
<td>0.11 (0.96)</td>
<td>0.07 (0.99)</td>
<td>0.09 (1.07)</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>0.78</td>
<td>0.96 (0.35, 3.11)</td>
<td>—</td>
<td>—</td>
<td>0.36</td>
<td>0.31</td>
<td>0.25</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.13</td>
<td>2.63 (0.32, 2.82)</td>
<td>2.76</td>
<td>—</td>
<td>0.86</td>
<td>0.71</td>
<td>0.84</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>2.50</td>
<td>3.08 (1.40, 5.41)</td>
<td>0.98 (8.31)</td>
<td>—</td>
<td>0.43 (1.57)</td>
<td>0.25 (1.68)</td>
<td>0.33 (1.61)</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>3.05</td>
<td>3.73 (1.47, 11.86)</td>
<td>3.95 (1.74)</td>
<td>0.59 (3.94)</td>
<td>0.44 (3.69)</td>
<td>0.36 (3.57)</td>
<td>—</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.63</td>
<td>3.19 (1.04, 13.90)</td>
<td>3.34</td>
<td>1.19</td>
<td>1.01</td>
<td>0.85</td>
<td>—</td>
</tr>
</tbody>
</table>

Comparisons should be read from left to right. The estimate is located at the intersection of the treatments in the column heads and the treatments in the row heads. An RR value >1 favors the column-defining treatment. An RR value <1 favors the row-defining treatment.

Our study has some limitations. First, in some trials, DPP-4 inhibitors were used in combination with other antihyperglycemic drugs, which made it challenging to determine a direct link between DPP-4 inhibitors and HF risk. Second, the presence of several factors (e.g., drug doses and definitions of HF in the studies included in the analysis) could potentially increase the degree of heterogeneity among the studies. Because no relevant information was available, a meta-regression or subgroup analysis was not performed to explore these factors. Nevertheless, we used the random effect model to overcome the constraint of common variance among trials. Third, network inconsistency was noted in some poor analyses that included active comparator versus alogliptin, placebo versus vildagliptin, and placebo versus active comparator. The reasons for the inconsistency may be the extremely low incidence of HF and the small number of the head-to-head studies [21]. In our network meta-analysis, relative to alogliptin, the active comparator and placebo showed a trend to decrease the risk of HF (RR 0.44; 95% CI 0.20–0.92), respectively. The effect estimated from indirect comparison showed that the placebo had a lower HF risk compared with the active comparator (RR 0.44; 95% CI 0.20–0.90). However, placebo was significantly superior to the active comparator from the only three direct evidence (RR 1.3 × 10−6; 95% CI 6.20 × 10−6–0.11), which was not consistent with the results from indirect evidence. In short, a small number of studies comparing the active comparator versus placebo and the extremely low incidence of HF may have affected network consistency in those comparisons. Thus, the results of the network meta-analysis should be interpreted cautiously.

Overall, our study suggests that the HF risk needs to be taken into account when using DPP-4 inhibitors for patients with type 2 DM. Evidence suggests that differences exist among individual DPP-4 inhibitors and that vildagliptin seems to be the least harmful with regard to the risk of HF. Nevertheless, our results

\[\text{RR} = \frac{\text{Number of events in the treatment group}}{\text{Number of events in the control group}}\]
should be interpreted with caution, since some limitations are present. Hence, large RCTs with prespecified, well-defined safety outcomes are warranted to assess the impact of DPP-4 inhibitors on HF outcomes.

**Supplemental Materials**

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2017.04.010 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

**REFERENCES**


