Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis

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Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral antidiabetic agents that hold the potential of slowing the progress of type 2 diabetes mellitus. Their long-term safety is still a subject of debate. A systematic review of randomized, controlled trials was undertaken to comprehensively profile the safety of chronic treatment of type 2 diabetes mellitus with DPP-4 inhibitors. We searched data sources including MEDLINE, CENTRAL, publishers’ and manufacturers’ databases. Eligible trials were double-blind, randomized, placebo or active-controlled trials with ≥18 weeks duration in patients with type 2 diabetes reporting safety outcomes. Meta-analysis was performed separately for trials in which the control group received placebo (44 studies), another gliptin (3 studies) and any other antidiabetic drug (20 studies). Risk ratios with 95% confidence intervals were computed using a Mantel-Haenszel fixed-effect model for general safety outcomes, hypoglycaemia and adverse events by system organ class. Of 307 publications retrieved, 67 randomized, controlled trials met the eligibility criteria and were included in this review (4 alogliptin, 8 linagliptin, 8 saxagliptin, 20 sitagliptin, and 27 vildagliptin trials). Adverse events with gliptin treatment were at placebo level (relative risk (RR) 1.02 [0.99, 1.04]). No increased risk of infections was detectable (RR 0.98 [0.93, 1.05] compared to placebo and 1.02 [0.97, 1.07] compared to other antidiabetic drugs). Asthenia (RR 1.57 [1.09, 2.27]) as well as cardiac (RR 1.37 [1.00, 1.89]) and vascular disorders (RR 1.74 [1.05, 2.86] for linagliptin) emerged as adverse events associated with DPP-4 inhibitor treatment. The risk of hypoglycaemia was low with DPP-4 inhibitor treatment (RR 0.92 [0.74, 1.15] compared to placebo, RR 0.20 [0.17, 0.24] compared to sulphonylureas) in the absence of sulphonylurea or insulin co-therapy, but significantly elevated for combination therapy of sulphonylurea or insulin with sitagliptin or linagliptin (RR 1.86 [1.46, 2.37] compared to placebo). A large body of data supports the long-term safety of gliptin treatment and refutes an increased risk of infections. Further research is needed to clarify a possible link to asthenia, cardiac and vascular events. For combination therapy with insulin or insulin secretagogues, a careful choice of the agent used may limit the risk of hypoglycaemia.

Keywords: adverse drug reactions, antidiabetic drug, DPP-IV inhibitor, meta-analysis, type 2 diabetes

Introduction

Since the initial approval of sitagliptin five years ago, dipeptidyl peptidase-4 (DPP-4) inhibitors, or gliptins, have played an increasing role in the treatment of type 2 diabetes mellitus [1–3]. They represent a substantial advance in antidiabetic therapy, combining several advantages over other insulin secretagogues (i.e. sulphonylureas and glinides). Firstly, blood glucose control is achieved by stimulating insulin release in a glucose-dependent way. Therefore, patients treated with gliptins are at lower risk of hypoglycaemia compared to those using other insulin secretagogues [4]. Moreover, unlike the latter, the gliptins do not appear to lead to secondary failure of the insulin-secreting β-cells of the pancreas and were shown to maintain the secretory capacity of β-cells during 1-year treatment [5]. A growing body of evidence indicates that they may slow the progress of the disease [6].

The efficacy of DPP-4 inhibitors is in the same range as that of other antidiabetic drugs, and the gliptins are often prescribed in combination with the first-line agent metformin or other oral antidiabetic drugs in order to achieve tight glycaemic control [7]. Previous meta-analyses of gliptins administered as mono- or combination therapy have shown mean changes in HbA1c in the range of −0.27 to −0.80% (−3 to −9 mmol/mol) compared to placebo, sustained in studies over 12 to 52 weeks [7–12]. The beneficial effect of gliptins on blood glucose is not accompanied by a gain in body weight, and the risk of hypoglycaemia is low.

The safety profile of the gliptins appears to be benign. Various specific safety aspects have previously been explored in systematic reviews of randomized, controlled trials of DPP-4 inhibitors. Meta-analyses by Amori and Richter have identified an increased risk of infections including nasopharyngitis and urinary tract infections [8,9] and of headache [8] compared to all controls combined. Both analyses are limited by the availability of included studies within the covered timeframe (up to May 2007 and January 2008, respectively), with study durations...
of included trials ranging from 2 to 52 weeks. More importantly, both meta-analyses combined trials in which patients in the control groups received placebo with trials using active comparators. This procedure may mask adverse effects shared by gliptins and other antidiabetic drugs. It also constitutes the main limitation of published analyses of pooled patient-level data [13–17]. Monami et al., in contrast, compiled a meta-analysis of DPP-4 inhibitors compared to placebo [10]. They investigated the risk of cardiovascular events and of hypoglycaemia, as well as the overall risk of adverse events. None of the odds ratios obtained were significantly different from one, thus confirming a benign safety profile of DPP-4 inhibitors. For the evaluation of other adverse events, Monami et al. also combined placebo and active antidiabetic control groups.

The risk of serious adverse events is low [13,15]. However, several case reports of pancreatitis with DPP-4 inhibitor treatment have led to the inclusion of a warning statement on all product labels, and prompted an assessment of the pancreatitis risk based on observational pharmacy/health insurance claims [18–20] and pooled patient data [17,21]. These post hoc analyses do not support a significantly elevated risk of developing pancreatitis with gliptin treatment over the near threefold baseline risk that patients with diabetes have over healthy controls [22,23]. Data from RCTs published to date are insufficient for meta-analysis of pancreatitis data due to the low incidence and low rate of reporting this event [24].

Over the last 2 years, numerous RCTs with longer duration (up to 104 weeks) investigating the efficacy and safety of gliptins have been published, so that a large amount of additional medium- and long-term safety data has become available after completion of the reviews by Amori, Richter and Monami. The present systematic review and meta-analysis aims at providing a more complete adverse event profile of DPP-4 inhibitors in patients with type 2 diabetes compared to placebo and, separately, compared to other active oral antidiabetic agents. It analyses double-blind, randomized, placebo or active-controlled trials with ≥18 weeks duration reporting safety outcomes in patients with type 2 diabetes, with outcomes spanning general safety measures and hypoglycaemia, as well as effects on the immune system and other MedDRA system organ classes.

Methods

A preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist was used to describe the processing of references and studies [25].

Eligibility Criteria

Trials were included in the systematic review if they (i) involved patients diagnosed with type 2 diabetes mellitus, (ii) investigated a DPP-4 inhibitor as study medication (alogliptin, linagliptin, saxagliptin, sitagliptin or vildagliptin), (iii) were randomized, double-blind, and controlled by either placebo or an active comparator, (iv) reported safety data separately for each treatment group and (v) had a duration of at least 18 weeks. To ensure a high level of data quality, studies were excluded if double-blinding was not maintained throughout. Interim analyses were excluded if analyses at later stages of the trials were available, so that the most long-term safety data possible were used. No limitation was set for age, sex, ethnicity, baseline HbA1c and baseline body mass index (BMI) of the participants, or for background medication. No language restrictions were applied.

Information Sources and Search Strategy

The bibliographic databases MEDLINE (via PubMed) and CENTRAL as well as Springer (www.springerlink.com) and Wiley (onlinelibrary.wiley.com) online databases were searched for published articles up to 17 October 2011. The starting date of the search was unrestricted. Unpublished material was retrieved from manufacturer databases (www.clinicalstudyresults.org; trials.boehringer-ingelheim.com/ Home/TrialResults/index.jsp;www.novctrd.com/xtdWebApp/ clinicaltrialrepository/public/login.jsp;www.takeda.com/c-trl/report-summaries/article_53.html;www.astrazenecaclinicaltrials.com; www.astrazenecaclinicaltrials.com). The search employed in MEDLINE was limited to “randomized controlled trial”, and used the terms #1: alogliptin or linagliptin or saxagliptin or sitagliptin or vildagliptin, #2: diabet*, #3: adverse OR events OR event OR safety OR safe OR tolerated OR side effect, and #4: #1 AND #2 AND #3. In CENTRAL, to avoid duplicate records, this was supplemented by #5: #4 AND NOT ‘accession number’ near pubmed. The Wiley online library was searched using ‘alogliptin OR linagliptin OR saxagliptin OR sitagliptin OR vildagliptin (in Article Titles) AND adverse OR events OR event OR safety OR safe OR tolerated OR side effect (in All Fields) AND Randomized Controlled Trial (in All Fields) AND diabetes OR diabetic (in All Fields)’. Manufacturer databases were searched using only the International Nonproprietary Name of the drugs. Electronic searches, inclusion/exclusion of references and data extraction for included studies were performed by one reviewer (K. G.) and checked by the other (S. G.). Any disagreements were resolved by consensus.

Study Selection

The trials were assessed for eligibility based on information contained in the abstracts and, if inconclusive, the full texts of the publications retrieved. Data from more than one report on the same trial and with the same treatment duration were combined for inclusion in the systematic review.

Data Extraction Process and Outcomes

A predefined data set consisting of (i) an individual reference identifier (author and publication year), (ii) fundamental study data (indication, treatment duration, number of patients randomized, treatment arms and background medication), (iii) patient characteristics at baseline (mean age, sex and ethnicity, duration of type 2 diabetes mellitus, BMI and HbA1c), (iv) quality measures (description of random sequence generation and allocation concealment, blinding, set of patients analyzed for efficacy, dropout rate, funding source) and (v) indicators for quality and completeness of adverse event reporting (investigator-rated adverse events, reporting thresholds for...
MedDRA preferred terms, reporting of adverse event data by system organ class) were collected for each trial. Outcome measures were extracted from included trials using predefined checklists (developed on a sample set of included trials) with preferred terms completed as needed, and analyzed by one reviewer (K. G.), then checked by the other (S. G.). Outcomes evaluated in the meta-analysis consisted of general safety measures (sum of adverse events, serious adverse events, discontinuation due to adverse events and deaths), number of patients with hypoglycaemia, and sum of events in the nine most frequently reported system organ classes.

Data reported in the form of tables were extracted directly into MS Excel, and data reported in text form were tabulated. Whenever only percentages were reported, absolute numbers of participants experiencing the event were derived from percentages by multiplying the percentages by the number of patients in the safety population and rounding to the closest full figure. Data on adverse events were retrieved by the preferred terms reported in the publications and grouped by system organ class. Certain terms used in the publications were combined to allow for a more condensed collection of diversely reported data. Thus, ‘musculoskeletal pain’ includes myalgia, back pain, pain in extremity, sciatica, and cervicobrachial syndrome. Gastritis was combined with gastroenteritis, headache with migraine, hyperlipidaemia with hypercholesterolaemia and hypertriglyceridaemia, nasopharyngitis with pharyngitis and pharyngotonsillitis, and urinary tract infection with cystitis. The classification of oedema in included studies was not always clear, and was classified by us as a general disorder.

Summary Measures, Synthesis of Results and Additional Analyses

Meta-analyses for safety outcomes were conducted separately for comparisons against other gliptins, other antidiabetic agents, and placebo. Results of trials were pooled for each outcome using the RevMan software [26]. Adverse events were treated as dichotomous outcomes. Risk ratios were used as the summary measure and computed with a Mantel-Haenszel (M-H) fixed-effect model. Fixed-effect modelling was chosen on the grounds that the incidence of events was rather low, and the treated populations were relatively homogeneous [27,28].

Sensitivity analyses were performed for any significant result. Subgroup analyses were performed for individual DPP-4 inhibitors when compared against placebo, and for classes of comparators when DPP-4 inhibitors were compared against other antidiabetic drugs. The subgroups were considered evaluable only if they contained three or more studies. The significance of subgroup differences was evaluated by the $\chi^2$ test. Heterogeneity between studies was assessed using the $I^2$ statistic [29].

Risk of Bias Across Studies

Publication bias was assessed for each outcome by visually judging funnel plot asymmetry about the central axis. We plotted log RR on the x-axis and standard error on the y-axis.

Results

Search and Selection of Studies

The search results are summarized in figure 1. A total of 79 reports corresponding to 67 eligible trials were retrieved and included in the meta-analysis. All were randomized, controlled trials published in English (n = 78) or German (n = 1).

Study and Patient Characteristics

The key characteristics of included studies are summarized in Table S2 [30–86]. A DPP-4 inhibitor was received by 23,456 participants and a control by 15,300 participants in trials ranging from 18 to 104 weeks duration. This corresponds...

Figure 1. PRISMA flow diagram of randomized, controlled trials (RCT) with minimum 18 weeks duration evaluating the use of dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes. AD, antidiabetic drug; PBO, placebo; T2DM, type 2 diabetes mellitus; w, weeks.
to 36,570 patient-years of follow-up. Forty-four trials were placebo-controlled, the control groups of 20 trials involved an antidiabetic agent from another class and three were head-to-head trials of two DPP-4 inhibitors.

Participants were overweight or obese patients with type 2 diabetes mellitus, with a mean baseline BMI between 25 and 33 kg/m² and HbA1c in the range of 53–86 mmol/mol (7–10%). The patient demographics were balanced throughout studies; 53% of participants were men, 66% Caucasian and the mean age at baseline was 57. Elderly patients (mean age >65 years) were included in 6 of 67 studies, and Asian participants predominated in 3 of 67 studies. The co-medication varied, and so did the mean duration of disease, which ranged between 1 and 17 years.

Methodological Quality of Studies
Measures of the quality of included studies are shown in Table S1. Where reported, random sequence generation and allocation concealment were adequate. However, only 33 and 22% of studies, respectively, reported methods for random sequence generation and allocation concealment, so that selection bias cannot be excluded. Double-blinding was maintained throughout all studies, and double-dummy techniques were employed as appropriate. Primary efficacy analysis was performed by the intention-to-treat principle in 86% of studies, and 93% described discontinuations due to adverse events. Investigator-rated adverse events were reported in 52% of studies, for the remainder, the assessment method of adverse events was not disclosed. The mean discontinuation rate was 21%. All studies were manufacturer-sponsored.

Risk of Bias across Studies
Publication bias was not detectable by visually evaluating funnel plot asymmetry for any outcome (see Appendix S1).

Inconsistencies in reporting adverse events were observed both on system organ class and preferred-term level (Table S1). Presenting summary data by system organ class allows quantifying adverse events in full and identifying target organs for the main effects, which may then be analyzed in detail on a preferred-term level. Full reporting of adverse event numbers by system organ class was uncommon: half the studies (34 of 67) provided summary figures for one or no system organ class. The system organ classes evaluated in the present meta-analysis were reported in full in only 27% of studies, the remainder focussed on a varying set of system organ classes. The majority of studies (68%) used reporting thresholds for incidence of adverse events ranging from 1 to 5%. These reporting thresholds affect estimated control group risks and prevent calculation of meaningful numbers-needed-to-harm values.

General Safety Outcomes
The computed risk of adverse events, serious adverse events and discontinuations due to adverse events in this meta-analysis was at placebo level for all DPP-4 inhibitors (Tables 2–5 and S3). Subgroup analyses for individual gliptins showed that none was associated with a significantly elevated risk in these general safety measures, and no subgroup differences were detected by the $\chi^2$ test. The included studies were homogeneous with $I^2 < 50\%$, with the exception of two subgroups in Table 1. The results for individual studies including forest plots are provided in the online appendix (figures S3 and S4).

Less than one in 100 participants died during treatment, and only about 40% of studies reported any deaths. We used Peto odds ratio (OR) as the metric to analyze the rare deaths during treatment, and found them to be evenly distributed over intervention and placebo groups (Table S4, figure S5). No difference was detected in comparison to other antidiabetics, either (Table S5).

Hypoglycaemia
The number of patients with hypoglycaemia could be retrieved for 39 placebo-controlled trials. Some heterogeneity, as well as higher risk ratios for hypoglycaemia, was observed in the linagliptin and sitagliptin subgroups (Table S6). To clarify the observed hypoglycaemia risks, an additional analysis was performed of trials with sulphonylurea or insulin co-medication separately from trials that did not include these combinations. Without concomitant administration of insulin or sulphonylurea, no elevated risk of hypoglycaemia was observed for any gliptin, and heterogeneity was absent overall and for all subgroups with more than two studies (Table S7). In contrast, an elevated hypoglycaemia risk over placebo was associated with the concomitant administration of linagliptin or sitagliptin and insulin or a sulphonylurea (Table S8, figure 2). A $\chi^2$ test for subgroup differences was highly significant ($p = 0.003$). Sensitivity analysis was performed using a random-effects model, and the results remained consistent. However, the number of studies in each subgroup is low and heterogeneity is present, so that more data are needed to support these results. Among the three head-to-head trials included in this analysis, one compared sitagliptin and vildagliptin in patients with type 2 diabetes mellitus,
Table 2. Risk of any adverse events compared to other antidiabetic drugs.

<table>
<thead>
<tr>
<th>Outcome/subgroup</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Mean control group incidence</th>
<th>RR (M-H, fixed, 95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events, total</td>
<td>19</td>
<td>15 517</td>
<td>69.4%</td>
<td>0.94 [0.92, 0.96]</td>
<td>47%</td>
</tr>
<tr>
<td>DPP-4 against metformin</td>
<td>4</td>
<td>2758</td>
<td>51.7%</td>
<td>0.92 [0.86, 0.99]</td>
<td>0%</td>
</tr>
<tr>
<td>DPP-4 against sulphonylurea</td>
<td>9</td>
<td>9342</td>
<td>76.1%</td>
<td>0.94 [0.92, 0.97]</td>
<td>7%</td>
</tr>
<tr>
<td>DPP-4 against thiazolidinedione</td>
<td>3</td>
<td>1618</td>
<td>65.0%</td>
<td>1.01 [0.94, 1.07]</td>
<td>0%</td>
</tr>
<tr>
<td>DPP-4 against others</td>
<td>3</td>
<td>1799</td>
<td>65.0%</td>
<td>0.85 [0.79, 0.92]</td>
<td>89%</td>
</tr>
</tbody>
</table>

Table 3. Risk of serious adverse events compared to placebo.

<table>
<thead>
<tr>
<th>Group/subgroup</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Mean control group incidence</th>
<th>RR (M-H, fixed, 95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events, total</td>
<td>42</td>
<td>20 955</td>
<td>5.0%</td>
<td>0.96 [0.85, 1.09]</td>
<td>0%</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>4</td>
<td>1910</td>
<td>3.7%</td>
<td>1.30 [0.76, 2.22]</td>
<td>0%</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5</td>
<td>3438</td>
<td>7.7%</td>
<td>0.71 [0.47, 1.06]</td>
<td>36%</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>5</td>
<td>2850</td>
<td>4.3%</td>
<td>1.04 [0.79, 1.39]</td>
<td>0%</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>13</td>
<td>7011</td>
<td>6.0%</td>
<td>1.02 [0.81, 1.28]</td>
<td>11%</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>15</td>
<td>5746</td>
<td>5.0%</td>
<td>0.89 [0.71, 1.11]</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 4. Risk of serious adverse events compared to other antidiabetic drugs.

<table>
<thead>
<tr>
<th>Group/subgroup</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Mean control group incidence</th>
<th>RR (M-H, fixed, 95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events, total</td>
<td>20</td>
<td>15 848</td>
<td>8.4%</td>
<td>0.95 [0.86, 1.06]</td>
<td>17%</td>
</tr>
<tr>
<td>DPP-4 against metformin</td>
<td>4</td>
<td>2758</td>
<td>2.9%</td>
<td>1.07 [0.70, 1.62]</td>
<td>0%</td>
</tr>
<tr>
<td>DPP-4 against sulphonylurea</td>
<td>9</td>
<td>9342</td>
<td>11.4%</td>
<td>0.95 [0.85, 1.06]</td>
<td>21%</td>
</tr>
<tr>
<td>DPP-4 against thiazolidinedione</td>
<td>4</td>
<td>1949</td>
<td>6.4%</td>
<td>0.92 [0.65, 1.31]</td>
<td>72%</td>
</tr>
<tr>
<td>DPP-4 against others</td>
<td>3</td>
<td>1799</td>
<td>8.4%</td>
<td>0.94 [0.50, 1.77]</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 5. Risk of treatment discontinuation due to adverse events compared to placebo.

<table>
<thead>
<tr>
<th>Group/subgroup</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Mean control group incidence</th>
<th>RR (M-H, fixed, 95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuations</td>
<td>44</td>
<td>21 509</td>
<td>3.1%</td>
<td>1.04 [0.89, 1.22]</td>
<td>1%</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>4</td>
<td>1910</td>
<td>2.3%</td>
<td>1.15 [0.57, 2.32]</td>
<td>0%</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>6</td>
<td>3683</td>
<td>2.9%</td>
<td>0.85 [0.55, 1.30]</td>
<td>0%</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>5</td>
<td>2850</td>
<td>3.7%</td>
<td>1.35 [0.90, 2.03]</td>
<td>0%</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>13</td>
<td>7011</td>
<td>2.7%</td>
<td>1.00 [0.75, 1.33]</td>
<td>16%</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>16</td>
<td>6055</td>
<td>3.6%</td>
<td>1.01 [0.77, 1.33]</td>
<td>21%</td>
</tr>
</tbody>
</table>

diabetes mellitus and severe renal insufficiency, either untreated or treated with sulphonylurea, thiazolidinediones, insulin or gliptides as mono- or combination therapy. No difference between the agents could be detected in this trial, and we computed a RR of 1.02 [0.48, 2.17] using vildagliptin as the experimental agent and sitagliptin as the control.

**Safety Results by System Organ Class**

The incidence of reported adverse events was no different from placebo for most system organ classes (Table S9). This includes infections and infestations, gastrointestinal, metabolism/nutrition, musculoskeletal/connective tissue and skin/subcutaneous tissue disorders. It applies also to subgroup analyses for every individual gliptin (results not shown).

**Infections and Infestations.** The overall RR for all DPP-4 inhibitors compared to placebo that was computed for infections/infestations was 0.98, with a narrow 95% confidence interval (CI) of [0.93, 1.15]. Similarly, compared to other antidiabetic agents, it was 1.02 [0.97, 1.07]. However, we performed additional analyses because of previous signals of elevated infections risk [8,9]. Infections cited in the labels of DPP-4 inhibitors, i.e. nasopharyngitis, upper respiratory tract infections and urinary tract infections [87–89], were assessed individually.

The risk of upper respiratory and urinary tract infections was not significantly elevated compared to placebo overall (Table S10) and for all gliptin subgroups (results not shown). The risk of nasopharyngitis was marginally elevated in our meta-analysis of 34 gliptin trials (RR 1.13 [0.99, 1.29]), and was consistent in sensitivity analyses using random-effects, or using Peto OR as the summary statistic (Table S11, figure S6). Statistical significance was reached only in the sitagliptin subgroup (RR 1.35 [1.03, 1.77]), which included the largest...
Figure 2. Hypoglycaemia: comparison of dipeptidyl peptidase-4 (DPP-4) inhibitors against placebo, each with insulin or sulphonylurea co-medication.

number of patients. However, the other subgroups showed the same trend and a $\chi^2$ test did not reveal any subgroup differences ($p = 0.30$).

Cardiac and Vascular Disorders. Cardiac disorders were reported in less than half the placebo-controlled trials. The meta-analytical results in Table S12 show a trend towards elevated risk of cardiac disorders overall (see also figure S7). Only the linagliptin and vildagliptin subgroups were evaluable (five and seven included studies, respectively), but statistical significance was not reached in either. Because of the low reported event rate, sensitivity analysis was performed using Peto odds ratios (OR) as the summary estimate. Consistent results were obtained. The results were not significant with a random-effects model (RR 1.38 [0.81, 2.36]). In 11 active-controlled trials reporting cardiac disorders, no difference was found for this outcome between the gliptin and comparator groups (Table S13).

Twenty-five placebo-controlled trials reported vascular disorders (Table S14, figure S8). These were mostly at placebo level. However, a significant risk was computed based on four studies for patients taking linagliptin (RR 1.74 [1.05, 2.86]), which was consistent when using Peto ORs as the summary estimate (RR 1.65 [1.06, 2.59]). No heterogeneity was detected in this subgroup ($I^2 = 0\%$). A $\chi^2$ test for subgroup differences did not reach significance ($p = 0.16$). No elevated risk was observed for gliptins in active-controlled trials overall or in any comparator subgroup (Table S15).

General Disorders. The majority of adverse events in ‘general disorders’ were asthenia, fatigue and oedema. Meta-analysis of 23 placebo-controlled studies showed that the overall risk of general disorders was similar in patients taking gliptin or placebo (Table S16). Vildagliptin was a noteworthy exception, with a computed risk ratio of 1.29 [1.08, 1.54]. Sensitivity analysis indicated that the point estimate was similar using a random-effects model, though the result was not significant (RR 1.30 [0.99, 1.69]). Subgroup differences were not significant in a $\chi^2$ test ($p = 0.09$). Compared to other antidiabetic drugs with the exception of metformin, the gliptins led to a substantially lower risk of general disorders (Table S17).

To shed further light on this issue, a separate analysis was performed for asthenia and fatigue. Asthenia was reported as an adverse event only in vildagliptin studies and in one linagliptin study. Five vildagliptin studies contributed to a risk ratio of 1.57 [1.09, 2.77] (figure 3). The studies were homogeneous ($I^2 = 6\%$), and results remained significant in a sensitivity analysis for random-effects modelling or Peto OR. A
combined analysis of linagliptin and vildagliptin also yielded a significantly elevated asthenia risk (RR 1.53 [1.08, 2.16]). Based on an assumed control group risk of 3.7% (mean incidence in the six included studies), the NNH for asthenia is 59.

In contrast, vildagliptin does not affect the incidence of fatigue compared to placebo (RR 1.08 [0.67, 1.75]), and sitagliptin even shows a beneficial effect (RR 0.50 [0.29, 0.89], figure S9). The studies in each subgroup were homogeneous, and the result was consistent with random-effects modelling.

Nervous System Disorders. A slightly elevated risk of 1.14 [1.02, 1.26] for nervous system disorders, mainly dizziness and headache, was observed in comparison to placebo (Table S18, figure S10). The studies were homogeneous (I² = 0%), but sensitivity analysis showed that the risk was no longer significant using random-effects modelling (RR 1.10 [0.99, 1.22]). Statistical significance was not reached for any individual agent. The risk was not elevated compared to other antidiabetics (Table S19).

Head-to-Head Trials of DPP-4 Inhibitors

No differences between the agents were detected in head-to-head trials of saxagliptin (one trial) or vildagliptin (two trials), each compared against sitagliptin. The only exception, a lower risk of skin or subcutaneous tissue disorders with saxagliptin compared to sitagliptin (RR 0.40 [0.18, 0.89]) was not judged clinically significant by the authors [30].

Discussion

Summary of Evidence

The present review and meta-analysis of 67 medium- or long-term RCTs of DPP-4 inhibitors contributes to the available evidence that these agents are well tolerated in the treatment of type 2 diabetes mellitus. The incidence of adverse events and serious adverse events was no different from placebo, and patients treated with gliptins experienced less adverse events and were less likely to discontinue due to adverse events than with most other antidiabetic agents. The results for total adverse events are in line with those of the earlier systematic analysis of placebo-controlled trials by Monami et al. [10]. No previous meta-analysis investigated the risk for serious adverse events and discontinuations due to adverse events compared to placebo, and our findings thus provide further evidence in support of the overall safety of DPP-4 inhibitors.

The pooled clinical trial data are still insufficiently powered to detect a beneficial or detrimental effect on mortality. Our results for death during gliptin treatment show a trend towards a reduced risk, based on 17 placebo-controlled trials (Peto OR 0.78 [0.42, 1.44]) and 15 active-controlled trials (Peto OR 0.73 [0.45, 1.20]), and correspond well with the OR computed by Monami based on 17 placebo- or active-controlled trials (M-H OR 0.78 [0.40, 1.51]). Larger trials need to be awaited for more precise mortality data.

The risk of hypoglycaemia is known to be low for DPP-4 inhibitors [7,90]. Our results provide a refined picture. Thus, 29 studies with almost 15,000 participants show that the risk of hypoglycaemia is at placebo level for all gliptins in the absence of insulin or sulphonylurea co-therapy. Ten trials with over 4700 participants give an indication that patients concomitantly treated with a gliptin and insulin or a sulphonylurea are at increased risk of hypoglycaemia over placebo (this was previously noted for sitagliptin, see Ref. [91]), and that there may be differences for individual agents. Vildagliptin and saxagliptin appear safer in this respect than linagliptin and sitagliptin in our meta-analysis. In the one available head-to-head trial, this finding is not corroborated. The trial was, however, conducted in a special population (148 patients with severe renal insufficiency), and provided no details on co-medication. Thus, further studies are needed to clarify these differing hypoglycaemia potentials.

We also present the most comprehensive evaluation to date of the risk of infections with DPP-4 inhibitors compared to placebo, based on 39 placebo-controlled trials involving over 18,000 participants. The data refute any association of gliptin therapy with an increased risk of infections. Such risk is extensively discussed in the literature because DPP-4 is the same protein as CD26, a marker for T-cell activation. A nested case–control study of the WHO database Vigibase found increased post-marketing reports on infections [92], though the data evaluated in this study are likely subject to reporting bias [93]. In contrast, T-cell activation was shown in vitro to be directly connected with CD26 signal transduction but independent of the proteolytic activity of CD26/DPP-4 [94]. Our data do, however, show a trend for an increased nasopharyngitis risk that reached significance only for sitagliptin. This may be attributed to an exacerbation of the inflammatory reaction in the nasal mucosa when DPP-4 is inhibited, leading to enhanced symptoms of nasopharyngitis [95]. Such symptoms are likely related to an enhanced local response of the nasal mucosa to injury or infection in patients treated with DPP-4 inhibitors, rather than to a systemic effect on the immune system.

Long-term cardiovascular safety studies of several DPP-4 inhibitors are ongoing. While their results are still unavailable, meta-analysis of clinical trials may provide a first indication of possible cardiovascular safety issues. Pooled analyses of patient-level clinical trial data for several gliptins (each using mixed placebo/other antidiabetic drug comparator groups) have not previously identified any signs for elevated risk related to specified cardiovascular endpoints including cardiovascular-related mortality, myocardial infarction and stroke [13,16,96,97]. Our study showed a trend for an elevated risk of cardiac disorders with gliptin treatment, and a significantly elevated risk of vascular disorders for linagliptin.

These can be found at www.clinicaltrials.gov, registered under the study numbers NCT00968708 (alogliptin, placebo-controlled), NCT01243424 (linagliptin, glimepiride-controlled), NCT01107886 (saxagliptin, placebo-controlled), NCT01086280 (saxagliptin observational study, active-controlled) and NCT00790205 (sitagliptin, placebo-controlled).
**Strengths and Limitations**

The strengths of the present review include the high quality of evidence that is due to the inclusion of only randomized, double-blind, controlled clinical trials. Moreover, the review is based on a large body of data and provides a specific focus on safety. It is the first systematic review to include the most recently approved gliptins. Some of the findings were not previously identified even in large analyses of pooled patient-level data from clinical trials, presumably because these did not separately evaluate a comparison of the respective agents against placebo.

Like other meta-analyses of published data, this study has some limitations that need to be recognized when interpreting the results. Summary data were used, which leads to loss of important information compared to patient-level data, such as the severity and time to event. Events occurring below the reporting thresholds applied in certain publications may go unnoticed. Moreover, the NNHs calculated from the risk ratios and control group risks may not be meaningful because of inaccurate estimation of control group risks. Some inconsistency in the classification of events into system organ class categories is likely to be present and cannot be assessed based on the data available. By evaluating adverse events by system organ class, rather than individually, a qualitative imbalance of events may not be noticed. Therefore, nervous system disorders are unlikely to impact treatment decisions.

**Conclusions**

DPP-4 inhibitors are a safe treatment option for patients with type 2 diabetes mellitus. Concerns over immune effects of gliptins were dispelled and should not influence future prescribing behaviour. A marginally increased risk of nasopharyngitis is likely to result from an aggravation of local symptoms of infectious disease in the nasal mucosa, so that local vasoconstrictory or anti-inflammatory medication may suffice for treating DPP-4-associated nasopharyngitis.

As part of a combination therapy with a sulphonylurea or insulin, the risk of hypoglycaemia is elevated with sitagliptin or linagliptin. Based on the evidence presented herein, vildagliptin and saxagliptin appear to be safer agents to use in this context. For patients intended for such combination therapy, the risk...
of hypoglycaemia clearly needs to be balanced with other, patient-specific issues such as renal and hepatic function [100]. Treatment with DPP-4 inhibitors was associated with a small but significant increase in nervous system disorders compared to placebo (mainly headache and dizziness). The risk was lower than with sulphonylurea treatment, similar to other antidiabetic drugs, and no differences between the agents were seen. Overall, this appears to be acceptable when considering the benefits achieved by gliptin treatment.

We also identified a 1.5-fold risk of asthenia associated with vildagliptin or linagliptin treatment. Related data for the other gliptins should be made available. Depending on the severity of the symptoms, an NNH of 59 may well be clinically relevant, and asthenia symptoms should receive special attention in clinical practice. A tendency for increased risk of in cardiac and vascular disorders was detected when comparing certain gliptin treatments to placebo, but statistical significance was marginal. The results of ongoing clinical outcome trials for cardiovascular effects and mortality will be needed to disprove or substantiate this finding. In the meantime, patients prescribed any gliptin should be closely monitored for signs of cardiovascular disease.

**Conflict of Interest**

The authors do not declare any conflict of interest relevant to this manuscript.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

- Appendix S1. Risk of Bias Across Studies.
- Figure S1. Funnel plots for serious adverse events compared against placebo (A) and other antidiabetic agents (B).
- Figure S2. Funnel plots for general disorders compared against placebo (A). (B) is the funnel plot for alogliptin, saxagliptin and sitagliptin, which do not report asthenia. (C) is the funnel plot for linagliptin and vildagliptin, which report asthenia.
- Figure S3. Total adverse events: Comparison of DPP-4 inhibitors against placebo.
- Figure S4. Total adverse events: Comparison of DPP-4 inhibitors against other antidiabetic drugs.
- Figure S5. Deaths during treatment: Comparison of DPP-4 inhibitors against placebo (OR, Peto, FE).
- Figure S6. Nasopharyngitis: Comparison of DPP-4 inhibitors against placebo.
- Figure S7. Cardiac disorders: Comparison of DPP-4 inhibitors against placebo.
- Figure S8. Vascular disorders: Comparison of DPP-4 inhibitors against placebo.
- Figure S9. Fatigue: Comparison of DPP-4 inhibitors against placebo.
- Figure S10. Nervous system disorders: Comparison of DPP-4 inhibitors against placebo.
- Table S1. Summary of methodological study quality, and indicators of selective outcome reporting. Double-blind maintained in all studies. All studies manufacturer-sponsored.

**Table S2.** Key characteristics of included studies.

**Table S3.** Risk of treatment discontinuation due to adverse events compared to other antidiabetic drugs.

**Table S4.** Risk of death during treatment compared to placebo (Peto odds ratio).

**Table S5.** Risk of death during treatment compared to other antidiabetic drugs (Peto odds ratio).

**Table S6.** Risk of hypoglycaemia compared to placebo.

**Table S7.** Risk of hypoglycaemia compared to placebo—no insulin/sulphonylurea co-medication.

**Table S8.** Risk of hypoglycaemia compared to placebo, each with insulin/sulphonylurea co-medication.

**Table S9.** Risk of adverse events by system organ class, compared to placebo.

**Table S10.** Risk of upper respiratory and urinary tract infections compared to placebo.

**Table S11.** Risk of nasopharyngitis compared to placebo.

**Table S12.** Risk of cardiac disorders compared to placebo.

**Table S13.** Risk of cardiac disorders compared to other antidiabetic drugs.

**Table S14.** Risk of vascular disorders compared to placebo.

**Table S15.** Risk of vascular disorders compared to other antidiabetic drugs.

**Table S16.** Risk of general disorders compared to placebo.

**Table S17.** Risk of general disorders compared to other antidiabetic drugs.

**Table S18.** Risk of nervous system disorders compared to placebo.

**Table S19.** Risk of nervous system disorders compared to other antidiabetic drugs.

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**References**


99. Glimepride (Amaryl®) was associated with a somewhat elevated rate of asthenia compared to placebo (1.6% vs. 1%). US Food and Drug Administration. Label approved on 04/06/2009 for Amaryl, NDA no. 020496. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020496s021lbl.pdf. Accessed 15 November 2011.