**BMJ Open**  
Glycaemic durability with dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials

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**ABSTRACT**

**Objectives:** To evaluate glycaemic durability with dipeptidyl peptidase-4 (DPP-4) inhibitors in type 2 diabetes.

**Design:** A systematic review and meta-analysis of long-term randomised trials of DPP-4 inhibitors on haemoglobin A1c (HbA1c) was conducted. Electronic searches were carried out on the following databases: MEDLINE, EMBASE, Scopus and Web of Knowledge to December 2013. Searches were supplemented by a review of trial registries and references from identified trials. Trials were included if they lasted at least 76 weeks, and had intermediate and final assessments of HbA1c. Citations and full-text articles were screened by two reviewers.

**Participants:** Adults with type 2 diabetes.

**Interventions:** Any DPP-4 inhibitor (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin).

**Outcome measures:** The difference between final and intermediate HbA1c assessment was the primary outcome.

**Results:** We screened 461 citations and reviewed 12 articles reporting 12 trials in 14,829 participants. All trials were of 76 weeks duration at least. The difference in HbA1c changes between final and intermediate points averaged 0.22% (95% CI 0.15% to 0.29%), with high heterogeneity (I²=91%, p<0.0001). Estimates of differences were not affected by the analysis of six extension trials (0.24%, 0.02 to 0.46), or five trials in which a DPP-4 inhibitor was added to metformin (0.24%, 0.16 to 0.32).

**Conclusions:** There is evidence that the effect of DPP-4 inhibitors on HbA1c in type 2 diabetes significantly declines during the second year of treatment. Future research should focus on the characteristics of patients that benefit most from DPP-4 inhibitors in terms of glycaemic durability.

**Strengths and limitations of this study**

- It is the first systematic review of randomised trials assessing the glucose-lowering effect of dipeptidyl peptidase-4 (DPP-4) inhibitors as a function of time in trials with a long follow-up.
- The statistical power of our attempts to pool data is supported by a sufficient number of trials published until now and the relatively high number of participants in the published trials.
- There is high heterogeneity in primary analysis and sensitivity or subgroup analyses.
- Available evidence to individualise the characteristics of the patient with diabetes who benefits most from DPP-4 inhibitors in terms of glycaemic durability is limited.

**INTRODUCTION**

The optimal drug sequence after metformin failure is an area of uncertainty.1,2 Sulfonylureas are the most commonly added oral antidiabetic drugs in this scenario3; the dipeptidyl-peptidase 4 (DPP-4) inhibitors may offer a non-inferior glucose-lowering efficacy, with a reduced risk of hypoglycaemia and weight gain.4 Moreover, DPP-4 inhibitors may protect pancreatic β-cells from enhanced apoptosis in animal models of diabetes,5 and also improve several markers of β-cell function in type 2 diabetes.6 Intuitively, a positive influence of DPP-4 inhibitors on β-cell function may attenuate the inherently progressive nature of β-cell loss.

We hypothesised that durability of glycaemic control may be a surrogate marker to test the hypothesis that DPP-4 inhibitors influence β-cell loss: randomised trials evaluating the long-term (up to 108 weeks) effect of DPP-4 inhibitors on haemoglobin A1c (HbA1c) level are available and may be used as an indicator of glycaemic durability.

**METHODS**

**Eligibility criteria**
We followed the PRISMA (Preferred Reporting Items for Systematic reviews and
Meta-Analyses) checklist for reporting systematic reviews and meta-analyses. We carried out this systematic review in accordance with the study protocol (see online supplementary appendix 1). Peer-reviewed journal articles and conference abstracts that reported the results of a randomised controlled trial and met the following eligibility criteria were eligible for inclusion: (1) trials reporting the effect of DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin) on the HbA1c level in participants with type 2 diabetes who were either drug naïve, or on background therapy with metformin or other oral agents; (2) lasting at least 76 weeks and (3) having final and intermediate assessment of HbA1c, with the intermediate point assessed between 24 and 52 weeks. We have shown that the relation between the HbA1c response to DPP-4 inhibitors and time is quite linear until between 24 and 52 weeks. We included primary trials and extension trials. We excluded trials if the intervention included the initiation of two agents at the same time, and the doses of DPP-4 inhibitors were different from those approved in the clinical practice (sitagliptin, 100 mg once daily; vildagliptin, 50 mg twice daily; saxagliptin, 5 mg once daily; linagliptin, 5 mg once daily; alogliptin, 25 mg once daily). The search had no language restriction; however, we excluded reviews, editorials, comments, letters and abstracts.

Search strategy
We performed an electronic search for randomised trials evaluating DPP-4 inhibitors in patients with type 2 diabetes through December 2013. We searched MEDLINE, EMBASE, Scopus and Web of Knowledge using the following terms as Medical Subject Heading and keywords: type 2 diabetes (T2DM, NIDDM, non-insulin-dependent diabetes), glycated haemoglobin (haemoglobin A1c, HbA1c, A1C), DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin), clinical trials. We searched for additional trials in the prescribing information documents of approved medications, at relevant web sites (eg, http://www.clinicalstudyresults.org and http://www.clinicaltrials.gov), and in personal reference lists of recovered articles.

Study selection, data extraction and quality assessment
The relevance of studies was assessed with a hierarchical approach on the basis of title, abstract and the full manuscript. Two reviewers (KE and DG) independently screened the titles and abstracts of identified citations to select those requiring full-text assessment. Where there was disagreement, a third reviewer (MIM) assessed the records to reach a consensus. Full-text articles were further assessed and data were entered into a prespecified table that included information on authors, year of publication, sample size, type of DPP-4 inhibitor, duration of follow-up, comparator drug, baseline HbA1c and outcomes. Of the selected trials, only study arms assessing the efficacy of DPP-4 inhibitors were included in the analysis, whereas any other arm (placebo or comparator drug) of the same trial was excluded.

Data analysis
We used the Cochrane Collaboration’s tool to assess risk of bias at the outcome level. Bias was assessed in duplicate with disagreements resolved by a third reviewer. The assessed domains were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and completeness of outcome data.

We used the difference between decrease of HbA1c from baseline at the end of follow-up (76–104 weeks) versus A1C decrease at intermediate assessments (24–52 weeks) during DPP-4 inhibitor administration as an index of glycaemic durability. The difference between final and intermediate HbA1c assessment was the primary end point. To calculate the overall difference between the two periods, each study was weighted by the reciprocal of the variance for HbA1c change. In a conservative approach, the random-effect estimates of mean differences, which allow for variation of true effects across studies, were taken as ‘main results’. Because variances for HbA1c change between final and intermediate end points were not directly reported, they were calculated by assuming a correlation coefficient of 0.5. A sensitivity analysis was performed assuming a correlation of 0.25 and 0.75; subgroup analyses were also performed for primary trials, extension trials and ‘add-on’ metformin trials. Heterogeneity between studies was assessed by using Q statistic and I². A p value of Q statistic less than 0.10 was considered significant. Data were analysed using Stata, V.11.0 (StataCorp., College Station, Texas, USA).

RESULTS
A total of 751 citations were identified (figure 1) from electronic searches. A further 11 relevant publications were identified as cited by included trial reports. After removing duplicates, we screened 461 citations. Based on the title and abstract, 447 were assessed as ineligible. The full text of the remaining 14 articles was assessed for eligibility. Further assessment of these articles revealed that two did not meet the inclusion criteria, one because the dose of saxagliptin was twofold higher than the recommended 5 mg daily dose, and the other because the intermediate Hb1c assessment occurred at 12 weeks.

Duration and settings
A total of 12 articles were eligible for inclusion. All studies were randomised controlled trials (table 1); most trials were multinational and sponsored by industry. The trials were published between 2008 and 2013. Six trials were an extension of previous randomised trials (table 1). All trials were double blind, including the six extension trials.

Intervention
All trials assessed the effect of a DPP-4 inhibitor versus placebo or a comparator drug on HbA1c level in
patients with type 2 diabetes. In five trials, the DPP-4 inhibitor was added to ongoing metformin treatment; in three trials, the patients were either drug naive or suspended the previous treatment; in the remaining four trials, the DPP-4 inhibitor was added to a thiazolidinedione or to a multiple antidiabetic therapy.

Outcomes
All trials included a definition of the primary outcome, which was the change in HbA1c from baseline to the end of the follow-up in 10 trials.

Risk of bias
All trials were deemed to have a low risk of selection bias (random sequence generation) and most trials were assessed as having a low risk of attrition bias (figure 2). Most trials provided incomplete information on allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Primary outcome
Trial findings are summarised in table 2. The difference in HbA1c changes between final and intermediate points averaged 0.22% (95% CI 0.15% to 0.29%, p<0.0001). There was substantial heterogeneity between the results of trials included in the pooled analysis of the primary outcome ($\chi^2$ test for heterogeneity, $p<0.0001; I^2=91\%$).

Sensitivity analysis assuming lower (0.25) or higher (0.75) correlation coefficients of variance did not change results (0.21% and 0.22%, respectively, $p<0.0001$). Subgroup analyses evaluated whether differences existed between primary or extension studies, or if the addition of the DPP-4 inhibitor to metformin behaved differently from the other studies. Estimates of differences were not significantly affected by the analysis of the six extension trials (0.24%, 0.02 to 0.46, p=0.036), or the five trials in which the DPP-4 inhibitor was added to metformin (0.24%, 0.16 to 0.32, p<0.0001; table 2).

DISCUSSION
Declining $\beta$-cell function is the predominant reason for deterioration in glucose tolerance and largely explains the difficulty in maintaining target levels of HbA1c with traditional glucose-lowering agents. The idea that DPP-4 inhibitors may alleviate $\beta$-cell death in animal models seems still attractive and potentially may be associated...
Table 1  Characteristics of trials included in the analysis

<table>
<thead>
<tr>
<th>Author, year and reference</th>
<th>Patients’ number</th>
<th>Type of DPP-4 inhibitors</th>
<th>Follow-up weeks</th>
<th>Comparator drug</th>
<th>Add-on to</th>
<th>Baseline HbA1c % (mmol/mol)</th>
<th>ΔHbA1c (%) T1: 24–52 weeks</th>
<th>ΔHbA1c (%) T2: 76–104 weeks</th>
<th>Difference (%) T2–T1 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foley, 2009 13</td>
<td>409</td>
<td>Vilda</td>
<td>104</td>
<td>Gliclazide</td>
<td>Naive</td>
<td>8.5 (69)</td>
<td>−0.9</td>
<td>−0.5</td>
<td>0.4 (0.20 to 0.58)</td>
</tr>
<tr>
<td>Matthews, 2010 14</td>
<td>1051</td>
<td>Vilda</td>
<td>104</td>
<td>Glimepiride</td>
<td>Metformin</td>
<td>7.3 (56)</td>
<td>−0.25</td>
<td>−0.1</td>
<td>0.15 (0.11 to 0.19)</td>
</tr>
<tr>
<td>Seck, 2010 15</td>
<td>248</td>
<td>Sita</td>
<td>104</td>
<td>Glipizide</td>
<td>Metformin</td>
<td>7.3 (56)</td>
<td>−0.8</td>
<td>−0.54</td>
<td>0.26 (0.17 to 0.35)</td>
</tr>
<tr>
<td>Gallwitz, 2012 16</td>
<td>764</td>
<td>Lina</td>
<td>104</td>
<td>Glimepiride</td>
<td>Metformin</td>
<td>7.7 (61)</td>
<td>−0.38</td>
<td>−0.16</td>
<td>0.22 (0.16 to 0.28)</td>
</tr>
<tr>
<td>Scirce, 2013 17</td>
<td>8280</td>
<td>Saxa</td>
<td>108</td>
<td>Placebo</td>
<td>Variable</td>
<td>8.0 (64)</td>
<td>−0.5</td>
<td>−0.4</td>
<td>0.10 (0.08 to 0.26)</td>
</tr>
<tr>
<td>White, 2013 18</td>
<td>2071</td>
<td>Saxa</td>
<td>104</td>
<td>Placebo</td>
<td>Multiple</td>
<td>8.0 (64)</td>
<td>−1.0</td>
<td>−1.0</td>
<td>0 (−0.17 to 0.17)</td>
</tr>
<tr>
<td>Goke, 2008 19</td>
<td>305</td>
<td>Vilda</td>
<td>104</td>
<td>Metformin</td>
<td>Naive</td>
<td>8.4 (68)</td>
<td>0.54</td>
<td>−0.15</td>
<td>0.28 (0.09 to 0.47)</td>
</tr>
<tr>
<td>Rosenstock, 2009 20</td>
<td>354</td>
<td>Saxa</td>
<td>104</td>
<td>Rosiglitazone</td>
<td>Metformin</td>
<td>8.6 (70)</td>
<td>−1.1</td>
<td>−0.82</td>
<td>0.33 (−0.06 to 0.72)</td>
</tr>
<tr>
<td>Williams-Herman, 2010 21</td>
<td>52</td>
<td>Saxa</td>
<td>104</td>
<td>Metformin</td>
<td>None</td>
<td>8.5 (69)</td>
<td>−1.53</td>
<td>−1.2</td>
<td>0.57 (−0.64 to 0.72)</td>
</tr>
<tr>
<td>Chacra, 2011 22</td>
<td>56</td>
<td>Saxa</td>
<td>76</td>
<td>Glyburide</td>
<td>Glyburide</td>
<td>6.5 (69)</td>
<td>−0.44</td>
<td>−0.25</td>
<td>0.67 (0.50 to 0.84)</td>
</tr>
<tr>
<td>Holland, 2011 23</td>
<td>186</td>
<td>Saxa</td>
<td>76</td>
<td>Placebo</td>
<td>Thiazide</td>
<td>8.4 (68)</td>
<td>−0.94</td>
<td>−1.09</td>
<td>−0.15 (−0.31 to 0.01)</td>
</tr>
<tr>
<td>Goke, 2013 24</td>
<td>423</td>
<td>Saxa</td>
<td>104</td>
<td>Glipizide</td>
<td>Metformin</td>
<td>7.65 (60)</td>
<td>−0.74</td>
<td>−0.41</td>
<td>0.33 (0.26 to 0.40)</td>
</tr>
</tbody>
</table>

Six trials (19–24) are extension studies; Δ, difference from baseline.

alo, alogliptin; lina, linagliptin; sita, sitagliptin; saxa, saxagliptin; thiazo, thiazolidinedione; Vilda, vildagliptin.
Figure 2 Summary of authors’ judgements on the risk of bias in reviewed trials.

Table 2 Sensitivity and subgroup analyses

<table>
<thead>
<tr>
<th>Number of arms</th>
<th>Mean age (years)*</th>
<th>Mean basal HbA1c (%)*</th>
<th>Pooled differences T2-T1 HbA1c (%) (95% CI)</th>
<th>p Value</th>
<th>I² (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation 0.50</td>
<td>12</td>
<td>62.2</td>
<td>7.96</td>
<td>0.22 (0.15 to 0.29)</td>
<td>&lt;0.0001</td>
<td>91</td>
</tr>
<tr>
<td>Correlation 0.25</td>
<td>12</td>
<td>62.2</td>
<td>7.96</td>
<td>0.21 (0.14 to 0.29)</td>
<td>&lt;0.0001</td>
<td>86</td>
</tr>
<tr>
<td>Correlation 0.75</td>
<td>12</td>
<td>62.2</td>
<td>7.96</td>
<td>0.22 (0.15 to 0.29)</td>
<td>&lt;0.0001</td>
<td>95</td>
</tr>
<tr>
<td>Primary studies†</td>
<td>6</td>
<td>63</td>
<td>7.93</td>
<td>0.19 (0.13 to 0.25)</td>
<td>&lt;0.0001</td>
<td>86</td>
</tr>
<tr>
<td>Extension studies†</td>
<td>6</td>
<td>54.8</td>
<td>8.22</td>
<td>0.24 (0.02 to 0.46)</td>
<td>0.036</td>
<td>92</td>
</tr>
<tr>
<td>Metformin (add-on to)†</td>
<td>5</td>
<td>57.8</td>
<td>7.62</td>
<td>0.24 (0.16 to 0.32)</td>
<td>&lt;0.0001</td>
<td>82</td>
</tr>
</tbody>
</table>

*Mean value weighted by sample size.
†Assuming a 0.50 correlation.

REFERENCES


