Dipeptydil [dipeptidyl] peptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials

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CRD summary
This review found that in patients with type-2 diabetes, dipeptidyl peptidase-4 inhibitors reduced glycated haemoglobin, although to a lesser extent than sulphonylureas, with no weight gain and no hypoglycaemic risk. Lack of clarity in the presentation of results and some methodological limitations with the primary studies mean these conclusions should be interpreted with some caution.

Authors' objectives
To evaluate the safety and efficacy of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes.

Searching
MEDLINE was searched to November 2008. Search terms were reported. Unpublished trials were identified using an online trial register.

Study selection
Randomised controlled trials (RCTs) that compared dipeptidyl peptidase-4 inhibitors with placebo or other active drugs (oral hypoglycaemic agents and/or insulin) in patients with type 2 diabetes were eligible for inclusion. Studies had to be at least 12 weeks duration. Both parallel arm and crossover trials were eligible. The primary outcome was glycated haemoglobin (HbA1c). Secondary outcomes were body mass index (BMI), hypoglycaemia and adverse events.

Included studies evaluated the dipeptidyl peptidase-4 inhibitors vildagliptin (25mg to 100mg), sitagliptin (25mg to 200mg) and saxagliptin (2.5mg to 40mg). Comparator agents included placebo, glipizide, rosiglitazone, pioglitazone, acarbose and metformin. Add-on agents, where included, included metformin, pioglitazone, glimepiride, insulin and oral antidiabetic drugs. Trial duration ranged from 12 to 54 weeks. Mean age ranged from 51 to 68 years. Mean duration of diabetes ranged from one to 14.7 years.

Two reviewers independently assessed studies for inclusion; disagreements were resolved through referral to a third reviewer.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale of randomisation, blinding and withdrawals. Summary scores were not calculated. Disagreements were resolved through referral to a third reviewer.

Data extraction
Two reviewers independently extracted data to calculate odds ratios (ORs) for dichotomous data and mean differences for continuous data, each with 95% confidence intervals (CIs). Disagreements were resolved through referral to a third reviewer.

Methods of synthesis
Summary odds ratios and weighted mean differences (WMDs) together with 95% confidence intervals were estimated using random-effects models. Trials with zero events were excluded from the meta-analyses. Heterogeneity was assessed using $I^2$. Separate analyses were performed for trials of different dipeptidyl peptidase-4 inhibitors. Subgroup analysis was performed based on study duration, monotherapy or combined therapy, baseline HbA1 and duration of diabetes. Publication bias was assessed using Begg and Egger tests.

Results of the review
Forty-one studies (n=17,810 patients) were included: 32 published and nine unpublished studies. Only three studies provided an appropriate description of randomisation. Seven studies were adequately blinded, 33 studies provided an
appropriate description of withdrawals and 37 studies carried out an intention-to-treat analysis.

Results of meta-analyses were reported on summary forest plots; exact numerical results were unclear for most comparisons as was the number of studies that contributed to each meta-analysis. There was substantial heterogeneity between studies for HbA1c ($I^2=94.6\%$, $p<0.01$). When data for all placebo-controlled studies were combined there was a significant improvement in HbA1c. Effects were similar when results were stratified according to dipeptidyl peptidase-4 agent, whether the dipeptidyl peptidase-4 agent was administered as monotherapy or combined therapy, duration of therapy, baseline HbA1 and duration of diabetes. Dipeptidyl peptidase-4 inhibitors showed a similar effect to thiazolidinediones, but metformin and sulphonylureas were significantly more effective than dipeptidyl peptidase-4 inhibitors.

There was no significant difference in incidence of hypoglycaemia or for BMI between dipeptidyl peptidase-4 agents and placebo. Dipeptidyl peptidase-4 agents were associated with a significantly lower risk of hypoglycaemia than sulphonylureas and a significantly lower BMI compared to thiazolidinediones.

Risk of adverse events was similar for dipeptidyl peptidase-4 inhibitors and placebo and was significantly lower than sulphonylureas (OR 0.64, 95% CI 0.51 to 0.80; two trials), metformin (OR 0.78, 95% CI 0.61 to 1.00; two trials) and α-glucosidase inhibitors (OR 0.51, 95% CI 0.39 to 0.67; two trials). There was no significant difference in risk of death or cardiovascular events compared to control.

There was no evidence of publication bias ($p=0.13$).

**Authors’ conclusions**

Dipeptidyl peptidase-4 inhibitors reduced glycated haemoglobin, although to a lesser extent than sulphonylureas, with no weight gain and no hypoglycaemic risk.

**CRD commentary**

The review addressed a focused question supported by clearly defined inclusion criteria. The literature search involved only one medical database, but additional attempts were made to locate unpublished data. Appropriate steps were taken to minimise bias and errors at all stages of the review process. Study quality was assessed using some relevant criteria; allocation concealment was not considered. Appropriate methods were used to pool data. There was a lack of clarity in the presentation of results. Most meta-analyses were summarised using summary forest plots, which presented pooled results and not individual study results. These plots did not report the numerical results or show how many studies contributed to each meta-analysis, so it was difficult to interpret the results.

The authors’ conclusions appeared to be supported by the data, but lack of clarity in the presentation of results and some methodological limitations with the primary studies mean that these conclusions should be interpreted with some caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further data were needed to assess the long term safety of dipeptidyl peptidase-4 agents.

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**Bibliographic details**


**PubMedID**

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