Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis
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CRD summary
This review evaluated dipeptidyl peptidase-4 (DPP-4) inhibitors for glycaemic control in type 2 diabetes. The authors concluded that DPP-4 inhibitors were similarly effective to sulphonylureas or pioglitazone, with neutral effects on body weight, and inferior to metformin. Uncertain trial quality and some unclear interpretation of the results suggests the reliability of the review is uncertain.

Authors' objectives
To evaluate the efficacy and safety of dipeptidyl-4 (DPP-4) inhibitors compared with metformin as monotherapy, or with other commonly used hypoglycaemic drugs combined with metformin, in adults with type 2 diabetes mellitus.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to March 2011. There were no language restrictions. Full search strategies were reported. Conference abstracts were handsearched. Unpublished trials were sought from pharmaceutical company websites and clinical trial registers.

Study selection
Randomised controlled trials (RCTs) that compared a DPP-4 inhibitor with metformin as monotherapy or with a sulphonylurea, basal insulin, pioglitazone or glucagon-like peptide-1 (GLP-1) agonist combined with metformin in non-pregnant adults (at least 18 years of age) with type 2 diabetes were eligible for inclusion. Intervention duration had to be at least 12 weeks. The primary outcome of interest was change in glycated haemoglobin (HbA1c) from baseline to end of intervention. Rosiglitazone and hypoglycaemic drugs not used widely in clinical practice (listed in the paper) were excluded.

Most of the included trials were industry-sponsored and compared a DPP-4 inhibitor (sitagliptin, vildagliptin, saxagliptin and linagliptin; doses reported in the paper) with metformin as monotherapy or combined with a sulphonylurea. There were no comparisons with insulin combined with metformin. Baseline HbA1c ranged from 7.2% to 9.4%. Mean disease duration ranged from one to 7.3 years. Study duration ranged from 12 weeks (primary study) to 206 weeks (primary study plus extension phase). Total study duration was at least 52 weeks in just over half of the included studies. Additional outcomes measured were change in body weight and proportion of patients who achieved HbA1c less than 7%. Safety outcomes included: experience of at least one hypoglycaemic event; discontinuation rate from any adverse events; serious adverse events; all-cause mortality; and incidence of nasopharyngitis, urinary tract infection, upper respiratory infection, nausea, vomiting and diarrhoea.

Two reviewers independently selected the studies for inclusion except unpublished studies, which were identified by one reviewer. Disagreements were resolved by involving a third reviewer.

Assessment of study quality
Trial quality was assessed using the Cochrane Risk of Bias tool for randomisation, allocation concealment, blinding, completeness of outcome data and selective reporting. Overall risk of bias for each trial was considered high, low or unclear.

Two reviewers independently carried out the quality assessment and a consensus was agreed with a third reviewer.

Data extraction
Data were extracted or calculated to enable presentation of relative risks (RR) for dichotomous outcomes and mean differences for continuous outcomes, each with 95% confidence intervals (CI). Intention-to-treat data were extracted where possible. Study authors and pharmaceutical companies were contacted for any missing data.
Two reviewers independently extracted the data. Discrepancies were resolved by consensus.

**Methods of synthesis**

Relative risks and weighted mean differences (WMDs) were pooled in random-effects meta-analyses weighted by the inverse variance method. Analyses used the highest dose and longest duration of follow-up. Statistical heterogeneity was assessed using the $I^2$ statistic: values of 30% to 60% represented moderate variation and over 75% considerable variation. Planned sensitivity analysis included removal of trials with high risk of bias; other sensitivity analyses excluded unpublished studies and used data only from the main phase (not the extension) of included trials. A narrative synthesis of adverse events was presented. Publication bias was assessed using a funnel plot and Egger's test.

**Results of the review**

Twenty-six reports (19 studies, 7,136 participants) were included in the review. Risk of bias was considered to be low in three reports, high in 14 reports and unclear in nine reports. All except three studies were double-blind.

DPP-4 inhibitors were associated with a smaller decline in HbA$_1c$ (WMD 0.20, 95% CI 0.08 to 0.32; seven trials, $I^2=60$%), and a lower proportion of patients who achieved HbA$_1c$ less than 7% (RR 1.18, 95% CI 1.07 to 1.29; seven trial, $I^2=34$%), which favoured metformin monotherapy.

When combined with metformin, there was a statistically significant smaller decline in HbA$_1c$ when DPP-4 inhibitors (as a second-line treatment) were compared with other hypoglycaemic drugs (overall WMD 0.12, 95% CI 0.04 to 0.20; 10 trials, $I^2=70$%). Removal of poorer quality trials did not alter these results. DPP-4 inhibitors were less effective than sulphonylurea (WMD 0.07, 95% CI 0.03 to 0.11; six trials, $I^2=0$%) and GLP-1 agonists (WMD 0.49, 95% CI 0.31 to 0.67; two trials, $I^2=27$%) in reducing HbA$_1c$. There was no significant difference in the comparison with pioglitazone (three trials, $I^2=40$%). Achievement of the HbA$_1c$ target of less than 7% statistically favoured pioglitazone (RR 1.33, 95% CI 1.09 to 1.63; two trials, $I^2=0$%) and GLP-1 agonists (RR 1.82, 95% CI 1.50 to 2.21; two trials, $I^2=0$%; figures from forest plot, error in text). There was no significant difference for sulphonylureas (five trials, $I^2=26$%).

DPP-4 inhibitors as monotherapy were less effective in reducing body weight than metformin (WMD 1.50, 95% CI 0.90 to 2.11; five trials, $I^2=74$%). When combined with metformin, DPP-4 inhibitors achieved significantly greater body weight reduction than sulphonylurea (WMD -1.92, 95% CI -2.34 to -1.49; four trials, $I^2=69$%) and pioglitazone (WMD -2.96, 95% CI -4.13 to -1.78; two trials, $I^2=79$%). There was no significant difference in the comparison with GLP-1 agonists (two trials, $I^2=0$%).

Risk of adverse events was generally lower for DPP-4 inhibitors (results reported in the paper). There was no evidence of publication bias.

**Authors’ conclusions**

When added to metformin, DPP-4 inhibitors can lower HbA$_1c$ in a similar way to sulphonylureas or pioglitazone, with neutral effects on body weight in patients with type 2 diabetes. DPP-4 inhibitors as monotherapy appeared to be inferior to metformin in terms of glycaemic efficacy and reduction in body weight.

**CRD commentary**

The research question was clear. The inclusion criteria were somewhat ambiguous, but the authors appeared to apply them consistently. Various data sources were searched and attempts were made to minimise publication and language biases. The review process was conducted with efforts to maximise transparency and reduce error and bias. A relevant quality assessment tool was applied; it appeared that the reliability of most trials was uncertain or poor. Study details were presented clearly. The chosen method of synthesis took account of statistical heterogeneity, which was high in some analyses.

This was largely a well-conducted review, but the conclusions appear to underestimate some of the statistically significant findings presented. This, together with the inclusion of trials with less than satisfactory quality, means that the reliability of the review is uncertain.

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

**Practice:** The authors appeared to suggest that metformin should continue to be the first-line treatment for glycaemic
control in patients with type 2 diabetes, but DPP-4 inhibitors could be an alternative option in those who are intolerant to metformin because of gastrointestinal adverse events.

**Research:** The authors stated a need for more head-to-head trials to evaluate potential differences in efficacy and safety between individual DPP-4 inhibitors. They also stated that more trials were needed to compare DPP-4 inhibitors with pioglitazone, GLP-1 agonists or basal insulin as second-line treatment. Research should consider the cost-effectiveness of DPP-4 inhibitors (in view of their higher unit cost).

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