Efficacy and safety of dipeptidyl peptidase-4 inhibitors in type 2 diabetes: meta-analysis

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CRD summary
This large review concluded that Dipeptidyl peptidase-4 (DPP-4) inhibitors reduced A1C levels compared to placebo with comparable safety, but other hyperglycaemics may have similar efficacy. High heterogeneity and the need for indirect comparison limit the reliability of these conclusions although the effectiveness of DPP-4 inhibitors in reducing A1C levels compared to placebo is likely to be reliable.

Authors' objectives
To assess the efficacy and safety of Dipeptidyl peptidase-4 (DPP-4) inhibitors, including sitagliptin, saxagliptin, vildagliptin and linagliptin in type 2 diabetes.

Searching
MEDLINE was searched for publications in English from inception to November 2011 using specified search terms. Trials websites, including ClinicalTrials.gov, were searched for unpublished material and reference lists were handsearched for additional studies.

Study selection
RCTs of DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin and linagliptin) for use in patients aged 18 years or older with type 2 diabetes that met the following criteria: (1) compared DPP-4 inhibitors with either placebo or oral hypoglycaemic medications, (2) treated patients for at least 12 weeks, and (3) had at least one baseline and post-treatment efficacy and/or safety outcome of interest. Efficacy was measured as mean change in haemoglobin A1C and body weight. Hypoglycaemia and reported adverse events were safety outcomes.

Most trials compared a DPP-4 inhibitor (as monotherapy or add on therapy) to placebo but control arms included active comparators in some cases. Trial duration ranged from 12 to 52 weeks. Seven trials conducted in Japan enrolled only Japanese patients and were analysed separately from the remaining trials. Patients were older in the Japanese trials (mean age 59.1 years versus 55.4 years) and had a longer duration of type 2 diabetes mellitus (6.19 years versus 4.84 years), lower A1C at baseline (7.70% versus 8.15%), and lower body mass index (BMI) (24.7 versus 30.8) compared to patients in the other trials. The trials all used the currently recommended doses of DPP-4 (details reported in the paper).

Study selection was performed independently by two reviewers with discrepancies resolved by consensus.

Assessment of study quality
Study quality was assessed using the Jadad scale by two reviewers independently.

Data extraction
Mean changes from baseline in A1C and body weight were extracted to allow calculation of mean differences and associated 95% confidence intervals. Dichotomous outcomes (hypoglycaemia and adverse events) were extracted as events and sample sizes (intention-to-treat not specified) to allow calculation of odds ratios and associated 95% confidence intervals. Study authors were contacted for missing data and zero cell frequencies were imputed as 0.5.

Data extraction was performed independently by two reviewers with discrepancies resolved by consensus.

Methods of synthesis
Random effects meta-analyses were performed to calculate weighted mean differences, pooled odds ratios and associated 95% confidence intervals with measures ($I^2$) and tests ($X^2$) for heterogeneity. The authors interpreted $I^2$ greater than 50% as substantial. Funnel plots and Egger regression tests were used to assess potential for publication bias. A large number of subgroup analyses were conducted to explore heterogeneity related to type of DPP-4 inhibitor, add on therapy, duration, baseline A1C and separating Japanese trials.

Results of the review
Sixty-two trials were included overall, most of which enrolled more than 200 participants with a Jadad score of four or more which suggested minimal risk of bias (although more than 10% of trials did not have a quality assessment).

DPP-4 inhibitors lowered haemoglobin A1C more than placebo (WMD -0.76%; 95% CI -0.83% to -0.68%; 17,838 participants in 59 trials). There was substantial heterogeneity ($I^2=82\%$) and a statistically significant difference in the pooled effects of Japanese and non-Japanese trials (Japanese trials WMD -1.67%; 95% CI -1.89% to -1.44%, seven trials; non-Japanese trials WMD -0.65%; 95% CI -0.71% to -0.60%; 55 trials). DPP-4 inhibitors had similar A1C levels compared to other hypoglycaemic agents (WMD 0.04%, 95% CI -0.09% to 0.16%; 18 RCTs) but heterogeneity was substantial ($I^2=90\%$).

DPP-4 inhibitors showed a small weight gain compared with placebo (32 trials; WMD 0.21 kg; 95% CI 0.15 to 0.27; $I^2=53\%$), but the increase was not significantly different from that with other hypoglycaemic agents (10 trials; WMD -0.04 kg; 95% CI -0.36 to 0.29; $I^2=98\%$). There was no detectable difference in weight gain between Japanese and non-Japanese trials.

DPP-4 inhibitors showed a higher risk of hypoglycaemia (odds ratio 1.32; 95% CI 1.04 to 1.67, 18,101 patients in 47 trials; $I^2=25\%$) compared to placebo. The risk of hypoglycaemia was not significantly different between DPP-4 inhibitors and other hypoglycaemic agents. There was no detectable difference in risk of hypoglycaemia between Japanese and non-Japanese trials.

There was no difference in reported adverse events between DPP-4 inhibitors and placebo (OR 1.00; 95% CI 0.90 to 1.10) but there was a lower risk of reported adverse events with DPP-4 inhibitors compared to other hypoglycaemic agents (OR 0.86, 95% CI 0.74 to 0.99; 15 trials, 12,772 participants). Eggers tests suggested publication bias for the change in A1C amongst placebo trials but not where active comparators were concerned. Other results were reported in the paper.

**Authors’ conclusions**
DPP-4 inhibitors were associated with a reduction in A1C with comparable safety profiles compared to placebo, but no significant difference in A1C compared to other hyperglycaemic agents. Differences in efficacy and safety were observed between Japanese and non-Japanese patients.

**CRD commentary**
The authors used appropriate methods to minimise potential biases in the acquisition, appraisal and synthesis of evidence notwithstanding some potential for language bias. A large evidence base was available to the authors, but it had several serious limitations. Firstly, clinical and statistical heterogeneity were very high which necessitated exploration of inconsistency. This was conducted using large numbers of subgroup analyses which increased the probability of chance findings. Secondly, although trial quality was assessed, it was not always reported, and important aspects of trial design such as duration, or clinical characteristics such as baseline A1C were not accounted for or addressed by corollary meta-regression analyses. The desire to compare multiple DPP-4 inhibitors and other hyperglycaemics could best be achieved using network meta-analysis rather than multiple indirect comparisons. Cautious interpretation of the results was therefore a prerequisite for the generation of reliable conclusions. The authors’ conclusion that DPP-4 inhibitors reduce A1C was probably reliable although considerable unexplained heterogeneity surrounds this result.

Overall there was an elevated risk of hypoglycaemia compared to placebo so the comparability of safety profiles was based on clinical judgement as was the comparison of effectiveness in relation to other hypoglycaemic agents. Different analysts may reach different conclusions regarding the substantive importance of the differences between treatments to those of the authors. There was a difference between Japanese trials and non-Japanese trials but it was unclear whether this difference was due to chance or to variation in characteristics of the trials.

The authors’ suggestion that further research is required to evaluate the long term safety and efficacy of DPP-4 inhibitors appears judicious in relation to the evidence presented.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinical interpretation of the results in Japanese patients may be limited.
Research: The authors stated that further evaluation of long-term efficacy and safety for both Japanese and non-Japanese populations was needed.

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