Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials

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CRD summary
This review concluded that a greater proportion of type 2 diabetic patients could achieve the glycated haemoglobin target of below 7% with dipeptidyl peptidase-4 inhibitors compared with placebo, without weight gain or hypoglycaemic risk, but that dipeptidyl peptidase-4 inhibitors were not different from comparator drugs. Based on the results presented in the paper, these conclusions appear appropriate.

Authors' objectives
To assess the efficacy of the dipeptidyl peptidase-4 inhibitors vildagliptin, sitagliptin, saxagliptin and alogliptin to reach a glycated haemoglobin (HbA1c) target of less than 7% in people with type 2 diabetes.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL electronic databases were searched from inception to September 2010 for studies published in peer-reviewed journals. Search terms were reported. Websites and personal reference lists were searched to identify relevant trials.

Study selection
Studies were included if they were randomised controlled trials (RCTs) that evaluated the addition of dipeptidyl peptidase-4 inhibitors on glycated haemoglobin levels in non-pregnant adults with type 2 diabetes. Participants needed to be either drug naive or on background therapy with metformin or other agents. RCTs had to include at least 30 participants in each study arm and measure glycated haemoglobin levels after a minimum of 12 weeks. Studies that included the initiation of two agents at the same time or used doses that were different from the maximum dose recommended in clinical practice were excluded.

Included studies evaluated vildagliptin (100mg/day), sitagliptin (100mg/day), saxagliptin (5mg/day), and alogliptin (12.5 or 25mg/day) against placebo and/or comparator drugs (such as metformin, glipizide, acarbose, glimepiride, exenatide, lixisenatide and glitazones). Mean participant age ranged from 50.2 to 58.4 years. Mean baseline A1C ranged from 7.3% to 9.6%. More than half of the studies included participants on oral antidiabetic background medication, approximately one quarter discontinued background oral antidiabetic drugs prior to randomisation and one quarter included only drug-naive participants. Most studies were industry sponsored multinational trials.

The authors did not state how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using the Jadad criteria of randomisation, blinding and reporting of withdrawals to give a score up to a maximum of 5. RCTs that scored less than 3 were considered of lower methodological quality.

The authors did not state how many reviewers performed the assessment.

Data extraction
Outcomes extracted from the included studies were: proportion of patients who reached the glycated haemoglobin value of less than 7%, overall hypoglycaemia, absolute changes in glycated haemoglobin and changes in body weight. Odds ratios (ORs) and relative risks (RRs) were extracted or calculated for dichotomous data and weighted mean differences (WMDs) were calculated for continuous data.

Data were extracted independently by two reviewers, with disagreements resolved by consensus.

Methods of synthesis
Pooled odds ratios, risk ratios and weighted mean differences, each with 95% confidence intervals (CIs), were
calculated for each dipeptidyl peptidase-4 inhibitor versus placebo and active comparator drugs using random-effect
models. Heterogeneity was assessed with $I^2$. Publication bias was assessed using the Macaskill funnel-plot regression
method. Subgroup and sensitivity analyses were performed.

**Results of the review**

Forty-three RCTs (19,101 patients) were included in the review. Follow-up ranged from 12 to 52 weeks. Most studies
were labelled as double-blind or triple-blind.

All dipeptidyl peptidase-4 inhibitors resulted in a greater proportion of patients reaching the glycated haemoglobin
target of less than 7% than placebo: vildagliptin (OR 3.29, 95% CI 2.5 to 4.01; seven studies), sitagliptin (OR 3.15, 95%
CI 2.47 to 3.72; 12 studies), saxagliptin (OR 2.81, 95% CI 2.31 to 3.22; five studies), alogliptin 12.5mg (OR 3.8, 95%
CI 2.9 to 4.8; four studies) and alogliptin 25mg (OR 3.76, 95% CI 2.85 to 4.7; four studies). Around 40% of patients
who received dipeptidyl peptidase-4 inhibitors achieved this outcome. Absolute reductions in glycated haemoglobin
level were statistically significant versus placebo. There were no significant differences in hypoglycaemia. $I^2$ values of
at least 50% were observed for most analyses. However, there were no significant differences between dipeptidyl
peptidase-4 inhibitors and active comparator drugs.

Results of weight gain, subgroup and sensitivity analyses were presented in the paper. There was no evidence of
publication bias.

**Authors' conclusions**

A greater proportion of type 2 diabetic patients can achieve the glycated haemoglobin target of less than 7% with
dipeptidyl peptidase-4 inhibitors compared to placebo, with no weight gain and no hypoglycaemic risk when used alone.
dipeptidyl peptidase-4 inhibitors were not different from comparator drugs.

**CRD commentary**

This review was based on a clearly defined question supported by appropriate inclusion criteria. Attempts were made to
minimise errors and bias during data extraction; it was unclear whether this was the case for the initial selection of
studies. Some relevant details of the included studies (such as individual study quality) were not reported. Other aspects
of the review process appeared to be well conducted. Based on the results presented in the paper, the authors' conclusions appear appropriate.

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

**Research:** The authors stated that future trials should take into account the strong relationship between baseline glycated
haemoglobin and the glycated haemoglobin target outcome and that long-term follow-up was required to confirm the
effects of dipeptidyl peptidase-4 inhibitors in type-2 diabetes.

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

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.