Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials
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CRD summary
This review concluded that treatment with dipeptidyl peptidase-4 inhibitors reduced the incidence of major cardiovascular events, and all-cause mortality, for people with type 2 diabetes. Limitations in the reporting, and marginal differences in the significance of some effects across different drugs and types of events, suggest that these conclusions may be overly strong.

Authors' objectives
To assess the effectiveness of dipeptidyl peptidase (DPP)-4 inhibitors, for reducing the incidence of major cardiovascular events, in patients with type 2 diabetes.

Searching
MEDLINE and EMBASE were searched to March, 2012. Search terms were reported. Four clinical trial registers, and reviews of approved drugs from the US Food and Drug Administration and the European Medicines Agency, were searched.

Study selection
Eligible studies were randomised controlled trials, with a minimum duration of 24 weeks, that compared the effectiveness of DPP-4 inhibitors versus placebo or other active drugs (oral hypoglycaemic agents, insulin, or both), for patients with type 2 diabetes. The primary outcome was the incidence of major cardiovascular events (defined in the review).

In the included trials, the mean age of patients ranged from 49 to 72 years, and (where reported) their mean glycated haemoglobin level at the start ranged from 6.7 to 9.9%. The DPP-4 inhibitors examined were alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin. More than half of the control groups received placebo, and the others received active drugs, such as pioglitazone, glimepiride, or metformin. A few trials had placebo and active drug control groups. Trials lasted from 24 to 208 weeks.

Two reviewers independently selected trials for inclusion; any discrepancies were resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed using the criteria from the Jadad Scale (no details were reported).

Data extraction
Two reviewers independently extracted the outcomes, with any discrepancies resolved by a third reviewer. Odds ratios and 95% confidence intervals were calculated for dichotomous data (major cardiovascular events overall, acute myocardial infarction, stroke, all-cause mortality, and cardiovascular mortality), using intention-to-treat methods.

Methods of synthesis
Odds ratios and 95% confidence intervals, for the dichotomous data, were pooled using random-effects models. Statistical heterogeneity was assessed using $I^2$. Publication bias was assessed using a funnel plot and the Begg adjusted rank correlation test. Trials with no events were excluded from the meta-analyses; a sensitivity analysis was performed, with continuity correction, to avoid distortion due to each exclusion.

Results of the review
Seventy randomised controlled trials were included in the review (41,959 patients, ranging from 21 to 2,789 per trial); seven had no events. The results from the quality assessment were not reported.

Compared with placebo or active control, a statistically significant lower incidence of major cardiovascular events
overall was observed with DPP-4 inhibitors (OR 0.71, 95% CI 0.59 to 0.86; 63 trials).

Subgroup analyses of the five different drugs (sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin) all showed reductions in the incidence of major cardiovascular events, compared with control; two analyses (vildagliptin and saxagliptin) showed statistically significant differences between the drug and control (reported in paper).

Further comparisons revealed statistically significantly lower incidences of acute myocardial infarction (OR 0.64, 95% CI 0.44 to 0.94; 41 trials) and all-cause mortality (OR 0.60, 95% CI 0.41 to 0.88; 30 trials), with DPP-4 inhibitors. No other significant differences between treatment and control groups were found. No evidence of publication bias was found. Further results were reported in the review.

Authors' conclusions
The data from short- and medium-term trials showed that DPP-4 inhibitors reduced the incidence of major cardiovascular events and all-cause mortality, for patients with type 2 diabetes.

CRD commentary
The review question and inclusion criteria were broadly defined. Two major electronic databases were searched and efforts were made to locate relevant, unpublished trials. No evidence of publication bias was found. Efforts were taken to minimise reviewer error and bias during study selection and data extraction; this was unclear for quality assessment. The results of the quality assessment were not reported, so the extent to which individual trials risked within-study bias is unclear. Minimal trial details were presented, and these revealed some clinical variation between trials.

Some aspects of the analysis were not reported. For example, the way in which data from trials with more than one control arm were treated, and the dose regimens of the drugs were not stated. It is thus unclear whether double counting of data or confounding may have occurred, leaving the potential for over- or under-estimation of the effect of the DPP-4 inhibitors. The proportion of heterogeneity that was not due to chance, was not reported in any of the meta-analyses, so it is not possible to ascertain whether the methods of synthesis were appropriate. The way in which the subgroup analyses were performed, and limited information on the drug regimens and patient characteristics, mean that it cannot be known whether the inhibitor drugs had varying effects for different subgroups of patients with type 2 diabetes.

These limitations suggest that the authors' conclusions may be overly strong.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that the reduced risk of major cardiovascular events with DPP-4 inhibitors should be verified in ongoing trials, with long-term follow-up, using cardiovascular events as the primary endpoint.

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