DPP-4 inhibitors and lipids: systematic review and meta-analysis
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CRD summary
This meta-analysis suggested a possible beneficial effect of DPP-4 inhibitors on cholesterol that was small but statistically significant and could contribute to reduction of cardiovascular risk. Evidence limitations, study heterogeneity and potential confounding factors mean that the authors’ conclusions may not be reliable.

Authors' objectives
To assess the effects of dipeptidyl peptidase-4 inhibitors on lipid levels in diabetes patients.

Searching
MEDLINE, The Cochrane Library and ClinicalTrials.gov were searched to the end of 2010 for publications in English; search terms were reported but comprised only the names of relevant drugs. Reviews of approved drugs published by US Food and Drug Administration (FDA) and European Medicines Agency and published information provided by the FDA in response to queries during the approval process were handsearched.

Study selection
Randomised controlled trials (RCTs) of dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 1 or type 2 diabetes were eligible. Trials needed to include at least 100 patients (all groups) and last at least 24 weeks. Where both populations were enrolled in the same study, the trial was included only if separate outcome results were provided for type 1 and type 2 patients. Data had to be provided on total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides for all treatment groups (the primary outcomes). Secondary outcomes included mortality outcomes, stroke and vascular events (details reported in the paper).

Sitagliptin was the DPP-4 inhibitor in more than half of the studies; vildagliptin, alogliptin and linagliptin were also used. The comparative group in most studies was placebo; placebo/metformin, pioglitazone, metformin and glucagon-like peptide-1 receptor agonists were also used. Mean age ranged from 51 to 57 years. Mean glycated haemoglobin (HbA1c) ranged from 7.9% to 9.5%. Body mass index (BMI) ranged from 29.0 to 32.8 kg/m². Total cholesterol at baseline ranged from 4.50 to 5.40 mmol/L. HDL cholesterol at baseline ranged from 1.10 to 1.29 mmol/L. Triglycerides at baseline ranged from 1.77 to 2.59 mmol/L.

Assessment of study quality
There was no formal assessment of study quality.

Data extraction
For continuous data, mean differences were calculated with 95% confidence intervals (CI). Missing data were sought by reviewing other publications on the same trial, abstracts from congresses and dedicated websites.

Two independent reviewers performed the data extraction. Disagreements were resolved by a senior reviewer.

Methods of synthesis
Study results were pooled to give weighted mean differences (WMD) with 95% CIs using a random-effects model or a fixed-effect model where no heterogeneity was detected. The $I^2$ statistic was used to assess between-study heterogeneity. Publication bias was detected using Egger's test, Begg's test and visually using funnel plots.

Subgroup analyses were performed for each different DPP-4 inhibitor (random-effects model) and for different active comparators. A meta-regression was performed to assess the effect of putative moderators on plasma lipids, considering all the drugs together and each drug separately, mean age, diabetes duration, BMI, baseline lipid levels and HbA1c.

Results of the review
Seventeen RCTs were identified (8,961 participants, range 315 to 1,306). Only 13 studies were included in the meta-analysis as four studies did not report dispersion measures.
DPP-4 inhibitor versus controls significantly reduced total cholesterol (WMD -0.18 mmol/L, 95% CI -0.29 to -0.06; 13 studies) and triglycerides (WMD -0.15 mmol/L, 95% CI -0.26 to -0.03; 10 studies) but not HDL cholesterol (13 studies).

Subgroup analyses supported the main findings.

Meta-regression for the placebo-controlled trials found significant correlations that greater cholesterol reduction was associated with younger patients, lower diabetes duration, lower BMI, higher baseline cholesterol and higher HbA1c.

The authors stated that there was evidence of major publication bias.

**Authors' conclusions**

This meta-analysis suggested a possible beneficial effect of DPP-4 inhibitors on cholesterol which were small but could contribute to reduction of cardiovascular risk.

**CRD commentary**

The review addressed a well-defined question in terms of study design, participants, interventions and outcomes. Relevant databases were searched. The search included unpublished trials. Only studies published in English were included so some relevant studies may have been missed. There was evidence for publication bias. There was no formal assessment of study quality and little relevant data were reported to enable assessment of quality. Only RCTs were included. Sample sizes were not small. Efforts were made to reduce bias and error in data extraction; no such methods were reported for study selection. Some relevant study details were reported but no data were provided for the proportions of participants with types 1 and 2 diabetes, drug dosages or lengths of treatment and follow-up.

The synthesis was appropriate but was not related to diabetes type; probably all the patients had type 2 diabetes but this was not reported explicitly. I^2 values were not reported (these would have enabled assessment of between-study heterogeneity). The main analysis compared different drugs with a mixture of controls and the forest plots suggested heterogeneity. There were some labelling errors of figures 2C and 3A. The authors noted that the trials included patients with unsatisfactory glucose control who were not necessarily above lipid targets and that it was likely that some of the patients in the trials received lipid-lowering treatment.

The lack of information on study quality, confounding factors identified by the authors and the evidence for publication bias and potentially for study heterogeneity mean that the authors' conclusions may not be reliable.

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

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

**Research:** The authors stated that evidence needed to be confirmed by longer term trials designed for cardiovascular outcomes.

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