Effects on lipid profile of dipeptidyl peptidase 4 inhibitors, pioglitazone, acarbose, and sulfonylureas: meta-analysis of placebo-controlled trials


CRD summary
This review concluded that the available glucose-lowering drugs could have different effects on lipids, which could contribute to variations in cardiovascular risk. Limitations to the evidence, and a lack of information on dosages and trial quality, mean that the reliability of this review's findings is unclear; the tentative authors' conclusion is apt.

Authors' objectives
To determine the effects of dipeptidyl peptidase 4 (DPP4) inhibitors, pioglitazone, agents that stimulate insulin secretion (secretagogues), and acarbose on blood lipids, compared with placebo.

Searching
MEDLINE and The Cochrane Library were searched, for publications in English, up to November 2011. Search terms were reported.

Study selection
Placebo randomised controlled trials (RCTs) reporting total endpoint cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, for at least 200 patients with type 2 diabetes, were eligible for inclusion. Treatment had to have been planned to last 24 weeks.

In the included trials, the mean age of participants ranged from 51 to 62 years. Where reported, the mean duration of diabetes, at the start, ranged from 0.5 to 13.5 years, and the patients' mean body mass index ranged from 29.0 to 32.8 kg per m². Their mean glycated haemoglobin ranged from 6.8 to 10.2%, their total cholesterol levels ranged from 4.6 to 6.0 millimoles per litre (mmol/L), their HDL cholesterol ranged from 1.0 to 1.3 mmol/L (one trial reported a mean of 43.0 but this appears to be an error), and their triglycerides ranged from 1.8 to 3.1 mmol/L at the start of the trials, where reported. Treatment drugs included acarbose, glyburide, pioglitazone, sitagliptin, vildagliptin, allogliptin, linagliptin, and saxagliptin.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The authors did not report a quality assessment.

Data extraction
The mean start and end levels, and absolute or percentage variations in lipids were extracted, independently by two reviewers, to calculate mean differences, with 95% confidence intervals. Missing information was obtained by searching other publications on the same trial, or abstracts of communications at congresses, or dedicated websites. Any discrepancies in data extraction were resolved by a senior investigator.

Methods of synthesis
Mean differences and 95% confidence intervals were pooled, using a random-effects model, for each glucose-lowering agent. A fixed-effect model was applied if no statistical heterogeneity was indicated by I². A meta-regression was performed to investigate a possible correlation between changes in glycaemic and total cholesterol levels. Publication bias was assessed, using funnel plots, the Begg adjusted rank correlation test, and the Egger regression test.

Results of the review
Eighteen RCTs were included in the review, with over 10,526 patients (range 126 to 5,238; the participants in three trials were not reported).

Total cholesterol: Compared with placebo, statistically significant greater reductions in mean total cholesterol, from
start to end, were shown in groups receiving pioglitazone (MD -0.30, 95% CI -0.54 to -0.06; two trials), sulphonylureas (MD -0.23, 95% CI -0.39 to -0.09; two trials), and DPP4 inhibitors (MD -0.18, 95% CI -0.26 to -0.10; 10 trials). No statistically significant difference in change in total cholesterol level was observed between acarbose and placebo (two trials). No statistically significant correlation was observed between variations in glycaemic and total cholesterol levels (r=0.28; p>0.20).

HDL cholesterol: Compared with placebo, HDL cholesterol was increased significantly with acarbose (MD 0.04, 95% CI 0.02 to 0.06; two trials) and pioglitazone (MD 0.09, 95% CI 0.03 to 0.16; three trials). A statistically significant greater reduction in HDL cholesterol was observed with sulphonylureas versus placebo (MD -0.02, 95% CI -0.03 to -0.02; two trials). No statistically significant difference in change in HDL cholesterol was found between placebo and DPP4 inhibitors.

Triglycerides: Compared with placebo, statistically significant greater reductions in mean triglyceride levels, from start to end, were found with acarbose (MD -0.19, 95% CI -0.24 to -0.15; two trials), pioglitazone (MD -0.24, 95% CI -0.26 to -0.21; two trials), and DPP4 inhibitors (MD -0.19, 95% CI -0.34 to -0.05; nine trials). No statistically significant difference in change in triglyceride levels was found between sulphonylureas and placebo.

The funnel plot of all 18 trials suggested major publication bias. The results for LDL cholesterol were not reported.

Authors' conclusions
The available glucose-lowering drugs could have different effects on lipids, which could contribute to variations in cardiovascular risk.

CRD commentary
The review question was clear, and the inclusion criteria seem to have been sufficiently replicable. Two relevant electronic databases were searched, and the English-language restriction increased the risk of relevant studies being missed. The funnel plot suggested that major publication bias was probable. An attempt to minimise reviewer error and bias was made during data extraction, but this was not reported for study selection. No quality assessment of the included trials was reported, making it difficult to ascertain the extent to which any methodological flaws in the trials might have influenced their findings.

Some trial details were presented, but the dose regimens for the treatment drugs were not given. As a result, the appropriateness of the methods of synthesis were unclear. The authors suggested that the findings of their review should be interpreted with caution, due to limitations including the large underreporting of data on lipid parameters, and the relatively small number of trials included in the meta-analysis.

The limitations of the evidence, and the lack of information on dosages and trial quality, mean that the reliability of this review's findings is unclear; the tentative authors' conclusion is apt.

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

Research: The authors stated that a thorough investigation of the cardiovascular risk factors, in clinical trials of glucose-lowering drugs, would aid therapeutic choice for patients with type 2 diabetes.

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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.