Comparative efficacy of the addition of ezetimibe to statin vs statin titration in patients with hypercholesterolaemia: systematic review and meta-analysis

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CRD summary
This review concluded that the addition of ezetimibe to a statin was more effective in reducing low-density lipoprotein cholesterol and enabling more patients to achieve their goal, than doubling the dose of statin monotherapy, for the treatment of primary hypercholesterolaemia. These conclusions should be interpreted with caution due to the substantial variation observed for the pooled outcomes.

Authors' objectives
To assess the efficacy of statin titration versus the addition of ezetimibe, for the treatment of primary hypercholesterolaemia.

Searching
The following databases were searched for articles from January 1993 to March 2010: MEDLINE, EMBASE and Cochrane Database of Systematic Reviews. Search terms were reported. Reference lists of relevant reviews were screened.

Study selection
Randomised controlled trials (RCTs), of parallel-group, double-blind, single-blind or open-label design, were eligible for inclusion if they evaluated ezetimibe plus a statin versus up titration of statin monotherapy, with or without placebo. Patients had to be adults, aged over 18 years, with primary hypercholesterolaemia or hyperlipidaemia (defined using recognised criteria). The eligible trials had to last at least four weeks, for each treatment, and have a cholesterol-lowering diet or placebo run-in period of four weeks. Trials of patients who had not received statin therapy before, or whose cholesterol levels were not controlled by their existing statin monotherapy, were included. The review outcomes of primary interest were the proportion of patients achieving their low-density lipoprotein (LDL)-cholesterol goal, and the changes from baseline in LDL-cholesterol, high-density lipoprotein (HDL)-cholesterol, and total cholesterol.

Most of the included trials compared ezetimibe plus simvastatin or atorvastatin versus simvastatin or atorvastatin monotherapy. Three compared ezetimibe plus simvastatin versus atorvastatin monotherapy, and one compared ezetimibe plus simvastatin versus rosuvastatin monotherapy. The methods of statin titration varied between trials; in some, the dose was increased at regular intervals, while in others, the dose was increased only at baseline. Where reported, the run-in period before randomisation ranged from one to 14 weeks, and the duration of the intervention ranged from six weeks to 12 months.

Two reviewers independently assessed studies for inclusion, with any disagreements resolved by discussion.

Assessment of study quality
The quality of the trials was assessed using the Cochrane Collaboration's risk of bias assessment tool. This covered selection bias, performance bias, detection bias, attrition bias, and selective reporting. A quality rating of low, high or unclear was given for each trial.

Quality was assessed by one reviewer and checked by a second. Any disagreements were resolved by discussion.

Data extraction
For continuous variables, the means and standard deviations were extracted to calculate mean differences, with 95% confidence intervals. For dichotomous variables, event rates were extracted to calculate odds ratios, with 95% confidence intervals. The intention-to-treat data were extracted for the outcomes of primary interest.

The data were extracted by one reviewer and checked by a second reviewer. Any disagreements were resolved by discussion.
Methods of synthesis
Where appropriate, data from the included trials were combined in a meta-analysis. The pooled weighted mean differences or odd ratios, with 95% confidence intervals, were calculated. Statistical heterogeneity was assessed using $I^2$. A random-effects model was used for the meta-analysis if there was substantial heterogeneity, otherwise a fixed-effect model was used.

Subgroup analyses were performed for different types of statin, and different treatment periods. Sensitivity analysis was performed by excluding one trial that evaluated rosuvastatin and had a high risk of bias.

Results of the review
Thirteen RCTs were included in the meta-analysis (5,080 patients); 15 trials were eligible, but two open-label trials, with a high risk of bias, were excluded. Nine trials had a low or unclear risk of bias, and one other open-label trial (the only trial of rosuvastatin) had a high risk of bias.

Compared with statin up titration, the addition of ezetimibe was significantly associated with a percentage reduction in LDL-cholesterol levels (WMD -14.1%, 95% CI -16.1 to -12.1; 12 RCTs), a percentage reduction in total cholesterol (WMD -10.0%, 95% CI -11.5 to -8.5; 10 RCTs), and a percentage increase in HDL-cholesterol levels (WMD 1.8%, 95% CI 1.0 to 2.6; 11 RCTs). Substantial heterogeneity was observed for LDL-cholesterol ($I^2=65.8\%$) and total cholesterol ($I^2=68.4\%$) analyses.

The addition of ezetimibe was associated with an increase in the achievement of LDL-cholesterol goal (OR 2.38, 95% CI 1.89 to 2.98; nine RCTs). Substantial heterogeneity was observed ($I^2=55.4\%$).

Sensitivity analyses did not significantly alter the results. The results for other outcomes and subgroup analyses were reported.

Authors’ conclusions
The addition of ezetimibe to statin therapy was more effective, in reducing LDL-cholesterol and enabling more patients to achieve their goal, than doubling the dose of statin monotherapy.

CRD commentary
This review's inclusion criteria were clear. Relevant databases were searched. Efforts were made to find published, but not unpublished trials, which increased the possibility of publication bias. It was unclear whether language restrictions were applied, which made it difficult to assess the risk of language bias. Sufficient attempts were made to minimise errors and bias in the review process. Appropriate criteria were used to assess trial quality, but the number of included trials with a low risk of bias was unclear. Statistical heterogeneity was assessed, and the sources of heterogeneity were explored. Appropriate methods were used to pool the results.

The authors’ conclusions should be interpreted with caution, due to the inclusion of trials with unclear risks of bias, and substantial variation observed for the pooled outcomes.

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

Research: The authors stated that meta-analysis of individual patient data, for each treatment period and statin dose, was required. Subgroups should be analysed based on patient characteristics, such as starting levels of HDL- or LDL-cholesterol, and comorbidities, such as diabetes, cardiovascular disease, or obesity. Further data were needed for rosuvastatin. The authors stated that there was a trial ongoing (IMPROVE-IT) of patients with acute coronary syndrome, evaluating the effects, on cardiovascular outcomes, of the addition of ezetimibe to simvastatin.

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