Effectiveness of combination therapy with statin and another lipid-modifying agent compared with intensified statin monotherapy: a systematic review

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CRD summary
The authors concluded that lower-intensity statins combined with bile acid sequestrant or ezetimibe may be an alternative to higher-intensity statin monotherapy for high-risk statin-intolerant patients or those with a low response to statins; a cautious approach in practice was recommended. The authors' conclusion reflected the evidence presented and is likely to be reliable.

Authors' objectives
To evaluate the effectiveness of lower intensity statin combination therapy compared with higher intensity statin monotherapy in adults at high risk of atherosclerotic cardiovascular disease.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to July 2013 (the MEDLINE search was updated to November 2013) for articles published in English. Articles from a prior review (see Other Publications of Related Interest) and the reference lists of other relevant articles and reviews were screened. ClinicalTrials.gov was searched. Scientific information from pharmaceutical manufacturers was reviewed.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared a moderated combination statin regimen (including another lipid-modifying agent, such as bile acid sequestrant, ezetimibe, fibrate, niacin, or omega-3 fatty acid) versus higher-intensity statin monotherapy in adults at high risk of atherosclerotic cardiovascular disease (defined as low-density lipoprotein cholesterol level ≥ 4.91 mmol/L or ≥190 mg/dL; pre-existing atherosclerotic cardiovascular disease; or diabetes mellitus). The outcomes of interest were short-term lipid effects and long term clinical benefits. Non-randomised extensions of clinical trials more than 24 weeks duration, and US Food and Drug Administration reports, were also eligible to assess long-term benefits, serious adverse events, and harms.

Most included participants were men aged from 50 to 65 years old. None of the included trials contained patients with statin intolerance. Baseline mean low-density lipoprotein cholesterol levels varied; some were measured while participants were receiving lipid-modifying therapy. Various types of statins and doses were reported. Long-term clinical outcomes included mortality, acute coronary events, cerebrovascular events, and revascularisation procedures. The lipid outcome was low-density lipoprotein cholesterol level. Investigator-defined outcomes were adherence, adverse events, and withdrawals due to adverse events. Secondary outcomes were elevations in liver aminotransferase levels, elevated measures of muscle-related harm, acute kidney injury, or incident diabetes mellitus.

Two independent reviewers selected the studies for inclusion.

Assessment of study quality
Trial quality was assessed using the Cochrane risk of bias tool, and the Jadad score. The overall strength of evidence took account of risk of bias, consistency of results, directness and precision.

Two reviewers independently assessed trial quality.

Data extraction
Data were extracted by two reviewers to calculate mean differences and 95% confidence intervals. Statin doses were classified as being of low, mid, or high intensity (exact details were presented in a separate supplementary online table).

Methods of synthesis
A narrative synthesis was presented, and results were grouped by intervention.

**Results of the review**

Thirty-six RCTs were included in the review. Risk of bias was low to moderate (full details for each trial were not reported).

There was insufficient evidence to compare long-term outcomes (mortality, acute coronary events, cerebrovascular events, and revascularisation procedures) for any of the treatment comparisons. The duration of most studies was less than 20 weeks, and event rates were very low or none existent.

Low-intensity statin plus bile acid sequestrant reduced low-density lipoprotein cholesterol 0% to 14% more than mid-intensity monotherapy among high-risk hyperlipidaemic patients (four RCTs; moderate strength of evidence).

Mid-intensity statin plus ezetimibe reduced low-density lipoprotein cholesterol by 5% to 15% among patients with atherosclerotic cardiovascular disease (12 RCTs; moderate strength of evidence) and by 3% to 21% in patients with diabetes mellitus (11 RCTs; moderate strength of evidence) compared with high-intensity statin monotherapy.

There was insufficient evidence to evaluate the effects of combination therapies with fibrates, niacin, and omega-3 fatty acids on low-density lipoprotein cholesterol levels.

Adherence to treatment was high, adverse events were generally similar between groups, and secondary harms occurred infrequently (where reported).

**Authors' conclusions**

Lower-intensity statin combined with bile acid sequestrant or ezetimibe may be alternatives to higher-intensity statin monotherapy among high-risk statin-intolerant patients or those with a less than anticipated low-density lipoprotein cholesterol response.

**CRD commentary**

The review question was clear and inclusion criteria were adequately specified. Appropriate data sources were searched, although language and publication restrictions may mean that relevant studies were overlooked. The review process was conducted with steps to help minimise error and bias.

Relevant quality assessment tools were used to assess the included studies, but full results of this assessment were not reported. Variation amongst the included studies meant that a narrative synthesis was appropriate.

The authors' conclusion and recommendations for practice and research reflected the evidence presented and are likely to be reliable.

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

**Practice:** The authors stated that clinicians could consider using a combination of lower-intensity statin with bile acid sequestrant or ezetimibe in high-risk patients who were intolerant or unresponsive to statins, although this decision should be treated with caution, given the lack of evidence on long-term clinical benefits and harms.

**Research:** The authors stated that longer duration (more than 12 months) trials were needed to evaluate long-term clinical outcomes and harms in statin-intolerant and statin-unresponsive patients.

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