Systematic review: comparative effectiveness and harms of combinations of lipid-modifying agents and high-dose statin monotherapy

Sharma M, Ansari M T, Abou-Setta A M, Soares-Weiser K, Ooi T C, Sears M, Yazdi F, Tsertsvadze A, Moher D

CRD summary
This review concluded that there was insufficient evidence to support the benefit for mortality, myocardial infarction, stroke, and revascularisation procedures of statin combination therapy over high-dose monotherapy in high-risk patients needing intensive lipid-lowering therapy. The authors' conclusion reflected the evidence presented, but the reliability is potentially compromised by search restrictions and unclear quality of included studies.

Authors' objectives
To compare the benefits and harms of high-dose statin monotherapy with combination therapy in adults at high risk of coronary disease.

Searching
MEDLINE, EMBASE, and the Cochrane Library were searched (with dates from 1966 to May 2009). Additional searching was conducted via Scopus for references that cited eight expert-nominated articles, the Internet, and the US Food and Drug Administration statistical and medical reviews of drug applications. Further published and unpublished material was requested from the manufacturers Abbott, AstraZeneca, and Merck/Schering-Plough Pharmaceuticals, and from study authors. English-language studies were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) of mixed-risk adults treated with combinations of statins and bile-acid sequestrants, fibrates, ezetimibe, niacin, or ω-3 fatty acids, compared with statin monotherapy, were eligible for inclusion in the review. Randomised comparative studies longer than 24 weeks duration, and reporting on clinical outcomes, serious adverse events, and cancer incidence, were also eligible.

The primary outcomes of interest were all-cause mortality and vascular death. Other outcomes included were myocardial infarction, acute coronary syndrome, stroke, transient ischaemic attack, and revascularisation procedures. The following surrogate outcomes were considered: attainment of ATP (adenosine triphosphate) III low-density lipoprotein cholesterol goals, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, and measures of carotid or coronary atherosclerosis. Also analysed were: serious adverse events; cancer; withdrawals due to adverse events and incidence of at least one adverse event; elevated serum aminotransferase levels; hepatitis; myalgia; creatine kinase levels exceeding 10 times the upper limit of normal; rhabdomyolysis; and treatment adherence.

The review attempted to focus on high-risk patients requiring intensive lipid-lowering therapy (defined as those with a 10 year coronary heart disease risk greater than 20%, mean baseline low-density lipoprotein levels of at least 5.0 millimoles/litre (≥190 milligrams/decilitre, or both). The included statins were atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. Similar doses were used in combination and monotherapy. The majority of studies examined the statin-ezetimibe combination and reported short-term surrogate outcomes.

Two reviewers independently screened full papers for inclusion in the review, and disagreements were resolved by consensus.

Assessment of study quality
The authors assessed trial quality using predefined criteria to score the included trials as good, fair, or poor. The criteria were not detailed in the paper. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to further assess the strength of evidence.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data were extracted in order to calculate mean differences or odds ratios and 95% confidence intervals.

The authors did not state how many reviewers extracted the data.

**Methods of synthesis**
In the absence of heterogeneity, meta-analyses were conducted using the DerSimonian and Laird method. The Peto odds ratio was used for rare events. The method of assessing heterogeneity was not reported. The main analysis (in high-risk patients) compared a statin combined with another lipid-lowering agent with a high dose of the same statin in monotherapy. Double counting was avoided in trials with multiple unequal numbers of treatment groups.

**Results of the review**
Ninety-eight randomised controlled trial (RCTs) and four controlled clinical trials were included in the review.

**High-risk patients:** In high-risk patient samples, there were no statistically significant differences in mortality in any analysis comparing stain-ezetimibe and statin-fibrate with high-dose statin monotherapy (three trials; 605 patients). The same result was noted for those comparing monotherapy with various doses and types of statins in combination with ezetimibe (14 trials; 6,275 patients). There were no trials comparing the effects of the two treatment types on myocardial infarction, transient ischemic attack, or revascularisation procedures. A significantly greater likelihood of attaining adenosine triphosphate (ATP) III low-density lipoprotein cholesterol goals was reported following combination therapy with simvastatin, odds ratio 7.21 (95% CI 4.30 to 12.08; two trials, 295 patients). All stain-ezetimibe trials found additional low-density lipoprotein cholesterol reductions (4 to 27%), with inconsistent results found for those investigating statin-bile-acid sequestrants. There were no statistically significant differences in measures of atherosclerosis (two trials).

**Diverse-risk patients:** In diverse patient risk samples, there were no statistically significant differences for mortality or other clinical outcomes, serious adverse events, cancer incidence, or high-density lipoprotein cholesterol levels. In 23 trials, the attainment of ATP III low-density lipoprotein cholesterol goals was higher with statin-ezetimibe combination treatment. Low-density lipoprotein cholesterol reductions (ranging from 3 to 27%) were reported in trials of lower dose statin-combination treatments. Monotherapy showed greater low-density lipoprotein cholesterol reductions when compared with combination therapy comprising statin-ω-3 fatty acids, mean difference 5.26% (95% CI 1.79 to 8.74). Withdrawals due to adverse events were high following statin-niacin therapy, odds ratio 2.38 (95% CI: 1.63 to 3.47; 10 trials). Significantly more patients having at least one adverse event were reported when receiving statin-bile-acid sequestrant combination therapy, odds ratio 2.19 (95% CI 1.28 to 3.75; four trials).

**Authors' conclusions**
There was insufficient evidence to support the benefit for mortality, myocardial infarction, stroke and revascularisation procedures of combination therapy over high-dose statin monotherapy in high-risk patients needing intensive lipid-lowering therapy. There was limited evidence favouring statin-ezetimibe therapy in achieving low-density lipoprotein cholesterol goals.

**CRD commentary**
The review question was clear and was supported by detailed and potentially reproducible inclusion criteria. The inclusion of diverse-risk patients, in addition to those at high-risk, was a departure from the objective; justification for this was provided by the authors. The search strategy included several sources of published and unpublished material, which minimised the threat of publication bias. The restriction to English language studies may mean that relevant material was missed, and language bias introduced. The review process appeared to be carried out with sufficient transparency only in the procedure for study selection.

The absence of reporting of any detailed study quality assessment limits the interpretation of the review's reliability, as it was not possible to verify the authors' conclusions about overall methodological quality. Although the inclusion of study details was prohibitive due to the large number included, there was very little information by way of summary characteristics. The method of synthesis appeared to be appropriate in the presence of heterogeneity, but the method to assess variation was not reported.

The authors' conclusion reflected the evidence presented, but the reliability is potentially compromised by search
restrictions and unclear study quality.

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

**Practice:** The authors stated that the benefits, risks, and costs of combination therapy need to be clearly defined before this intervention recommended for widespread use.

**Research:** The authors stated that long term trials were needed to determine mortality and vascular outcomes in high-risk patients, women, frail elderly and in racial or ethnic subgroups.

**Funding**
Agency for Healthcare Research and Quality, contract number 290-02-0021.

**Bibliographic details**

**Original Paper URL**
http://www.annals.org/cgi/content/full/0000605-200911030-00144v1

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Antilipemic Agents; Drug Combinations; Drug Toxicity; Dyslipidemias; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Simvastatin

**AccessionNumber**
12009107567

**Date bibliographic record published**
02/09/2009

**Date abstract record published**
09/09/2009

**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.