Are statins created equal: evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention

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CRD summary
This review assessed the relative efficacy of pravastatin, simvastatin and atorvastatin. The authors concluded that the evidence suggests there is no statistically significant difference in long-term cardiovascular outcomes between standard doses of these statins. Statements on relative efficacy were based on indirect comparisons, thus the authors’ cautious conclusion appears appropriate.

Authors' objectives
To assess the relative efficacy of pravastatin, simvastatin and atorvastatin.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched from 1980 to 2004 for publications in the English language; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Completed randomised controlled trials (RCTs) with at least 1,000 participants and with a follow-up of at least 1 year were eligible for inclusion. The average duration of follow-up in the included studies was 3 to 6 years.

Specific interventions included in the review
Studies that compared pravastatin, simvastatin or atorvastatin with placebo were eligible for inclusion. Studies could use additional medications if these were applied equally to all treatment groups. Studies that compared any of the specified statins with usual care were also identified and used in sensitivity analyses. The included studies used statins in standard doses: 40 mg pravastatin, 20 to 40 mg simvastatin and 10 mg atorvastatin.

Participants included in the review
Studies with participants of any age or gender were eligible for inclusion. The characteristics of the patients in the included studies differed. Some studies were of primary prevention while others were of secondary prevention; some included patients with and without a history of cardiovascular disease (CVD) but at high risk for cardiovascular events; and some recruited specific subgroups (men aged less than 65 years, patients aged 65 years or older, and patients with hypertension or diabetes). The studies recruited patients with varying levels of baseline cholesterol (including moderate and high levels).

Outcomes assessed in the review
Studies that assessed CVD or mortality were eligible for inclusion. The review assessed major coronary events (fatal coronary heart disease and nonfatal myocardial infarction), major cerebrovascular events (fatal and nonfatal strokes), all cardiovascular deaths (coronary and cerebrovascular) and all-cause mortality.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed for blinding, methods used to recruit patients, attrition and noncompliance. The authors did not state how many reviewers performed the validity assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each outcome of interest, the number of events and the total number of participants were extracted from original publications and relevant sub-studies and used to calculate the relative risk (RR) with 95% confidence interval (CI). The percentage difference between treatments in the net change in total cholesterol and low- and high-density lipoprotein from baseline was also extracted for each study.

Methods of synthesis
How were the studies combined?
Pooled RRs with 95% CIs were calculated using a random-effects model (DerSimonian and Laird) for all studies combined and then with studies grouped according to the statin evaluated. The effects of each pair of different statins were compared for each outcome of interest using an adjusted indirect comparison method.

How were differences between studies investigated?
Heterogeneity was examined graphically using a L’Abbe plot and tested using the chi-squared statistic. Meta-analyses were repeated after including the identified studies that compared staines with usual care and using a fixed-effect model to calculate the pooled RRs.

Results of the review
Eight placebo-controlled RCTs: 4 RCTs of pravastatin (n=25,572), 2 RCTs of simvastatin (n=24,980) and 2 RCTs of atorvastatin (n=13,143). Two additional RCTs that compared staines with usual care were included in the sensitivity analyses: one was of pravastatin (n=10,355) and the other was of atorvastatin (n=1,600).

All studies were double-blind and recruited consecutive patients. Attrition rates were reported as 3% or less. The average rate of noncompliance was reported as 15% or less.

All but one of the included studies (one of the usual care studies) reported a similar percentage change in total cholesterol and low-density cholesterol.

The L’Abbe plot showed that active treatment reduced major coronary events in all studies.

The only meta-analysis for which significant statistical heterogeneity was found was that of all-cause mortality among the studies of simvastatin (p=0.03).

For all included studies, statins significantly reduced fatal and nonfatal myocardial infarction (RR 0.75, 95% CI: 0.69, 0.81), fatal and nonfatal stroke (RR 0.81, 95% CI: 0.73, 0.89), all cardiovascular death (RR 0.82, 95% CI: 0.75, 0.89) and all-cause mortality (RR 0.85, 95% CI: 0.79, 0.92).

The meta-analysis of individual staines showed that all staines significantly reduced major coronary events compared with placebo: the RR was 0.78 (95% CI: 0.72, 0.83) for pravastatin versus placebo, 0.72 (95% CI: 0.67, 0.79) for simvastatin versus placebo, and 0.61 (95% CI: 0.48, 0.77) for atorvastatin versus placebo.

Adjusted indirect comparisons showed no statistically significant difference between staines for combined fatal coronary heart disease and nonfatal myocardial infarction: the RR was 0.93 (95% CI: 0.84, 1.03, p=0.18) for simvastatin versus pravastatin, 0.84 (95% CI: 0.66, 1.08, p=0.18) for atorvastatin versus simvastatin, and 0.79 (95% CI: 0.61, 1.02, p=0.06) for atorvastatin versus pravastatin. Similarly, there was no statistically significant difference between staines for fatal and nonfatal stroke, all cardiovascular death and all-cause mortality. After including the 2 RCTs with a usual-care control group, atorvastatin was found to reduce major coronary events compared with simvastatin (RR 0.79, 95% CI: 0.63, 0.99, p=0.04) and pravastatin (RR 0.71, 95% CI: 0.56, 0.90, p=0.004). There were no statistically significant differences between staines for other review outcomes.

Authors’ conclusions
Evidence suggests that there is no statistically significant difference in long-term cardiovascular outcomes between
standard doses of pravastatin, simvastatin and atorvastatin.

**CRD commentary**
The review addressed a clear question that was defined in terms of the intervention, outcomes and study design. The search was limited to English language reports listed in two databases but, given that only very large RCTs were sought, this limited search was likely to have identified the major relevant studies. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. Validity was discussed with respect to relevant criteria and summary information provided on the included studies was adequate.

Statistical heterogeneity was assessed. The studies appear to have been appropriately pooled using meta-analysis, although the authors did comment on the clinical heterogeneity amongst the studies. Statements on relative efficacy were based on indirect comparisons. The circumstances that needed to be met for such a comparison to be valid were discussed and on this basis the comparison appeared valid. The lack of reporting of review methods undermines the strength of the evidence but, overall, the authors' cautious conclusion appears appropriate.

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

Research: The authors noted that the wide CIs for some pairwise comparisons may suggest that more evidence is required. However, ongoing studies and large well-designed observational studies may provide further information.

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