A systematic review and meta-analysis on the therapeutic equivalence of statins

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CRD summary
This review found reductions of low-density lipoprotein (LDL) cholesterol decreased with statin dose. Equivalent doses could be found for most statins to achieve common goals of LDL cholesterol levels. The authors' conclusions were based on the evidence presented, but some methodological flaws made the reliability of the conclusions unclear.

Authors' objectives
To compare the efficacy and safety profiles of various statins at different doses and determine the therapeutically equivalent doses of statins required to achieve specific low-density lipoprotein (LDL-C) lowering effect in patients with hyperlipidaemia.

Searching
Searches were undertaken of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) for trials published between 2005 and April 2006 in either English or Chinese. Trials included in a previous review by Oregon Health Resources Commission (OHRC) were retrieved. References of retrieved studies were checked to identify further studies.

Study selection
Randomised controlled trials of at least four weeks duration that evaluated direct comparisons of various statins in patients aged 18 years and older with hyperlipidaemia were eligible for inclusion. Trials that did not report primary data were excluded.

The primary outcomes were changes in LDL-C. Six statins were evaluated in the review: lovastatin (10mg to 80mg), simvastatin (10mg 80mg), pravastatin (10mg 40mg), fluvastatin (20mg 80mg), atorvastatin (10mg to 80mg) and rosuvastatin (5mg to 40mg). Other outcomes evaluated were all-cause mortality, myocardial infarction, hospitalisation for unstable angina, revascularisation, stroke, peripheral arterial disease and (in long-term studies) incidence of coronary heart disease. Muscle toxicity, creatine kinase abnormalities and abnormalities in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were specific adverse events that were also assessed.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed in terms of random assignment, allocation concealment, blinding of patients, outcome assessors and care providers, and attrition rates. Studies were graded A (all four criteria met) to E (no criteria met).

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

Data extraction
Data were extracted to calculate mean differences and 95% confidence intervals (CI) for the primary outcomes where different ranges of LDL-C reduction were determined (<20%, 20% to 30%, 30% to 40% and >40%). The incidence of coronary heart disease was noted in long-term studies.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The pooled weighted mean difference (WMD) and 95% CIs were calculated using a fixed-effect model. Statistical heterogeneity was evaluated using Cochran's Q (p<0.10 indicated statistical heterogeneity).
Results of the review
Seventy-five trials (n=10,757) were included in the review: 60 trials from the previous OHRC review and 15 trials published since. One hundred and forty head-to-head comparisons were made between different statin types. Fifty-one studies (68%) were graded B or better for methodological quality. Three trials adequately reported appropriate methods of allocation concealment. The authors stated that attrition rates were similar for both groups across the trials.

Of statins that could decrease LDL-C by 30% to 40%, statistically significant differences were found for the comparisons: atorvastatin 10mg and lovastatin 40mg (WMD 7.00, 95% CI 2.87 to 11.13; n=89), atorvastatin 10mg and lovastatin 80 mg (WMD -10.00, 95% CI -15.25 to -4.75; n=84), atorvastatin 10mg and simvastatin 20mg (WMD 2.17, 95% CI 1.20 to 3.14, n=5,075), lovastatin 80mg and simvastatin 20mg (WMD 13.00, 95% CI 7.36 to 18.64; n=60) and fluvastatin 80mg and lovastatin 80mg (WMD -9.00, 95% CI -17.01 to -0.99; n=52).

Significant differences were also observed for statins shown to reduce LDL-C by 20% to 30%: fluvastatin 40mg and lovastatin 20mg (WMD -4.81, 95% CI -7.25 to -2.36; n=496), fluvastatin 40mg and pravastatin 40mg (WMD -9.37, 95% CI -14.50 to -4.24; n=87), fluvastatin 40mg and simvastatin 10mg (WMD -4.01, 95% CI -4.77 to -3.26; n=300), simvastatin 10mg and lovastatin 20mg (WMD -3.50, 95% CI -4.70 to -2.31; n=1,773), simvastatin 10mg and pravastatin 20mg (WMD -3.87, 95% CI -4.62 to -3.12; n=945) and simvastatin 10mg and pravastatin 40mg (WMD 2.27, 95% CI 0.31 to 4.23; n=421). Significant statistical heterogeneity was found only for the comparison of pravastatin 40mg and simvastatin 10mg (p=0.07).

Atorvastatin at 80mg was observed to confer statistically significant benefits in one trial of protection against unstable angina (3.8% compared to 5.1%) and revascularisation (16.3% compared to 18.8%) than pravastatin at 40mg.

Atorvastatin at the same dose was associated with fewer myocardial infarctions, peripheral arterial disease and revascularisations than simvastatin at 20mg.

The authors reported that the studies that evaluated rosuvastatin reported a higher adverse event rate than other comparison arms. Incidence of raised ALT/AST levels was less than 1% in most trials.

Authors’ conclusions
In general, reduction of LDL cholesterol decreased with the dose of the stain. Equivalent doses could be found for most statins to achieve common goals of LDL cholesterol levels. Although there were some significant differences noted between statin types, most of the time these were less than 7% and might not have significant implications in clinical practice.

CRD commentary
The review addressed some clear questions. Criteria for inclusion of trials in the review were clearly stipulated. Appropriate electronic databases were used to search for relevant studies, but the restriction of the review to trials published in certain languages risked language biases. There were few attempts to identify unpublished studies, so there was a risk of publication biases. The authors reported no steps to minimise errors and biases at any stage of the review process. The decision to pool data appeared justified given the lack of statistical heterogeneity identified across the results for the outcomes. The authors correctly acknowledged the limitations of the data and noted that many results were based on head-to-head studies with small sample sizes.

The authors’ conclusions were based on the evidence presented, but potential for biases made the reliability of the conclusions unclear.

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

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