COMPARATIVE CLINICAL EFFICACY OF STATINS: 
A SYSTEMATIC REVIEW AND MIXED TREATMENT COMPARISON

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STUDY PROTOCOL

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Background

Cardiovascular disease (CVD) is the leading cause of death and a major cause of disability worldwide. In 2003, in the United States alone, CVD accounted for more than 800 thousand deaths. It continues to be a major contributor to health disparities and rising health care costs. In 2006, the economic burden of CVD exceeded $400 billion.

Blood cholesterol levels are a strong predictor of mortality and morbidity associated with CVD. Statins act to lower blood cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis. Currently there are six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosvastatin, simvastatin) marketed in the United States for the almost identical indication of “reducing elevated total-cholesterol, low-density lipoprotein-C, apolipoprotein-B, non-high-density lipoprotein-C, and triglyceride levels and increasing high-density lipoprotein in patients with primary hypercholesterolemia.”

Statins are used for the secondary prevention of cardiovascular events in patients with CVD (including a history of angina or acute myocardial infarction, peripheral arterial disease, or a history of stroke) and for primary prevention in patients who are at increased risk of cardiovascular events because of factors such as smoking, hypertension and diabetes. It is recommended that statins are used in conjunction with lifestyle measures (diet, smoking cessation and exercise) and other appropriate interventions (e.g. adequate control of chronic conditions such as hypertension and diabetes).

Statin therapy, initially focused on patients with established cardiovascular disease, has become widely common as the limits of treatment expanded over time to include persons at progressively lower risk of developing cardiovascular events. As the number of patients in need for statin therapy continues to increase, information regarding the relative clinical value of statins is needed to better inform not only patients and prescribers, but also payers. It is particularly difficult to determine the exact threshold of the level of baseline risk for cardiovascular events at which to start prescription or tailor therapy to patients most likely to benefit from statin treatment.

A large body of literature has demonstrated the clinical efficacy and safety of statins for both primary and secondary prevention of CVD events. There are three main limitations of the literature synthesizing the evidence on the efficacy and safety of statin therapy:
1. The majority of published meta-analyses include only direct evidence.

Based on a review of the literature, meta-analyses are largely pair-wise comparisons, often comparing statins to placebo or conventional treatment group. Hence, they are often limited to placebo-controlled studies, with active-comparator trials only assessed in isolation. This focus on placebo-controlled trials has limitations as there is a large number of active-comparator statin trials, which can contribute to the evidence base. It is therefore important to synthesize the totality of the evidence base on statins.

2. The extent to which individual statins differ in terms of efficacy and acceptability is unclear.

Although prescribers and guideline developers widely believe that similar drugs do not differ in terms of their clinical efficacy, empirical evidence suggests that there may be differences between individual drugs in a class.\textsuperscript{13, 14} A number of researchers suggested that assuming that all drugs with a similar mechanism of action are equivalent and can be used interchangeably may be clinically unwarranted.\textsuperscript{15-17} With the basic mechanism of cholesterol lowering remaining the same, the six statins differ to a various extent in pharmacological properties and they may differ in terms of their clinical efficacy.\textsuperscript{18, 19} As with many drugs in so-called drug classes, the extent to which individual statins vary in terms of efficacy and acceptability is unclear.\textsuperscript{20} This is because of the fact that most randomized clinical trials have not tested different statins head-to-head. Additionally, almost all of the meta-analyses ‘lumped’ all statins together as one intervention.\textsuperscript{4, 7-11, 21-23}

3. Quantitative syntheses of randomized trials have not taken into account the dose-response relationship of statins.

The majority of published meta-analyses did not explicitly address the potential impact of dose on the clinical efficacy and safety of statins under the assumption that statins at their respective doses have similar clinical efficacy. This assumption cannot be validated and has not been verified in clinical data.

Overcoming the limitations of the literature

Combination of direct and indirect evidence: Methodological advances in statistical synthesis approaches, called mixed treatment comparisons (also known as network meta-analyses), facilitate
the combination of direct and indirect evidence by incorporating both direct (when statins are compared to each other within a trial) and indirect comparisons (when statins are compared between trials with a common comparator treatment, which is often placebo). 

Evaluation of the comparative efficacy and acceptability of individual statins: By implication of including both direct and indirect evidence, attempts at statistically synthesizing the existing body of evidence are no longer limited to a pair-wise comparisons. Rather, they are capable of comparing all relevant statins even when they are not trialed against each other.

Mixed treatment comparisons can summarize randomized trials of individual statins to provide point estimates (together with uncertainty estimates) for their association with a given endpoint, as well as an estimate of incoherence (that is, a measure of how well the entire network of statins fits together). Mixed treatment comparison methods have been used successfully in other fields of medicine and resulted in influential publications.

Evaluation of the impact of dose on the comparative efficacy and acceptability of individual statins: Meta-regression techniques can incorporate the impact of dose on the efficacy and safety of statins. These methods have been developed and implemented in various therapeutic areas.

**Study Objectives**

In the current study, the objective is to systematically review the clinical literature to identify and document the comparative clinical efficacy of statins on the basis of both direct and indirect evidence.

Statistical analyses will be conducted to rank the available statins in terms of their efficacy and safety. The objective of the statistical analysis will be to quantitatively compare the clinical efficacy and safety of six statins on the basis of:

1. Surrogate endpoints (for example, reductions in blood cholesterol levels)
2. Clinical events (for example, reductions in the risk of developing CVD events)
Research Questions

The proposed study will address the following research questions:

1. What is the comparative clinical efficacy and safety of individual statins on the basis of surrogate outcomes independently of the effect on clinical outcomes in primary prevention, secondary prevention, and mixed patient populations?
2. What is the comparative clinical efficacy and safety of individual statins on the basis of clinical outcomes in primary prevention, secondary prevention, and mixed patient populations?

Methods

Identification of Studies

The systematic review will be conducted based on the most up-to-date NHS Centre for Dissemination and Review guidelines. Search terms will be pre-defined, and searches will be conducted in MEDLINE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and Health Technology Assessment Database (NHS HTA). These electronic databases will be searched starting from January 1, 1985 (approximately five years before the first statin was available on the market).

The search will employ the terms atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and Hydroxymethylglutaryl-CoA Reductase Inhibitors/therapeutic use. A manual search will also be performed using the authors' reference files and reference lists from original communications and review articles. Identified qualitative and quantitative systematic reviews (meta-analyses) will be manually reviewed to cross check references and confirm the comprehensiveness of study identification and selection.

Trial databases of regulatory agencies (the Food and Drug Administration (FDA) in the USA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the European Medicines Agency (EMA) in the EU) and ongoing trial registers (clinicaltrials.gov in the USA, ISRCTN and National Research Register in the UK) will be hand-searched for published, unpublished and ongoing randomized controlled trials.
Exclusion Criteria

The following exclusion criteria will be applied to the articles identified in each of the searches:

- Quasi-randomized trials or non-randomized studies
- Studies of multi-interventional therapies where the effect of the statin cannot be separated out
- Case reports, comments, letters, editorials, and review articles
- *In vitro* or animal studies
- Studies in populations other than primary and secondary prevention of CVD
- Studies in pediatric patient populations, less than 18 years old
- Studies with short follow-up duration (<4 weeks)
- Studies with no arms having more than 50 patients
- Studies not reporting detailed dosing regimens received by patients on all comparator arms (that is, it must be clear whether the study employed fixed or variable dosing regimens)

Inclusion Criteria

The following inclusion criteria will be applied to the articles identified by each of the searches:

- Randomized controlled studies (randomized, prospective, controlled design); both open-label and double-blind designs will be included
- Patients in at least one arm of the trial must receive atorvastatin, fluvastatin, losuvastatin, pravastatin, rosuvastatin, and simvastatin (either generic or brand-name formulations)
- The patients of interest are patients at least 18 years of age with, or at risk of developing, CVD (primary and secondary prevention populations)
- To be included in the statistical analysis, each selected study must report either surrogate endpoints (e.g. reductions in blood cholesterol levels), or clinical events of interest (e.g. reductions in the risk of developing CVD events). Outcomes of interest are also listed below.
Trials with crossover design will only be included if results are available from the first randomized period. Studies that compared multiple doses of the same statin will be included. Both fixed-dose and titration trials will be included.

Titles and abstracts of studies identified from the searches described above will be screened by one researcher based on the exclusion criteria (Level 1 screening; Figure below). Full texts of studies accepted at Level 1 will be further reviewed by two researchers at Level 2 employing the inclusion criteria (Figure). At Level 2, if there is an uncertainty on the study relevance, the reviewers will resolve the issue by consensus.

The inclusion/exclusion processes will be documented thoroughly, including completion of the PRISMA flow chart as shown below.  

A list of included and excluded studies with the reasons for exclusion will be established.

**Data Extraction**

We will use a structured data-abstraction form implemented in Microsoft Excel to ensure consistency of appraisal for each study.

Data on the following items will be extracted:

**Study-level Characteristics**

- Trial (trial reference)
• Population severity (narrative description of CVD risk factors of the patient population)
• Patient population (primary prevention, secondary prevention, or mixed population)
• Dosing regimen (fixed-dose or titration trial)
• Co-morbid conditions (condition of primary interest is diabetes)
• Concomitant medication usage
• Trial duration in weeks
• Follow-up duration in weeks (time point at which outcomes are reported)
• Primary statin and dosage
• Comparator(s) and dosage(s) (these can be other statin treatments, placebo, usual care, or no treatment)
• Number of patients in each study arm (number randomized to each study arm)

**Surrogate and Clinical Endpoints**

• Mean reduction in LDL concentration from baseline
• Mean reduction in HDL concentration from baseline
• Mean reduction in total cholesterol from baseline
• Number of CVD deaths (cardiovascular deaths)
• Number of stroke deaths (both hemorrhagic and ischemic stroke)
• Number of all-cause deaths (all-cause mortality)
• Number of CVD events (non-fatal myocardial infarctions, non-fatal stroke)
• Number of MACE events (composite outcome of CVD death, myocardial infarction, and stroke)

Once the list of included studies is finalized, two researchers will extract data independently. Discrepancies will be settled through consensus discussion. In the event of conflict, a third researcher will be recruited, whose decision will be considered final.
**Trial categorization and subgroups**

Whenever possible, included trials will be categorized as either primary or secondary prevention trials. Primary prevention trials are those that assessed the efficacy and safety of statins in patients free of CVD at baseline. Secondary prevention trials are those that evaluated statins in patients with established CVD. Given that a number of trials will include both primary and secondary prevention populations, these trials will be categorized as having a mixed patient population. In cases where study authors reported data separately on a sole primary prevention or secondary prevention group within a mixed trial, this information will be recorded for use in respective statistical analysis. To account for the possibility that the efficacy of statins may be different across clinically defined subgroups, further categorization will be conducted. Whenever available, results will be recorded by age (<65 or >65 years), sex, or diabetes status.

**Quality Assessment of Included Trials**

The quality of randomized controlled trials will be assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination. Where inadequate information on trial characteristics are provided, the trial authors will be contacted in order to obtain further information. As with data extraction, potential disagreements will be resolved by consensus.

**Statistical Analysis**

All analyses will be performed separately for primary prevention, secondary prevention, and mixed patient populations.

The analysis will be based on the total number of randomly assigned participants, irrespective of how the original study investigators analyzed the data. Therefore, outcome data for the intent-to-treat population will be used. When data on dropouts are carried forward and included in the efficacy evaluation (Last Observation Carried Forward, LOCF), they will be analyzed according to the primary studies.

**Synthesis of Results**

Included trials will first be summarized in terms of patient and trial characteristics. Trial and patient population characteristics will be tabulated, describing the types of direct and indirect comparisons and some important variables, both clinical and methodological (such as trial population, year of publication, age, risk of CVD, sponsorship, etc.).
For each pair-wise comparison between statins, the relative effect will be calculated with a 95% CI. First, we will perform classical pair-wise meta-analyses to synthesize studies that compare the same interventions using the Der Simonian Laird method.\textsuperscript{35} Forest plots of the relative treatment effects from the individual trials and pair-wise meta-analyses will be visually inspected to search for groups and outliers. This will be statistically supplemented by using the $I^2$ measure, which will be used to estimate the percentage of total variation among studies that can be considered to be due to heterogeneity.\textsuperscript{36} Rough thresholds of 25%, 50%, and 75% will be used to define low, moderate, and high heterogeneity.

To determine the comparative effects of statins, we will conduct mixed treatment comparisons. In these analyses, study-level relative treatment effects will be combined using both fixed- and random-effects models within a Bayesian framework using Markov chain Monte Carlo methods in WinBUGS.\textsuperscript{24-27, 37} This will be based on modeling the outcomes in every treatment group of every study, and specifying the relations among the relative effects across studies making different comparisons. The probability that each statin is the most efficacious regimen will be assessed by calculating the treatment effect for each statin compared with the common comparator treatment, and counting the proportion of iterations of the Markov chain in which each drug has the highest treatment effect, the second highest, and so on.

Relevant time points of interest for the mixed treatment analysis will be determined once data extraction is complete. A rate-based model (using hazard rates and their ratios) may be needed to take into account outcomes reported at different follow-up times.

Relative treatment effects will be determined using an “unconstrained” model for the control arm rate of the studies.\textsuperscript{25} Thus, the analysis will not allow one study’s placebo rate to give any information about another study’s; there will be no “borrowed strength” across study placebo rates.

Both fixed-effects and random-effects models will be developed for the statistical analysis. The fixed-effects models will be run under the assumption that every trial has an identical underlying A vs. B effect. The random-effects model, which is a more conservative assumption when taking into account potential heterogeneity, will assume that every trial has an identical underlying mean effect, but some degree of variation may be present. The choice of a fixed or random effect meta-analysis model will be made by comparing models regarding their goodness of fit to the data. The goodness of fit will be estimated by calculating the difference between the deviance for the fitted model and the deviance for the saturated model (which fits the data perfectly).
To estimate inconsistency between direct and indirect evidence, we will calculate the ratio of relative effects for indirect versus direct evidence. Inconsistency will be defined as the disagreement between direct and indirect evidence with a 95% CI excluding 1. More formally, we will adopt the node-split method. In the node-split method, a model that assumes consistency across the entire set of comparisons in the treatment network will be compared with one that relaxes the consistency assumption for the individual comparison (node) being assessed. Using this method, the amount of agreement between the direct and indirect evidence will be formally measured.

A systematic procedure will be followed to ensure that the choice of initial values used in WinBugs models do not have a substantial impact on the findings. The convergence of models in WinBugs will be initially challenged by performing 3-chain analyses with widely dispersed starting values and evaluating their convergence using the Brooks-Gelman-Rubin (BGR) diagnostic plots.

**Consideration of Dose**

In contrast to the approach adopted by earlier statin meta-analyses, studies that used variable doses (titrating) will not be excluded. Instead, where trials provided data on the proportion of patients at each dose, the number in the treatment arm will be proportioned out to the correct dosage (and hence included in the analysis). Even where trials did not provide data on the proportion of patients at each dose, trials will be categorized as ‘titration trials’ and included in the analysis.

Four sets of analyses will be conducted to explicitly consider the impact of dose on the comparative treatment effects of statins. The first set of analyses will pool trials with fixed-dose and titration designs to evaluate the comparative efficacy and safety of statins irrespective of dose. Secondary analyses will include only titration trials.

The effect of dose on comparative treatment effects will be an essential consideration in additional statistical analyses. As the literature does not provide a clear answer as to how dose should be taken into account, two types of analyses will be conducted. One set of mixed treatment comparison analyses will be conducted for the dose-specific comparators (e.g. rosuvastatin 10-20mg vs. atorvastatin 10-20mg). Therefore, drug efficacy will be defined as the reduction in cholesterol concentration (or the reduction in CVD event occurrence) for a given dose. This analysis will compare all potential drug-dose combinations (comparing 18 dose-drug combinations to each other: 6 statins, each with low-medium-high dosages). Another set of analyses will be conducted for comparisons at the drug-level (e.g. rosuvastatin vs. atorvastatin) and will compare six statins. The drug-level analysis will use a meta-regression to take into account the dose-response relationship of each individual
statin. Recent methodological advances allow meta-regression techniques to be applied to mixed treatment comparisons.\textsuperscript{30, 31}

Planned sensitivity analyses

1. **Dosing regimen:** Based on the understanding that titration trials may provide essential information that better represent actual clinical practice, analyses will test the sensitivity of separating out the comparative effect of statins in titration trials.

2. **Baseline risk:** We will perform exploratory meta-regressions (using study-level age, LDL, HDL as covariates) to evaluate whether the effects of baseline severity and the size of the relative treatment effect can be separated.

3. **Trial duration:** It has been suggested that statin therapy does not immediately impact on the number of patients having a CVD event. Therefore, studies shorter than 20 weeks of follow-up will be excluded in analyses of CVD outcomes.

4. **Priors:** Sensitivity of the findings to prior distributions will be evaluated by varying the prior distributions from less informative to more informative values and examining the variability observed in the credibility intervals of point estimates. One prior will be extremely vague, while the other (to be employed in the base-case analyses) will be vague but slightly informative.

5. **Population:** Sensitivity of the findings to patient populations (primary prevention, secondary prevention, mixed) will be assessed in comprehensive analyses by first pooling all trials together and then introducing meta-regression coefficients to take into account potential differences across patient populations.

6. **Publication year:** Sensitivity of the findings to publication year (as a proxy for evolving trial protocols and potentially different patient populations over the years) will be assessed by incorporating publication year as a meta-regression coefficient in the analysis.

7. **Blinding in trials:** It is possible that the findings obtained in double-blind trials differ than those from open-label trials. To test the sensitivity of the findings to the blinding in trials, separate analyses will be conducted for double-blind and open-label trials.
References


40. Sheffield School of Health and Related Research (ScHARR). Technology assessment report commissioned by the HTA Programme on behalf of The National Institute for Clinical Excellence2005.