Comparison of sequential rosuvastatin doses in hypercholesterolaemia: a meta-analysis of randomised controlled trials

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CRD summary
This review provided evidence for improved efficacy, as assessed by surrogate markers, in treating patients with hypercholesterolaemia with each sequential titration of rosuvastatin and a generally consistent tolerability profile across the dose range. The authors’ conclusions reflect the evidence presented, but the lack of validity assessment and lack of reporting of some data made the reliability of the conclusions uncertain.

Authors’ objectives
To quantify the benefits and risks associated with sequential rosuvastatin titrations across dosage range for the treatment of patients with hypercholesterolaemia.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE were searched to April 2008 for English-language publications; search terms were reported. The clinical trials website of US National Institute of Health and the clinical trials website of AstraZeneca (manufacturer of rosuvastatin) were searched.

Study selection
Randomised controlled trials (or studies that included a forced-titration protocol that ensured the similarity of patients who received different doses of direct comparisons) of hypercholesterolaemia patients that compared at least one of rosuvastatin 5mg/day versus 10 mg/day, 10mg/day versus 20 mg/day and 20 mg/day versus 40 mg/day (either through head-to-head or a forced titration) were eligible for inclusion. Any additional treatments were required to be given equally between groups. Outcomes for efficacy were limited to surrogate markers of morbidity and mortality and included low-density lipoprotein cholesterol (LDL-C) levels, high-density lipoprotein cholesterol (HDL-C) levels, total cholesterol and HDL-C ratio and apolipoprotein B to apolipoprotein A-I (apoB/apoA-I) ratio. Tolerability measures included muscular, hepatic and renal adverse events.

Most of the included studies were head-to-head; nine were forced titration comparisons, three of which reported unequal treatment lengths. Some studies reported subgroups of patients who were Asian, had a high risk of coronary artery disease without diabetes or had diabetes. All the studies were conducted in multiple study centres. Around half of the studies were conducted in North America.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Allocation concealment was assessed as A (clearly adequate), B (possibly adequate) and C (clearly inadequate).

Two reviewers independently assessed validity.

Data extraction
Data were extracted for benefit outcomes and used to calculate absolute mean difference and corresponding 95% confidence intervals (CI). Data were extracted for risk outcomes and used to calculate relative risk (RR) and corresponding 95% CIs. Calculations were on an intention-to-treat basis. Primary study authors and study sponsors were contacted for additional data where necessary.

The authors did not state how many reviewers extracted data.
Methods of synthesis
A fixed-effect model was used to calculate pooled relative risks and weighted mean differences (WMD) with corresponding 95% CIs. Heterogeneity was assessed using the $I^2$ statistic.

Sensitivity analyses were conducted to evaluate the effects of: using a random-effects model for each outcome; exclusion of studies with Asian populations; restricting analysis of safety outcomes to head-to-head data only; and from data derived from comparisons with identical treatment periods. Subgroup analyses were planned for data on patients with diabetes or high risk of coronary artery disease with diabetes or coronary artery disease without diabetes.

Results of the review
Twenty-six studies (approximately 6,912 participants) were included in the review: 17 studies used head-to-head comparisons (n=4,319) and nine used forced titration comparisons (n=1,873).

Rosuvastatin 5mg/day versus 10 mg/day: Significant benefit was reported for higher dose rosuvastatin for LDL-C (WMD 6.25%, 95% CI 4.93% to 7.57%; 12 RCTs), total cholesterol/HDL-C ratio (WMD 4.76 %, 95% CI 3.58% to 5.94%, $I^2=54.7\%$) and apoB/apoA-I ratio (WMD 5.18%, 95% CI 3.81 to 6.54, $I^2=26.9\%$). Benefit was reported for higher dose rosuvastatin for HDL-C, but this did not reach statistical significance.

Rosuvastatin 10mg/day versus 20 mg/day: Significant benefit was reported for higher dose rosuvastatin for LDL-C (WMD 5.84% 95% CI 5.13 to 6.56; 17 RCTs), HDL-C (WMD -0.78%, 95% CI -1.44% to -0.12%, $I^2=33.9\%$), total cholesterol/HDL-C ratio (WMD 4.56%, 95% CI 3.88% to 5.23%) and apoB/apoA-I ratio (WMD 4.75%, 95% CI 3.86% to 5.63%).

Rosuvastatin 20mg/day versus 40mg/day: There was significant benefit reported for higher dose rosuvastatin for LDL-C (WMD 5.03%, 95% CI 4.28% to 5.79%; 13 RCTs), total cholesterol/HDL-C ratio (WMD 3.40%, 95% CI 2.63% to 4.18%) and apoB/apoA-I ratio (WMD 2.82%, 95% CI 1.60% to 4.04%). Greater benefit was reported for the lower dose of rosuvastatin for HDL-C, but this was not statistically significant.

When one study that included patients with Fredrickson type IIb or IV hypertriglyceridaemia was removed from the analysis, heterogeneity was reduced or removed (further details were reported). Sensitivity analyses did not significantly alter results (data not presented). Results of subgroup analyses were reported.

Tolerability: There were no significant differences for any adverse events for comparisons of rosuvastatin for 5mg/day and 10mg/day, and between 10mg/day and 20mg/day. There was a significantly higher risk of proteinuria with rosuvastatin 40mg/day compared to 20mg/day (RR 0.30, 95% CI 0.12 to 0.76). There were no significant differences between groups for other adverse events. There was evidence of low heterogeneity for the comparison between 20mg/day and 40mg/day rosuvastatin for myalgia ($I^2=24\%$). The results of sensitivity and subgroup analyses were similar (data not presented). There were no reports of rhabdomyolysis, myopathy, liver failure or hepatitis for any of the rosuvastatin dosages.

Authors' conclusions
This review provided evidence for improved efficacy, as assessed by surrogate markers, in treating patients with hypercholesterolaemia with each sequential titration of rosuvastatin and a generally consistent tolerability profile across the dose range.

CRD commentary
The review question was clearly defined with appropriate inclusion criteria. Several relevant sources were searched, but the restriction to studies published in English meant there was potential for language and publication biases; the authors stated they searched the manufacturer’s database to reduce the likelihood of this. Validity was assessed in terms of allocation concealment, but no results of the assessment or any other validity criteria were presented and so the reliability of the synthesis was uncertain. Appropriate methods to reduce reviewer error and bias were reported for study selection and validity assessment; it was unclear whether such methods were used for data extraction. Few details of participants were reported, so it was not possible to assess the generalisability of the results. The authors did not
report length of follow-up for the included studies.

The main analyses included studies of different designs (randomised head-to-head and non-randomised forced titration studies) and this may not have been appropriate, particularly as non-randomised forced-titration studies are prone to some biases. However, the authors conducted sensitivity analyses and found no significant differences in results for head-to-head studies only compared with combined analyses. The likelihood for statistical heterogeneity was assessed and explored.

Two authors were full-time employees of AstraZeneca UK Ltd (manufacturer of rosvastatin). One author received honoraria from AstraZeneca for consultancy on trial steering committees, but received no funding for this review.

The authors conclusions' reflected the evidence presented, but the lack of validity assessment and lack of reporting of some data made the reliability of the conclusions uncertain.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that a study of the cost-effectiveness of the different doses of rosvastatin would be conducted.

**Funding**

Two authors were full-time employees of AstraZeneca UK Ltd; one author received no funding from AstraZeneca UK Ltd.

**Bibliographic details**


**PubMedID**

20028194

**DOI**

10.1185/03007990903513980

**Original Paper URL**

http://informahealthcare.com/doi/abs/10.1185/03007990903513980

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Female; Fluorobenzenes /administration & dosage /adverse effects; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /administration & dosage /adverse effects; Hypercholesterolemia /blood /drug therapy; Lipoproteins /blood; MEDLINE; Male; Pyrimidines /administration & dosage /adverse effects; Randomized Controlled Trials as Topic; Risk Factors; Rosuvastatin Calcium; Sulfonamides /administration & dosage /adverse effects

**AccessionNumber**

12010002307

**Date bibliographic record published**

04/08/2010

**Date abstract record published**
11/05/2011

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.