Efficacy of statin therapy in chronic systolic cardiac insufficiency: a meta-analysis
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CRD summary
This review concluded that statins had little effect on clinical outcomes in chronic heart failure populations; there may be differences across individual statins and in younger people. The results were dominated by two large studies of rosuvastatin. The authors’ conclusions reflect the evidence presented, particularly uncertainties relating to different statins, and seem reliable in terms of answering the review question.

Authors' objectives
To assess the effects of statins on clinical outcomes in people with chronic systolic heart failure.

Searching
PubMed, EMBASE and The Cochrane Library were searched to February 2011. The search terms were reported. Bibliographies and citations of relevant articles were checked for additional studies.

Study selection
Eligible randomised controlled trials (RCTs) compared the effects of statins to control (placebo or no statin) in people with chronic systolic heart failure of any aetiology, with low left ventricular ejection fraction (less than 45%). Studies had to report clinical outcomes such as: all-cause mortality; rehospitalisation for worsening heart failure; death from pump failure or cardiovascular cause; non-fatal myocardial infarction; or stroke.

In the included studies, where stated, mean ages ranged from 38 to 73 years, and between 61 and 86% of participants were men. In three trials chronic systolic heart failure was of ischaemic origin, in four non-ischaemic and in the remaining six of mixed origin. Baseline low left ventricular ejection fraction ranged from 25 to 38%. Most participants used rosuvastatin (10mg/day), other trials used atorvastatin (10 to 40mg/day) or simvastatin (5 to 40mg/day). In most trials mean follow-up ranged from two to 12 months, one small trial for 31 months and in two large trials median follow-up was 33 to 47 months.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by consensus and consultation with a third author.

Assessment of study quality
Quality was assessed using the Jadad score, based on items related to allocation concealment, method of randomisation, blinding, losses to follow-up and intention-to-treat analysis. The maximum score was five.

It wasn't clear how many reviewers assessed quality.

Data extraction
Data were extracted by two reviewers independently to calculate risk ratio (RR) and 95% confidence intervals (CI).

Methods of synthesis
Pooled risk ratio and 95% confidence intervals were calculated using Mantel-Haenszel's random-effects model. Heterogeneity was assessed using I² (more than 75% indicated very large inconsistency). Subgroup analyses investigated the effects of participants' age, different statins, proportion with ischaemic aetiology and baseline low left ventricular ejection fraction. Sensitivity analyses were undertaken removing each trial one at a time, the two large trials and low quality studies (Jadad score less than 3).

Results of the review
Thirteen RCTs (10,447 participants were included). Two large trials on rosuvastatin accounted for 9,585 participants, other sample sizes ranged from 22 to 202 participants. The two large studies scored 5 and 4 respectively for quality, of the small studies one scored 5, two scored four, four scored 3, and two each scored 2 and 1.
Compared to control, statins had no statistically significant effect on all-cause mortality ($I^2=38\%$; nine trials), death from cardiovascular cause ($I^2=0\%$; five trials) or pump failure ($I^2=0\%$; three trials), or rehospitalisation for heart failure ($I^2=33\%$; 10 trials). There was a non-statistically significant reduction in non-fatal myocardial infarction (RR 0.84, 95% CI 0.68 to 1.02, $I^2=0\%$; three trials).

In sensitivity analyses removal of one large trial resulted in a statistically significant reduction in rehospitalisation with statins, (RR 0.66, 95% CI 0.44 to 0.98, $I^2=29\%$), and there was a non-statistically significant reduction in all-cause mortality. These benefits became more pronounced when both large studies were removed. Other sensitivity analyses showed no statistically significant influence on results.

Subgroup analyses showed the use of atorvastatin reduced all-cause mortality and rehospitalisation, and that in those under 65 years, statins reduced all-cause mortality and rehospitalisation. Other variables showed no statistically significant effect.

**Authors' conclusions**
Statins appeared to have little effect on clinical outcomes in overall chronic systolic heart failure populations. There may have been differences in the effect of different statins and in younger participants

**CRD commentary**
The aims of this review were clearly stated in terms of study inclusion criteria. The search covered several relevant sources, but it was unclear whether language restrictions were applied or unpublished studies were sought. Potentially relevant data may have been missed. The methods of study selection and data extraction were those aimed at reducing reviewer error or bias, those for quality assessment weren’t clear. Quality was assessed and most studies were moderate to high quality. The methods of synthesis appeared generally appropriate and statistical heterogeneity was assessed. Sensitivity analyses indicated that there may have been differences in results between the very large studies and the smaller studies. Most data came from two large better quality studies that assessed rosuvastatin. A large number of subgroup analyses were undertaken which increased the possibility of any individual effect being as a result of chance.

The authors’ conclusions reflect the evidence presented, particularly uncertainties relating to different effects across different statins, and seem reliable in terms of answering the review question.

**Implications of the review for practice and research**
**Practice**: The authors stated that use of statins in people with chronic systolic heart failure may be effective when restricted to specific statins or patients.

**Research**: The authors stated that further research was needed to assess the effects of statins on people with different severity of chronic systolic heart failure, and of different ages. Research was also needed to assess any differences in different types of statins.

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