What role for statins: a review and economic model


Authors' objectives
The review aimed to answer the following questions:

1. By how much do low fat and other diets reduce blood cholesterol? And how effective are such effects in reducing coronary heart disease (CHD) risk?

2. Does treatment with statins reduce CHD events and are relative reductions in these events independent of the level of CHD risk?

3. How effective are non-cholesterol lowering drug treatments (i.e. aspirin, beta-blockers, and antihypertensives) for reducing CHD risk relative to dietary modifications and cholesterol lowering drug treatments?

4. What is the relative cost-effectiveness of different approaches to reducing cholesterol and/or CHD?

Searching
MEDLINE and the Cochrane CENTRAL Register were searched from 1993 to Nov 1997 (search terms listed). In addition, the reference lists of retrieved articles and previous meta-analyses were searched. Investigators working in the field were also asked if they knew of additional references. Original data from investigators and industry databases were not examined. No language restrictions were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled parallel group trials with at least 6mths follow-up were included in the review.

Specific interventions included in the review
Statins (e.g. pravastatin, simvastatin and lovastatin) were combined with and compared to other treatments for lowering cardiovascular risk (e.g. aspirin, ACE inhibitors, beta-blockers, calcium antagonists, diuretics, nitrates, fish oil, Mediterranean diet and smoking advice) or compared to placebo.

Participants included in the review
Men and women with CHD (primary prevention) or who are potentially at risk from CHD. Studies involving children were excluded from the review.

Outcomes assessed in the review
Clinical events such as total mortality, CHD mortality, stroke mortality, non-fatal myocardial infarction (MI), and non-fatal stroke were included as outcome measures. In addition, surgical revascularisation end-points (coronary artery bypass surgery (CABG), percutaneous angioplasty (PTCA)) and regression of atheroma identified by angioplasty were also examined.

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

Assessment of study quality
The authors do not state that they assessed validity.
Data extraction
Data were extracted using a specially developed form and effect sizes were estimated using a statistical package. The authors do not state how many authors performed the data extraction. Information reported in data tables includes: bibliographic details, participant details, intervention details, length of follow-up, numbers of participants, number of deaths (all, CHD and stroke deaths), number of non-fatal events (MI, stroke, CABG, PTCA), baseline and % reduction in cholesterol.

Methods of synthesis
How were the studies combined?
Effect sizes were pooled using a fixed-effect model. Odds ratios (ORs) with 95% confidence intervals (CI), relative risks (RR) with 95% CI and numbers needed to treat (NNT) were presented where appropriate.

How were differences between studies investigated?
Heterogeneity was investigated using sensitivity analyses.

Results of the review
Twenty-three RCTs of statins were included. Ten studies (7 primary and 3 secondary prevention, n=22,909 participants) looked at pravastatin; four (all secondary prevention, n=5,160 participants) looked at simvastatin; eight (2 primary and 6 secondary prevention, n=17,029 participants) looked at lovastatin. Thirty-nine RCTs (4 primary and 35 secondary prevention, n=43,675 participants) looked at other cholesterol-lowering drugs.

Data from the 23 trials of statins demonstrated significant reductions in CHD events. In secondary prevention (prevention amongst people with evidence of cardiovascular disease) the relative reductions in total and CHD mortality were 21% (95% CI: 14, 27) and 26% (95% CI: 17, 34) respectively. There were similar reductions for non-fatal myocardial infarctions and greater reductions for combined end points (including revascularisation end points).

1. Efficacy of treatment with statins for primary prevention.

Total mortality: OR=0.79 (95% CI: 0.73, 0.86).

CHD mortality: OR=0.74 (95% CI: 0.66, 0.83).

Non-fatal MI: OR=0.70 (85% CI: 0.61, 0.80).

In primary prevention (amongst people with no sign of CHD) there were significant reductions for combined end points and non-fatal myocardial infarction, but not for total and CHD mortality. The primary prevention trials were too small to have adequate power to detect effects on mortality outcomes alone. Statins were effective across a wide range of levels of blood cholesterol, including levels considered normal in the UK.

Total mortality: OR=0.89 (95% CI: 0.73, 1.08).

CHD mortality: OR=0.76 (95% CI: 0.54, 1.06).

Non-fatal MI: OR=0.64 (85% CI: 0.53, 0.77).

Other treatments for primary prevention included advice on smoking cessation, nicotine replacement and antihypertensive drugs.

2. Efficacy of other treatments for secondary prevention.

Effects on cardiovascular mortality:

Tobacco smoking advice: RR=0.99 (95% CI: 0.98, 1.0).
Nicotine replacement: RR=0.98 (95% CI: 0.98, 0.99).
Aspirin: RR=0.98 (95% CI: 0.78, 1.18).
Anti-hypertensive drugs: RR=0.79 (95% CI: 0.71, 0.87) <60yrs; RR=0.75 (95% CI: 0.64, 0.88) >/=60yrs.
Statins: RR=0.68 (95% CI: 0.46, 1.00).
Other treatments considered for secondary prevention were advice on smoking cessation, aspirin, beta blockers, oily fish diet and Mediterranean diet.

Effects on cardiovascular mortality: Aspirin: RR=0.82 (95% CI: 0.76, 0.88).
Beta blockers: RR=0.78 (95% CI: 0.71, 0.87).
Statins: RR=0.74 (95% CI: 0.66, 0.83).
Tobacco smoking advice: RR=0.68 (95% CI: 0.57, 0.79).
Oily fish: RR=0.65 (95% CI: 0.5, 0.9).
Mediterranean diet: RR=0.24 (95% CI: 0.1, 0.8).

Except for smoking interventions, these treatments have numbers needed to treat that are broadly similar to those for statins.

Cost information
The cost-effectiveness of statins depends on the cost of the statin used and the CHD risk in the population treated. Gross, discounted estimates based on CHD risk in the trials considered ranged from £5,400 to £13,300 per life-year gained at levels of risk expected in primary prevention, and from £3,800 to £9,300 at levels of risk consistent with secondary prevention. Use of low cost statins had the potential to reduce gross costs by 60%.

The cost-effectiveness of other treatments was much better than for statins. Gross discounted cost per life-year saved of aspirin (£53), bendrofluazide treatment for elderly people with hypertension (£45), low cost mixed drug antihypertensive regimens for middle-aged people (£1,509), beta blockers following myocardial infarction (£227) and Mediterranean diet following myocardial infarction (£293) were all lower than for statins.

Authors’ conclusions
The evidence on efficacy supports the use of statins over a wide range of CHD risks covering both primary and secondary prevention. Although statins are less cost-effective than other treatments, there is consensus that their use in secondary prevention is acceptable because they achieve effects additional to those of other treatments. However, there is evidence that these other treatments are insufficiently used in the UK and that greater efforts are required to ensure that highly cost-effective treatments are used optimally.

In public health terms, the major approaches to the primary prevention of CHD remain the fiscal and legislative control of tobacco, the reduction of hidden saturated fats and calories in the diet, encouraging and extending facilities available for physical activity throughout life, and the reduction of levels of poverty.

CRD commentary
This is a clearly presented review based on a reasonable search of the literature. The inclusion/exclusion criteria were clearly stated and only randomised controlled trials (RCTs) were included. However, publication bias may be a problem, as no attempts were made to include unpublished material. In addition, although only RCTs were included in the review, the validity of individual trials was not assessed. The authors also failed to give details of how studies were
selected for inclusion and how data were extracted. However, details of the individual studies were provided in clearly presented tables.

Study data were pooled using a fixed-effect model and differences between studies investigated using sensitivity analyses. This seems appropriate, although where appropriate a statistical measure of heterogeneity would have been helpful. Overall, considering the data presented the authors conclusions and implications would appear to be reasonable, although the aforementioned criticisms should be borne in mind.

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

**Practice:** The authors state that greater efforts are required to ensure that highly cost-effective alternative treatments to statins for CHD are used optimally.

**Research:** The authors state that further trials are needed. These should examine the long-term effects of dietary modification with the oily fish or Mediterranean diet; examine the effects of different types of statin and effects in people older than 75 years of age; continually survey statin-treated patients for long-term adverse effects; investigate the translation of effects of treatment from trials to clinical practice; evaluate CHD risk prediction scoring systems; and investigate patient preferences and determinants for specific types of treatments.

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