Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials
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Authors' objectives
To estimate the reduced risk of coronary heart disease and total mortality associated with statin drug treatment, particularly in elderly individuals and women.

Searching
MEDLINE was searched from 1966 to December 1998 using the following MeSH: 'hydroxy-methyl-glutaryl-CoA reductase inhibitors', 'simvastatin', 'lovastatin', 'pravastatin', 'coronary disease' and 'myocardial infarction'. In addition, the keywords 'statin' and 'coronary heart disease' were used. The search was restricted to those studies conducted in human participants, published in English language journals, and classified as clinical trials in the MEDLINE database. A manual search was also performed using the authors' reference files and reference lists from original communications and review articles.

Study selection
Study designs of evaluations included in the review
Only randomised, placebo-controlled trials were included. All the trials identified were double-blind.

Specific interventions included in the review
Treatment with statins for a duration of at least 4 years. The statins investigated were simvastatin, pravastatin and lovastatin. Only placebo-controlled studies were included.

Participants included in the review
The inclusion and exclusion criteria for patient were not stated. The mean age of the participants was 59 years. In one included study, only men younger than 65 years were included. The remaining four trials included women and participants who were aged 65 years or older. Three trials were conducted in patients with a history of coronary heart disease (secondary prevention trials), whilst the other two were conducted in a healthy population (primary prevention trials).

Outcomes assessed in the review
Only studies with clinical disease or death as the primary end point were included. The major coronary events during treatment were abstracted as the primary outcome. These included: coronary death, fatal and nonfatal myocardial infarction, resuscitated cardiac arrest, unstable angina, and sudden cardiac death. In addition, data were abstracted on fatal coronary heart disease, deaths due to cardiovascular disease, deaths due to noncardiovascular conditions, and all-cause deaths during treatment.

The effect on blood lipids, i.e. total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides, was also considered.

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
All data were abstracted in duplicate using a standardised protocol and reporting form. Any disagreements were
resolved by consensus. The authors of the primary studies were not contacted for additional information.

The categories of data extracted from the study were: the name of the study, the year of publication, and the country of origin; the number of participants; the mean age, and the age and gender distributions of the participants; the presence of pre-existing myocardial infarction; the mean baseline levels of total-, LDL- and HDL- cholesterol, and triglycerides; the net changes in lipids during intervention; the type and dosage of statin; the duration of the intervention; and the results for major cardiovascular events.

Methods of synthesis
How were the studies combined?
The Peto method (see Other Publications of Related Interest) was used to calculate the pooled odds ratios (ORs) of outcomes associated with statin therapy, i.e. major cardiac events, cardiac deaths, cardiovascular deaths, noncardiovascular deaths, and all-cause deaths. Both the proportional (1 minus OR) and absolute risk reduction were used to measure the effect of statin drug treatment on the clinical outcomes. The numbers of each outcome were recorded for each study, for both the statin and placebo groups, using 2x2 tables. For each trial, the number of individuals in the treatment group in whom an end point of interest was observed (O), was compared with the number that would have been expected (E) if the treatment had no effect, on the basis of the overall experience in the treatment and control groups combined. If the treatment was beneficial, then the difference (O minus E) would tend to be negative. The differences from each trial were summed, and z-statistics were used to test whether the total difference differed from zero. The ORs were calculated using the difference (O minus E) divided by V, where V was the variance of the total differences. To calculate the pooled absolute risk, each study was weighted by its sample size. The number-needed-to-treat (NNT) was also calculated.

How were differences between studies investigated?
Chi-squared tests for heterogeneity were performed for the categories of major coronary events, coronary deaths, cardiovascular deaths, noncardiovascular deaths, and all-cause deaths.

A series of prestated subgroup analyses were performed to examine the effect of statin drug treatment on major coronary effects. First, the risk reductions of major coronary events and deaths were compared between two primary prevention trials and three secondary prevention trials. The risk reductions for major coronary events were calculated according to age and gender. A sensitivity analysis was conducted to explore the impact of excluding small non-outcome trials of short duration (less than 4 years) on the risk estimates. Twelve trials that were excluded from the primary analysis, which reported at least one major coronary event, were included in this analysis.

Results of the review
Five randomised, placebo-controlled, double-blind trials comprising a total of 30,817 participants were included.

The mean length of follow-up was 5.4 years. All the chi-squared tests for heterogeneity were non significant. Statin drug treatment was associated with a mean reduction (weighted by sample size) of 20% in the total cholesterol level, 28% in LDL-cholesterol levels, and 13% in triglyceride levels. However, it was also associated with a mean increase of 5% in HDL-cholesterol levels. Overall, statin drug treatment reduced the risk of major coronary events by 31% (95% confidence interval, CI: 26, 36, P<0.001) and fatal coronary disease by 29% (95% CI: 20, 36, P<0.001). Compared with the control groups, active treatment was associated with an absolute risk reduction in coronary disease of 36 events and 13 deaths per 1,000 patients. The NNT was 28 to prevent a major coronary event and 75 to prevent a death from coronary disease. Compared with the control groups, active treatment was associated with an absolute risk reduction in coronary disease of 36 events and 13 deaths per 1,000 patients. The NNT was 28 to prevent a major coronary event and 75 to prevent a death from coronary disease. Compared with the control groups, those receiving active treatment had a 21% reduction in all-cause mortality (95% CI: 14, 28, P<0.01) and a 27% reduction in the odds of cardiovascular mortality (95% CI: 19, 34, P<0.001). Active treatment was also associated with an absolute risk reduction of 16 and 14 deaths per 1,000 patients from all-causes and cardiovascular disease, respectively. The corresponding NNTs to prevent death were 61 (all-causes) and 69 (cardiovascular disease). Noncardiovascular mortality was similar in both the active treatment and control groups, with an OR of 0.93 (95% CI: 0.81, 1.07, P=0.29).

Treatment effects in primary and secondary prevention trials.

Active treatment was associated with a 34% risk reduction (95% CI: 23, 43, P<0.001) in major coronary events in the
2 primary prevention trials, and a 30% risk reduction (95% CI: 24, 35, P<0.001) in the 3 secondary prevention trials. In addition, it was associated with a lower risk of coronary disease mortality (OR 0.73, 95% CI: 0.51, 1.05, P=0.09), cardiovascular mortality (OR 0.68, 95% CI: 0.50, 0.93, P=0.01), and all-cause mortality (OR 0.87, 95% CI: 0.71, 1.06, P=0.18) in the 2 primary prevention trials. Active treatment was also associated with a lower risk of coronary disease mortality (OR 0.71, 95% CI: 0.63, 0.80, P<0.001), cardiovascular mortality (OR 0.73, 95% CI: 0.66, 0.82, P<0.001), and all-cause mortality (OR 0.77, 95% CI: 0.70, 0.85, P<0.001) in the 3 secondary prevention trials.

Active treatment was not significantly associated with a change in noncardiovascular mortality in either the 2 primary prevention trials (OR 1.04, 95% CI: 0.80, 1.35, P=0.75) or the 3 secondary prevention trials (OR 0.89, 95% CI: 0.75, 1.04, P=0.15).

Treatment effects according to gender and age.

The risk reduction in major coronary events was similar for women (29%, 95% CI: 13, 42, P<0.001) and for men (31%, 95% CI: 26, 35, P<0.001). The absolute risk reduction was also similar in women (33 deaths per 1,000 patients, 95% CI: 13, 52) and men (37 deaths per 1,000 patients, 95% CI: 29, 44).

The overall, proportional risk reduction was similar for persons aged at least 65 years (32%, 95% CI: 23, 39, P<0.001) and those aged younger than 65 years (31%, 95%: 24, 36, P<0.001). The absolute risk reduction was slightly higher in persons aged at least 65 years (44 deaths per 1,000 patients, 95% CI: 30, 58), compared with persons younger than 65 years (32 deaths per 1,000 patients, 95% CI: 24, 40).

Sensitivity analysis: after including the 12 small non-outcome trials, the estimates for risk reduction were virtually unchanged. The risk reduction was 31% (95% CI: 26, 35, P<0.001) for major coronary events, 28% (95% CI: 19, 35, P<0.001) for fatal coronary disease, 27% (95% CI: 19, 34, P<0.001) for cardiovascular disease mortality, and 22% (95% CI: 15, 28, P<0.001) for all-cause mortality. The mortality from noncardiovascular disease was not significantly different between the placebo and treatment groups (OR 0.91, 95% CI: 0.80, 1.04, P=0.18).

Safety: the OR was 0.99 (95% CI: 0.90, 1.08, P=0.76) for cancer cases and 1.25 (95% CI: 0.83, 1.89, P=0.29) for asymptomatic episodes of elevated creatine kinase concentrations (greater than 10 times the upper reference limit). The OR for increased aspartate or alanine aminotransferase levels (greater than 3 times the upper reference limit) was 1.13 (95% CI: 0.95, 1.33, P=0.17).

Authors' conclusions

Our meta-analysis indicated that the reduction in LDL-cholesterol associated with statin drug treatment resulted in a decreased risk of coronary heart disease and all-cause mortality. The risk reduction was similar for men and women, and for elderly and middle-aged people.

CRD commentary

The review question and the inclusion criteria were stated clearly. Details of the primary studies were tabulated, although the adverse effects and number of withdrawals or drop-outs were not reported. The chi-squared tests for heterogeneity were conducted before the data were combined.

The search strategy was limited in that only one database was searched and only English language publications were included. In addition, there was no attempt to identify unpublished literature, and consequently a publication bias cannot be ruled out. However, it is unlikely that a large study will have been missed.

The validity of the included studies was not assessed, but only double-blind randomised controlled trials were included. Furthermore, all the included studies had sample sizes of at least 4,000 and follow-up periods of at least 5 years. The approach used to synthesise the results of the individual studies was appropriate, and heterogeneity was investigated. A sensitivity analysis was performed, which demonstrated the robustness of the review's findings.

The authors' conclusions were supported by the results.
Implications of the review for practice and research
Practice: The authors state that the benefits, in terms of morbidity, of lowering LDL-cholesterol have been under appreciated, particularly in older age groups. Prevention of morbid events results in a lower prevalence of congestive heart failure, angina, significant arrhythmia and debilitating strokes. Such interventions are likely to have a beneficial effect on both the quality of life for the individual patients, and the cost of caring for older patients imposed on families and societies. By placing undue attention on mortality alone as a measure of the success or failure of an intervention, clinicians fail to account for the importance of avoiding such disabilities.

Research: The authors did not state any implications for further research.

Bibliographic details

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Other publications of related interest

This additional published commentary may also be of interest. Statins and risk of coronary heart disease [letters]. JAMA 2000;283:2935-6.

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MeSH
Aged; Anticholesteremic Agents /therapeutic use; Cholesterol, LDL /blood; Coronary Disease /epidemiology /prevention & control; Female; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /therapeutic use; Lipoproteins /blood; Male; Middle Aged; Mortality; Randomized Controlled Trials as Topic; Risk

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