The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaborators

CRD summary
This meta-analysis of individual patient data concluded that in individuals with five-year risk of major vascular events lower than 10%, each 1mmol/L reduction in low-density lipoprotein cholesterol produced an absolute reduction in major vascular events of about 11 per 1,000 over five years. The authors' conclusions are likely to be reliable.

Authors' objectives
To assess the effects of lowering low-density lipoprotein (LDL) cholesterol with statins in people at low-risk of vascular disease.

Searching
As reported in the study protocol (see Other Publications of Related Interest), studies were identified by computer-aided literature searches (no search terms were reported), manual searches of journals, examination of reference lists of trials and review articles, examination of abstracts and conference proceedings, collaboration with the trial register of the International Committee on Thrombosis and Haemostasis and by contacting colleagues, collaborators and drug manufacturers. Trials had to be reported by the end of 2009 and had to provide data for the review before June 2011.

Study selection
Eligible studies were unconfounded randomised controlled trials (RCTs) of at least one intervention where the main effect was to lower LDL cholesterol concentration and that recruited at least 1,000 participants. Studies needed a scheduled treatment duration of at least two years. The main outcomes of interest were major vascular events (defined as non-fatal myocardial infarction or coronary death, any stroke or a coronary revascularisation procedure), major coronary events (defined as non-fatal myocardial infarction or coronary death), stroke (subdivided by type), coronary revascularisation procedures, cancers and cause-specific mortality.

Most studies compared a standard statin regimen versus control. The other studies compared different statin intensities (further treatment/comparator details were not provided). Across the studies, the median predicted five-year risk of major vascular events ranged from 2.7% to 38.2%. Across the risk groups, mean ages ranged from 59 to 66 years, the proportion of patients with diabetes ranged from 4% to 44% and most participants were male.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Individual patient data (IPD) were checked for internal consistency and completeness and for balance between groups, as reported in the study protocol. Any queries were referred to the principal investigator of the trial concerned.

Data extraction
Using Cox proportional hazard models (two different models were used: one for statin versus control and one for more versus less intensive statin regimens) participants were assigned to one of five baseline categories of five-year risk of a major vascular event (<5%, ≥5% to <10%, ≥10% to <20%, ≥20% to <30% and ≥30%). Data for the intention-to-treat population were extracted in order to calculate rate ratios (RR) per 1.0mmol/L reduction in LDL cholesterol with 95% or 99% confidence intervals (CI).

Methods of synthesis
Meta-analyses were performed to produce overall pooled rate ratios and rate ratios for each baseline risk category, with studies weighted by the absolute LDL cholesterol difference at one year. X² tests were used to assess for heterogeneity across risk categories. Subgroup analyses examined the effect of baseline age, gender, baseline LDL cholesterol and previous history of vascular disease.
Results of the review

Twenty-seven RCTs were included (174,149 participants, range 1,255 to 20,536).

Reduction of LDL cholesterol with a statin reduced the risk of major vascular events by 21% for each 1mmol/L reduction (RR 0.79, 95% CI 0.77 to 0.81) irrespective of age, gender and baseline LDL cholesterol. By baseline risk the reduction was at least as big in the two lowest risk categories. Rate ratios were (lowest to highest risk): 0.62 (99% CI 0.47 to 0.81), 0.69 (99% CI 0.60 to 0.79), 0.79 (99% CI 0.74 to 0.85), 0.81 (99% CI 0.77 to 0.86) and 0.79 (99% CI 0.74 to 0.84); Χ²=4.3, p=0.04.

For stroke, the reduction in risk in participants with five-year risk of major vascular events lower than 10% was similar to that seen in higher risk categories. In participants with no history of vascular disease, statins reduced the risks of vascular (RR 0.85, 95% CI 0.77 to 0.95) and all-cause mortality (RR 0.91, 95% CI 0.85 to 0.97), with proportional reductions being similar by baseline risk. There was no evidence that reduction of LDL cholesterol with a statin increased cancer incidence, cancer mortality or other non-vascular mortality.

The estimated absolute reduction in major vascular events in participants with a five-year risk lower than 10% was around 11 per 1,000 over five years for each 1.0mmol/L reduction in LDL cholesterol (4.1% statin or more intensive statin regimen versus 5.2% control or less intensive regimen).

Further results were reported.

Authors' conclusions

In individuals with five-year risk of major vascular events lower than 10%, each 1mmol/L reduction in LDL cholesterol produced an absolute reduction in major vascular events of about 11 per 1,000 over five years. This benefit greatly exceeded any known hazards of statin therapy.

CRD commentary

The title and introduction of the meta-analysis clearly related to statins, but the stated inclusion criteria implied that other cholesterol-lowering interventions (such as fibrates, which were mentioned in the protocol) were eligible; this was likely to be due to a simple reporting error. Trials were located using a range of appropriate methods. Although not reported in this paper, the protocol specified use of appropriate methods for checking individual patient data for consistency and completeness. Basic individual study details were provided and more detail was presented by risk category. The statistical methods used for the meta-analyses appeared appropriate.

The authors' conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that under present guidelines individuals with five-year risk of major vascular events lower than 10% would not typically be regarded as suitable for LDL-lowering statin therapy and that their report suggested that these guidelines might need to be reconsidered.

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

Funding

British Heart Foundation; UK Medical Research Council; Cancer Research UK; European Community Biomed Programme; Australian National Health and Medical Research Council; National Heart Foundation, Australia.

Bibliographic details

Cholesterol Treatment Trialists’ (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380(9841): 11-17

PubMedID

22607822
DOI
10.1016/S0140-6736(12)60367-5

Original Paper URL
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2812%2960367-5/abstract

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Cholesterol, LDL /blood; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /therapeutic use; Practice Guidelines as Topic; Randomized Controlled Trials as Topic; Risk Assessment /methods; Treatment Outcome; Vascular Diseases /blood /epidemiology /prevention & control

AccessionNumber
12012023329

Date bibliographic record published
22/05/2012

Date abstract record published
01/06/2012

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.