

## Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials

Michael Pignone, Christopher Phillips, Cynthia Mulrow

### Abstract

**Objective** To summarise the effect of primary prevention with lipid lowering drugs on coronary heart disease events, coronary heart disease mortality, and all cause mortality.

**Design** Meta-analysis.

**Identification** Systematic search of the Medline database from January 1994 to June 1999 for English language studies examining drug treatment for lipid disorders (use of the MeSH terms “hyperlipidemia” and “anticholesteremic agents,” keyword searches for individual drug names, and a search strategy for identifying randomised trials to capture relevant articles); identification of older studies through systematic reviews and hand search of bibliographies.

**Inclusion criteria** All randomised trials of at least one year's duration that examined drug treatment for patients with no known coronary heart disease, cerebrovascular disease, or peripheral vascular disease and that measured clinical end points, including all cause mortality, coronary heart disease mortality, and non-fatal myocardial infarctions.

**Data extraction** Review of the articles and extracted relevant data by two authors separately, with disagreements resolved by consensus.

**Results** Four studies met eligibility criteria. Drug treatment reduced the odds of a coronary heart disease event by 30% (summary odds ratio 0.70, 95% confidence interval 0.62 to 0.79) but not the odds of all cause mortality (0.94, 0.81 to 1.09). When statin drugs were considered alone, no substantial differences in results were found.

**Conclusions** Treatment with lipid lowering drugs lasting five to seven years reduces coronary heart disease events but not all cause mortality in people with no known cardiovascular disease.

### Introduction

The effectiveness of drug treatment for lipid disorders in patients with no history of coronary heart disease has been controversial.<sup>1-3</sup> Although the effectiveness of lipid lowering agents for secondary prevention in people with lipid disorders is strongly supported, primary prevention trials and systematic reviews have reached mixed conclusions about the effect of lipid lowering on mortality from coronary heart disease and on all cause mortality. Earlier reviews cautioned against

drug treatment in patients with low to moderate risk of death from coronary heart disease because of possible increases in all cause mortality with treatment.<sup>4</sup> A more recent review of lipid lowering treatment with hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) found that coronary heart disease events and all cause mortality were decreased in primary prevention populations.<sup>5</sup> Reviews, however, have not included data from the large air force/Texas coronary prevention study, which examined the effect of drug treatment in men and women with poor ratios of total cholesterol concentration to high density lipoprotein cholesterol concentration and a modest risk (0.5-1% a year) of coronary heart disease events.<sup>6</sup>

We performed an updated systematic review and quantitative meta-analysis of primary prevention trials to estimate the effect of lipid lowering drugs on the incidence of any coronary heart disease events, on coronary heart disease mortality, and on all cause mortality.

### Methods

We searched the Medline database for articles published from January 1994 to June 1999, using the MeSH subject headings “hyperlipidemia” and “anticholesteremic agents,” MeSH terms or keywords for individual drug names, and a combination of subject headings and key words designed to identify randomised trials. We also searched the clinical trials registry of the *Cochrane Library* (Oxford, UK: Update Software, 1999) and the bibliographies of systematic reviews and clinical practice guidelines.

Two authors (MP and CP) separately reviewed the abstracts produced by the literature search to identify studies that were randomised trials which lasted at least one year and which measured clinical end points, including coronary heart disease events, coronary heart disease mortality, and all cause mortality. We excluded non-randomised studies, trials lasting less than one year, and trials examining only the change in serum cholesterol concentrations or angiographic outcomes. We also excluded studies published in languages other than English, studies published in abstract form only, and studies of secondary prevention.

For articles meeting inclusion criteria, we extracted the relevant data. Meta-analysis was performed with the Peto method for fixed effects models. Graphs of the

*Editorial by*  
Hulley et al

Division of General Internal Medicine, 5039 Old Clinic Building, University of North Carolina, Chapel Hill, NC 27599-7110, USA

Michael Pignone  
*assistant professor of medicine*

Preventive Medicine Residency Program, University of North Carolina, Chapel Hill

Christopher Phillips  
*resident in preventive medicine*

Division of General Internal Medicine, Audie L Murphy VA Hospital, San Antonio, TX 78284, USA

Cynthia Mulrow  
*professor of medicine*

Correspondence to: M Pignone  
pignone@med.unc.edu

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Study characteristics

	LRC	HHS	WOSCOPS	AFCAPS/TexCAPS
Drug (dose)	Colestyramine (24 g four times daily)	Gemfibrozil (600 mg twice daily)	Pravastatin (40 mg four times daily)	Lovastatin (20-40 mg four times daily)
Study duration (years)	7	5	5	5
No of subjects (intervention/control)	1906/1900	2051/2030	3302/3293	3304/3301
Mean age (years)	48	47	55	58
% of male subjects	100	100	100	85
Mean initial total cholesterol (mmol/l)	7.5	7.4	7.0	5.7
Mean reduction in total cholesterol (%)	8.5†	10‡	20‡	18§

LRC=Lipid Research Clinic primary prevention trial; HHS=Helsinki heart study; WOSCOPS=west of Scotland coronary prevention study; AFCAPS/TexCAPS=air force/Texas coronary prevention study.

\*Not intention to treat analysis. With intention to treat, the difference was 16% at five years.

†At 7.4 years.

‡At 5 years.

§At 1 year.

outcomes for included trials were examined visually and by using the  $\chi^2$  test to identify heterogeneity in the outcome variables across different studies. The results are displayed as summary odds ratios and 95% confidence intervals for the effect of drug treatment on total coronary heart disease events, coronary heart disease mortality alone, and all cause mortality.

Results

Trial characteristics

Our searches identified 516 articles; four articles met all inclusion criteria,<sup>6-9</sup> and four studies were considered to be "possibly suitable for inclusion."<sup>10-13</sup> The table shows the basic study characteristics.

Main results

Treatment reduced the relative risk of coronary heart disease events by 30% compared with placebo (summary odds ratio 0.70, 95% confidence interval 0.62 to 0.79) (figure). The relative risk of coronary heart disease mortality was reduced by 29% (0.71, 0.56 to 0.91). There was either a small or no effect on all cause mortality (0.94, 0.81 to 1.09). In each of these analyses, the results of  $\chi^2$  tests for heterogeneity were not significant ( $P > 0.10$ ).

Sensitivity analysis

The inclusion of the four studies that were considered possibly suitable for inclusion had little effect on the estimate of the reduction in coronary heart disease events (0.72, 0.65 to 0.80). The effect on coronary heart disease mortality was slightly attenuated for the six studies reporting this outcome (0.76, 0.61 to 0.94), and the effect on all cause mortality remained non-significant (1.02, 0.89 to 1.15). The  $\chi^2$  test for heterogeneity was significant only for the outcome of all cause mortality.

When limiting the meta-analysis to the three trials using statins the summary effect on the incidence of coronary heart disease events was slightly greater than for the main analysis (0.65, 0.55 to 0.77), as was the effect on deaths from coronary heart disease (0.65, 0.48 to 0.89). The effect on all cause mortality remained non-significant (0.89, 0.75 to 1.06). Results of tests for heterogeneity were non-significant for total coronary heart disease events and coronary heart disease mortality but were significant ( $P = 0.04$ ) for all cause mortality.

Effect of treatment on coronary heart disease events

Study	Treatment (No of events/ No of subjects)	Control (No of events/ No of subjects)	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)	Year
LRC	155/1906	187/1900	0.81 (0.65 to 1.01)	29.5	0.81 (0.65 to 1.01)	1984
HHS	56/2051	84/2030	0.65 (0.46 to 0.92)	14.1	0.65 (0.46 to 0.92)	1987
WOSCOPS	174/3302	248/3293	0.68 (0.56 to 0.83)	40.3	0.68 (0.56 to 0.83)	1995
AFCAPS/TexCAPS	56/3304	96/3301	0.58 (0.41 to 0.80)	16.2	0.58 (0.41 to 0.80)	1998
Total	441/10 563	615/10 524	0.70 (0.62 to 0.79)	100.0	0.70 (0.62 to 0.79)	

$\chi^2$  test for heterogeneity = 3.23 (df=3;P=0.36)

Effect of treatment on coronary heart disease mortality

Study	Treatment (No of events/ No of subjects)	Control (No of events/ No of subjects)	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)	Year
LRC	30/1906	38/1900	0.78 (0.48 to 1.27)	24.4	0.78 (0.48 to 1.27)	1984
HHS	14/2051	19/2030	0.73 (0.36 to 1.45)	12.4	0.73 (0.36 to 1.45)	1987
WOSCOPS	50/3302	73/3293	0.68 (0.47 to 0.98)	47.0	0.68 (0.47 to 0.98)	1995
AFCAPS/TexCAPS	17/3304	25/3301	0.68 (0.37 to 1.26)	16.2	0.68 (0.37 to 1.26)	1998
Total	111/10 563	155/10 524	0.71 (0.56 to 0.91)	100.0	0.71 (0.56 to 0.91)	

$\chi^2$  test for heterogeneity = 0.25 (df=3;P=0.97)

Effect of treatment on all cause mortality

Study	Treatment (No of events/ No of subjects)	Control (No of events/ No of subjects)	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)	Year
LRC	68/1906	71/1900	0.95 (0.68 to 1.34)	18.1	0.95 (0.68 to 1.34)	1984
HHS	45/2051	42/2030	1.06 (0.69 to 1.62)	10.9	1.06 (0.69 to 1.62)	1987
WOSCOPS	106/3302	135/3293	0.78 (0.60 to 1.01)	34.5	0.78 (0.60 to 1.01)	1995
AFCAPS/TexCAPS	152/3304	145/3301	1.05 (0.83 to 1.32)	36.5	1.05 (0.83 to 1.32)	1998
Total	371/10 563	393/10 524	0.94 (0.81 to 1.09)	100.0	0.94 (0.81 to 1.09)	

$\chi^2$  test for heterogeneity = 3.29 (df=3;P=0.35)

Effect of lipid lowering drugs (compared with placebo) on odds of coronary heart disease events, coronary heart disease mortality, and all cause mortality (fixed effects model).

LRC=Lipid Research Clinic primary prevention trial; HHS=Helsinki heart study; WOSCOPS=west of Scotland coronary prevention study; AFCAPS/TexCAPS=air force/Texas coronary prevention study

Discussion

Our meta-analysis of primary prevention trials shows that lipid lowering drugs reduce the relative odds of coronary heart disease events and coronary heart disease mortality by about 30% but that their effect on all cause mortality over five years is small and not significant. Limiting the analysis to trials that used statin drugs suggests a slightly stronger effect on all outcomes compared with analyses that used all trials, but it does not show a significant reduction in all cause mortality.

Our meta-analysis reaches a different conclusion from that of Hebert et al, who found that statin drugs reduced all cause mortality (0.74, 0.58 to 0.95).<sup>5</sup> Unlike Hebert et al, we included the results of the large air

force/Texas trial<sup>6</sup> and did not include the Kuopio atherosclerosis prevention study, a trial that included some subjects (10%) with histories of myocardial infarctions.<sup>14</sup>

The failure of drug treatment to reduce all cause mortality in primary prevention is most likely due to the generally low risk of mortality in the patient populations that were studied rather than some adverse effect of lipid lowering drugs or of lowering cholesterol concentrations. Treatment targeted specifically at primary prevention patients with higher levels of risk of coronary heart disease events might reduce all cause mortality. The trial with the participants at highest risk, for example, found a 22% reduction in the relative risk of all cause mortality, which was of borderline significance at five years ( $P=0.05$ ).<sup>9</sup> Lower risk populations might also achieve significant reductions in all cause mortality if they were treated for longer than those tested in the trials. We have insufficient data, however, on patients with low levels of risk.

Because the absolute risk of all cause mortality in primary prevention patients is relatively low (the risk among control subjects in these trials was only 2-4% over five years), the absolute benefit in lives saved will also be low initially. If the true relative risk reduction for all cause mortality were 10%, the number needed to treat for five years to prevent one death would be 250 to 500. If it were 20%, it would be 125 to 250. Preventing non-fatal events may also improve all cause mortality over a longer span than the five to seven years observed in these trials, but data about the magnitude of that effect are not currently available.

The decision about whether to use lipid lowering drugs for patients with no history of coronary heart disease is difficult and requires consideration of outcomes other than all cause mortality. The results of our meta-analysis suggest that treatment will reduce the relative risk of coronary heart disease events and coronary heart disease mortality by about 30%, independent of absolute risk. The absolute risk reduction from treatment, therefore, is proportional to the underlying risk in the person or populations being considered for treatment. The risk of coronary heart disease events and mortality, and hence the absolute risk reduction and number needed to treat, varies considerably in patients with no history of coronary heart disease and different combinations of coronary heart disease risk factors. Risk assessment tools can be used to determine the risk of individual patients and help providers and patients to decide about treatment.<sup>15 16</sup>

Generalising these results to other populations—such as people of non-European descent, women, and elderly people—is challenging because the included studies enrolled primarily middle aged men of European descent. The effect of treatment for women, elderly people, and men of non-European descent has not been directly studied, although there is little reason to believe that the effect would differ for non-Europeans or elderly people with similar baseline risks of coronary heart disease and similar lipid abnormalities. Also, the concomitant use of other drugs—such as chemoprophylaxis with aspirin or treatment with  $\beta$  blockers, which were not widely prescribed in these trials—may lower the absolute risk (and thus the potential absolute risk reductions) for large numbers of patients at moderate risk of coronary heart disease.

## What is already known on this topic

Randomised trials have found that drug treatment for lipid disorders reduces the incidence of coronary heart disease events in patients with no history of cardiovascular disease

Previous meta-analyses have reached conflicting conclusions about the effect of drug treatment on all cause mortality

## What this study adds

An updated meta-analysis shows that treatment with lipid lowering drugs reduces the relative risk of coronary heart disease events and mortality from coronary heart disease by about 30%

Overall, all cause mortality does not seem to be affected, perhaps because the relatively short follow up periods in the trials (five to seven years) do not allow sufficient time for differences to emerge in relatively low risk patients

Future research should examine whether the effects of lipid lowering treatment are similar for women and for people of non-European origin, groups that were not well represented in the trials included here. The effect of longer treatment (5-10 years) should also be examined to determine if it produces greater reductions in coronary heart disease events and possibly all cause mortality.

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## Randomised controlled trial of atraumatic versus standard needles for diagnostic lumbar puncture

S Rachel Thomas, D R S Jamieson, Keith W Muir

Editorial by Serpell and Rawal

Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF  
S Rachel Thomas  
lecturer

Keith W Muir  
locum consultant

Department of Neurology, Leeds General Infirmary, Leeds LS1 3EX  
D R S Jamieson  
consultant

Correspondence to:  
K W Muir  
k.muir@clinmed.gla.ac.uk

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### Abstract

**Objective** To compare the ease of use of atraumatic needles with standard needles for diagnostic lumbar puncture and the incidence of headache after their use.

**Design** Double blind, randomised controlled trial.

**Setting** Investigation ward of a neurology unit in a university hospital.

**Participants** 116 patients requiring elective diagnostic lumbar puncture.

**Interventions** Standardised protocol for lumbar puncture with 20 gauge atraumatic or standard needles.

**Outcome measures** The primary end point was intention to treat analysis of incidence of moderate to severe headache, assessed at one week by telephone interview. Secondary end points were incidence of headache at one week analysed by needle type, ease of use by operator according to a visual analogue scale, incidence of backache, and failure rate of puncture.

**Results** Valid outcome data were available for 97 of 101 patients randomised. Baseline characteristics were matched except for higher body mass index in the standard needle group. By an intention to treat analysis the absolute risk of moderate to severe headache with atraumatic needles was reduced by 26% (95% confidence interval 6% to 45%) compared with standard needles, but there was a non-significantly greater absolute risk of multiple attempts at lumbar puncture (14%, -4% to 32%). Higher body mass index was associated with an increased failure rate with atraumatic needles, but the reduced incidence of headache was maintained. The need for medical interventions was reduced by 20% (1% to 40%).

**Conclusions** Atraumatic needles significantly reduced the incidence of moderate to severe headache and the need for medical interventions after diagnostic lumbar punctures, but they were associated with a higher failure rate than standard needles.

### Introduction

Headache due to a reduced volume of cerebrospinal fluid and reduced pressure complicates a substantial proportion of lumbar punctures.<sup>1-3</sup> In the 1920s Greene hypothesised that complications could be reduced by using a smaller, tapered needle with a blunt tip, which would separate rather than cut dural fibres and thus reduce fluid leakage.<sup>4,5</sup> Atraumatic ("blunt") needles have been in clinical use since the 1950s, principally in anaesthetic practice, where there is substantial evidence of a reduced incidence of headache and other neurological complications after their use.<sup>6</sup>

Spinal anaesthesia and myelography differ from diagnostic lumbar puncture because smaller gauge needles are used, smaller volumes of cerebrospinal fluid are removed, and other fluids can be introduced. The incidence of headache after spinal anaesthesia is typically half that after diagnostic lumbar puncture.<sup>2,6</sup> Despite evidence that relevant physical characteristics of atraumatic needles, such as flow rates, are comparable to those of standard needles,<sup>6</sup> there are limited data on their benefit in diagnostic lumbar puncture. Also, there is a perception that atraumatic needles are more difficult to use than standard needles. Previous studies of diagnostic lumbar puncture have potentially been confounded by comparing different needle gauges, failing to define the operators' previous experience or the length of follow up, and not addressing technical difficulties.<sup>7-9</sup> The Cochrane Collaboration has identified only two methodologically adequate studies of atraumatic needles for diagnostic lumbar puncture (C Sudlow, personal communication). We aimed to compare the incidence of headache with atraumatic and standard needles and to evaluate technical difficulties.

### Participants and methods

#### Participants

A local pilot study established the feasibility of training medical staff on rotation in the use of atraumatic



The procedure for the operators appears on the BMJ's website