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# Relation of coronary heart disease incidence and total mortality to plasma cholesterol reduction in randomised trials: use of meta-analysis

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The first randomised trials designed to test the effect of plasma cholesterol reduction came out in the mid-sixties and were largely carried out on patients who already had coronary heart disease. The trials were small and had relatively few new incidents of coronary heart disease in the treatment groups. Even in these high risk populations no general agreement on the benefit of cholesterol lowering was reached, and there was even the suggestion of an excess of non-cardiac related deaths in the treated groups. The first meta-analysis of randomised trials of cholesterol lowering, however, found no indication of an excess of cancer or total mortality in the groups treated by diet.[1] Discussion about the value of lowering plasma lipid concentrations has continued, boosted by the finding of an excess total mortality in the treated group of the WHO clofibrate trial[2] and the findings from the four multifactorial trials (MRFIT,[3] WHO factory study,[4] the Finnish Miettinen study,[5] and the Primary Prevention Study in Gothenburg[6] that failed to show a reduction in all cause or coronary heart disease mortality. In fact, of the multifactorial trials only the Oslo diet and anti-smoking trial showed a beneficial effect of this combined intervention advice in high risk healthy men.[7]

The debate[8 9] about the advantages of plasma lipid lowering has continued world-wide and it is apparent that many trials have achieved a striking reduction in non-fatal coronary heart disease events.[8] The benefit of cholesterol reduction on coronary heart disease mortality, however, was again questioned after the 15 year extended follow up of the Finnish Miettinen study suggested an excess of coronary deaths in the treated group.[10]

Net cholesterol reduction has in fact been very modest—that is, about 5% overall in all published randomised trials. The Lipid Research Clinics Primary Prevention trial projected a 10% decrease in overall coronary heart disease risk from such a reduction in cholesterol[11] and the expected decrease in total mortality, especially in asymptomatic subjects in whom primary prevention is the aim, is even smaller. Thus, much of the controversy about total mortality and cholesterol reduction cannot be resolved, and indeed is the result of a lack of sufficient statistical power in the studies. Properly performed meta-analysis of the published trials can, albeit imperfectly, resolve this under powering.

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## Meta-analysis: methodological considerations

Appropriate meta-analysis should provide results with considerably greater statistical power for important end points and subgroups than single trials. It may also resolve controversies when studies do not accord and give answers to new questions not raised in the single trials. Another benefit is a major improvement in the precision of the estimates of effect size.

Meta-analysis is a statistical method that combines or integrates the results of several independent clinical trials which are considered by the analyst to be combinable.[12] Nevertheless, meta-analysis is not a totally objective science. A set of rigorous criteria for performing the analysis should be established before starting. For example, a protocol should be developed a priori and should cover important issues such as what studies are to be included or excluded. Should a weighted system be used to put more weight on "good" studies than "bad" ones? How do we select and define proper end points and how do we treat the questions of heterogeneity and sensitivity in study outcomes?

The introduction of a weighting system for good or bad trials would require an independent body of information, preferably given by sources other than the analyst. Items such as blindness, placebo control, and size can be graded and put together into a quality score for each trial and used as weights in a quality weighted or adjusted meta-analysis. But there can also be a subjective bias in weighting.

In any meta-analysis a key issue is whether the treatment effects seen in the trials are broadly similar or whether there is heterogeneity. Heterogeneity leads to one or more trials having a disproportionate effect on the result in either direction. It is a normal practice in meta-analysis to test for such heterogeneity[13] by $\chi^2$ testing. If one trial proves to be significantly out of line the circumstances particular to this trial need to be considered. It may be possible to adjust (by weighting) for this trial but at the cost of introducing a subjective bias. On the other hand if heterogeneity is ignored there is the risk that one trial will essentially determine the outcome of the meta-analysis.

The results from new plasma lipid lowering trials will emerge from several large trials that are under way, so in future meta-analysis will be based on more information. To avoid the

inherent problem of multiple looks at the data, methods must be developed to avoid inflation of type 1 errors—for example, sequential methods based on a non-fixed number of analyses of the data.[14]

## Meta-analysis of cholesterol lowering trials

There are several published meta-analyses of randomised trials of cholesterol reduction.[15-18] Only mine examined the dose response relation between cholesterol reduction and coronary heart disease incidence or total mortality risk.[18] Two multifactorial trials[5 6] were not included in my study. In the analysis I present here I include these two trials, and another recently published trial.[19] Thus I include 22 trials for total mortality and 19 for coronary heart disease incidence.

There is a great variation in design among all cholesterol lowering trials. The trials have open and placebo treated control groups, are of diet and drug treated active groups of primary and secondary prevention and they have single and multifactorial designs. Some intervention populations are at high risk and others were at normal risk and the trials varied greatly in duration and size. So any association between outcome and a risk factor that is common to all or most of the studies must be an important determinant of the potential for prevention.

In the present analysis I use the incidence of coronary heart disease (death from coronary heart disease and confirmed non-fatal infarction) and total mortality as the two end points according to the intention to treat principle. I have not considered end points that occurred after ordinary termination of a study, even if such additional results were reported. Nor have I included angiographic studies of atherosclerosis.

The cholesterol response was calculated as the percentage net difference in cholesterol between treatment groups during the trial phase. For all trials combined the weighted (by trial size) average of percentage net cholesterol difference was about 4–5%, depending on the end point analysed.

### STATISTICAL METHODS

The overall estimate of the treatment effect was obtained by averaging the odds ratio (OR) across all the studies.[13] This procedure also gives a 95% confidence interval for the average OR. A useful graphical display in this context is the Galbraith plot.[13] This method displays each trial as a single point. The vertical axis is the standard log OR and the horizontal axis is a measure of the sample size and thus gives an indication of the precision of the log OR estimation. A line is fitted to the points passing through the origin and calculated by least squares. The slope of this line gives the pooled OR and parallel lines at $\pm 2$SD give the normal variation. One advantage of such plots is that heterogeneous results are highlighted when points lie outside this range.

Analysis by weighted regression, modified for trial size, is used to analyse the dose response relation between log OR and the net difference in cholesterol. The slope of this regression will estimate the so-called cholesterol benefit ratio—that is, the percentage reduction in risk for each percentage reduction in cholesterol. The Lipid Research Clinics trial estimated that ratio was 2·0% for coronary heart disease.[7]

I use multiple weighted regression analysis to investigate whether this benefit ratio is dependent on other design characteristics such as diet or drug, primary or secondary prevention, or single or multifactorial trials.

### RESULTS OF META-ANALYSIS

Tables 1 and 2 and fig 1 show the details of 22 trials.[2-7 19-34] For coronary heart disease incidence (n=19) a clear benefit of treatment is observed (OR=0·91, 95% confidence interval (CI) 0·87 to 0·96). For total mortality, however, there was an estimated slight excess risk of treatment (OR=1·02, 95% CI 0·97 to 1·07). Table 3 shows that the extent of cholesterol reduction is different in various types of trial. Multifactor trials were not effective in reducing total cholesterol. The results of primary preventive diet trials were also poor.

Table 2 shows that the results in terms of coronary heart disease incidence and total mortality were heterogeneous.

To study this heterogeneity in more detail the results are presented for groups of trials (figs 2 and 3). Confidence intervals on the log OR scale are given for the two end points. Single factor trials had better effects than multi-factor trials on coronary heart disease incidence ($p<0·05$) and most of the difference can be explained by difference in cholesterol reduction between the two subgroups of trials. Secondary preventive trials were significantly better than primary preventive trials and again the difference can be explained by the difference in cholesterol reduction. The more modest difference in coronary heart disease reduction between diet trials and drug trials again accords with the more modest difference in cholesterol reduction produced by diet.

So before such trial subgroups can be compared adjustments must be made for differences in cholesterol reduction. Figure 4 shows the weighted regression line between log OR of coronary heart disease incidence and the percentage reduction in cholesterol (SE in parentheses). The slope of the line ($-0·025$) indicates that for each 1% reduction in cholesterol an associated 2·5% reduction in coronary heart disease incidence is to be expected on the average (cholesterol benefit ratio). This result was similar in single factor and in multi-factor trials (slope (single) = $-0·0248$; slope (multi) = $-0·0272$) that is, irrespective of the average magnitude of cholesterol reduction.

Figure 5 shows the dose response relation for total mortality. The slope was $-0·75$% for each 1% reduction in cholesterol. A com-

*Table 1 Design characteristics of trials included in the overview analysis of cholesterol lowering*

| Trial | Diet/ drug/ other | Primary/ secondary | Single/ multi-factor | Open/ blind | M/F | Age range (yr) | Mean age (yr) | Follow up (yr) | Baseline serum cholesterol (mg/dl) |
|---|---|---|---|---|---|---|---|---|---|
| MRFIT[3] | Diet | Primary | Multi | Open | M | 35–57 | 46 | 6–8 | 253 |
| Hjermann *et al*[7] | Diet | Primary | Multi | Open | M | 40–49 | 45 | 6–7½ | 325 |
| WHO fact[4] | Diet | Primary | Multi | Open | M | 40–59 | 48 | 5–6 | 216 |
| Acheson and Hutchinson[20] | Drug | Secondary | Single | Blind | M+F | — | — | ≦7 | 288 |
| Carlson *et al*[21] | Drug | Secondary | Single | Open | M+F | ≦70 | 59 | 3½ | 247 |
| RC of Scottish Society[22] | Drug | Secondary | Single | Blind | M+F | 40–69 | 52 | 6 | 266 |
| Coronary Drug Project[23] | Drug | Secondary | Single | Blind | M | 30–64 | 54 | 4½–8 | 249 |
| Newcastle upon Tyne[24] | Drug | Secondary | Single | Blind | M+F | ≦65 | 52 | 5 | 249 |
| Dorr *et al*[25] | Drug | Secondary | Single | Blind | M+F | 18+ | 54 | 3 | 307 |
| Dayton *et al*[26] | Diet | Secondary | Single | Open | M | 55+ | 66 | ≦8 | 234 |
| Leren[27] | Diet | Secondary | Single | Open | M | 30–64 | 56 | 5 | 296 |
| MRC[28] | Diet | Secondary | Single | Open | M | ≦60 | — | 2–7 | 272 |
| MRC[29] | Diet | Secondary | Single | Open | M | ≦65 | — | 6 | 263 |
| Rose *et al*[30] | Diet | Secondary | Single | Open | M+F | ≦70 | 55 | 2 | 260 |
| Woodhill *et al*[31] | Diet | Secondary | Single | Open | M | 30–59 | 49 | 2–7 | 282 |
| LRC-CPPT[32] | Drug | Primary | Single | Blind | M | 35–59 | 47 | 7–10 | 279 |
| WHO (clofibrate)[2] | Drug | Primary | Single | Blind | M | 30–59 | 45 | 5·3 (average) | 248 |
| Frick *et al*[33] | Drug | Primary | Single | Blind | M | 40–55 | 47 | 5 | 289 |
| Frantz *et al*[34] | Diet | Primary | Single | Open | M+F | All | — | 5 | — |
| Miettinen[5] | Other | Primary | Multi | Open | M | 40–55 | 48 | 5 | 275 |
| Gothenburg[6] | Other | Primary | Multi | Open | M | 47–55 | — | 10 | 250 |
| POSCH[19] | Other | Secondary | Single | Open | M+F | — | 51 | 9·7 | 251 |

*Table 2 Number of deaths and incidence of coronary heart disease, odds ratios and 95% confidence intervals, and percentage difference in cholesterol concentrations between treatment groups*

| Study | No T/C | Death T/C | CHD T/C | Death OR | Death 95% CI | CHD OR | CHD 95% CL | Δ % chol |
|---|---|---|---|---|---|---|---|---|
| MRFIT[3] | 6428/6438 | 265/260 | 227/280 | 1·022 | 1·217<br>0·858 | 0·990 | 1·174<br>0·836 | 2 |
| Hjermann *et al*[7] | 604/628 | 16/24 | 19/36 | 0·689 | 1·293<br>0·367 | 0·546 | 0·937<br>0·318 | 10 |
| WHO fact[4] | 24615/25169 | 997/924 | 773/756 | 1·108 | 1·213<br>1·011 | 1·047 | 1·159<br>0·946 | 1 |
| Acheson and Hutchinson[20] | 47/48 | 23/20 | — | 1·337 | 2.987<br>0·598 | — | —<br>— | 9 |
| Carlson *et al*[21] | 279/279 | 24/26 | 41/62 | 0·916 | 1·637<br>0·513 | 0·607 | 0·931<br>0·396 | 17 |
| RC of Scottish Society[22] | 264/273 | 34/38 | 59/76 | 0·914 | 1·502<br>0·557 | 0·747 | 1·103<br>0·506 | 14 |
| Coronary Drug Project[23] | 2222/2789 | 554/709 | 596/839 | 0·974<br>0·857 | 1·108 | 0·853<br>0·754 | 0·964 | 8 |
| Newcastle upon Tyne[24] | 244/253 | 27/48 | 55/89 | 0·540 | 0·882<br>0·331 | 0·542 | 0·798<br>0·368 | 13 |
| Dorr *et al*[25] | 1149/1129 | 37/48 | — | 0·751 | 1·158<br>0·487 | — | —<br>— | 10 |
| Dayton *et al*[26] | 424/422 | 174/177 | 60/88 | 0·963 | 1·266<br>0·733 | 0·629 | 0·896<br>0·441 | 13 |
| Leren[27] | 206/206 | 44/51 | 61/81 | 0·826 | 1·306<br>0·523 | 0·651 | 0·977<br>0·434 | 14 |
| MRC[28] | 199/194 | 28/32 | 40/39 | 0·829 | 1·436<br>0·479 | 1·000 | 1·637<br>0·611 | 16 |
| MRC[29] | 123/129 | 20/24 | 43/44 | 0·850 | 1·628<br>0·444 | 1·038 | 1·744<br>0·618 | 6 |
| Rose *et al*[30] | 54/26 | 6/1 | 13/4 | 2·456 | 12·729*<br>0·474 | 1·670 | 5·203<br>0·536 | 4 |
| Woodhill *et al*[31] | 231/237 | 39/28 | — | 1·510 | 2·532<br>0·901 | — | —<br>— | 5 |
| LRC-CPPT[32] | 1906/1900 | 68/71 | 155/187 | 0·953 | 1·337<br>0·679 | 0·811 | 1·013<br>0·650 | 9 |
| WHO (clofibrate)[2] | 5331/5296 | 128/87 | 167/208 | 1·466 | 1·921<br>1·119 | 0·792 | 0·973<br>0·644 | 9 |
| Frick *et al*[33] | 2051/2030 | 45/42 | 56/83 | 1·062 | 1·624<br>0·694 | 0·662 | 0·928<br>0·472 | 10 |
| Frantz *et al*[34] | 4922/4853 | 268/256 | 134/129 | 1·034 | 1·233<br>0·867 | 1·025 | 1·309<br>0·802 | 13 |
| Miettinen[5] | 612/610 | 10/5 | 19/9 | 1·967 | 5·415<br>0·707 | 2·069 | 4·375<br>0·978 | 6 |
| Gothenburg[6] | 10004/10011 | 1293/1304 | 837/836 | 0·991 | 1·076<br>0·913 | 1·002 | 1·108<br>0·907 | 0 |
| POSCH[19] | 421/417 | 49/62 | 82/125 | 0·755 | 1·127<br>0·507 | 0·569 | 0·779<br>0·416 | 23 |
| Total | | | | 1·020 | 1·068<br>0·974 | 0·909 | 0·955<br>0·866 | |
| | | | | $\chi^2_{21}$ (het) = 35·2 (p<0·05) | | $\chi^2_{18}$ (het) = 44·5 (p<0·001) | | |

*Uncertain owing to small numbers.
log OR ± SE logOR and Z score added for CHD.
CHD, coronary heart disease; OR, odds ratio.

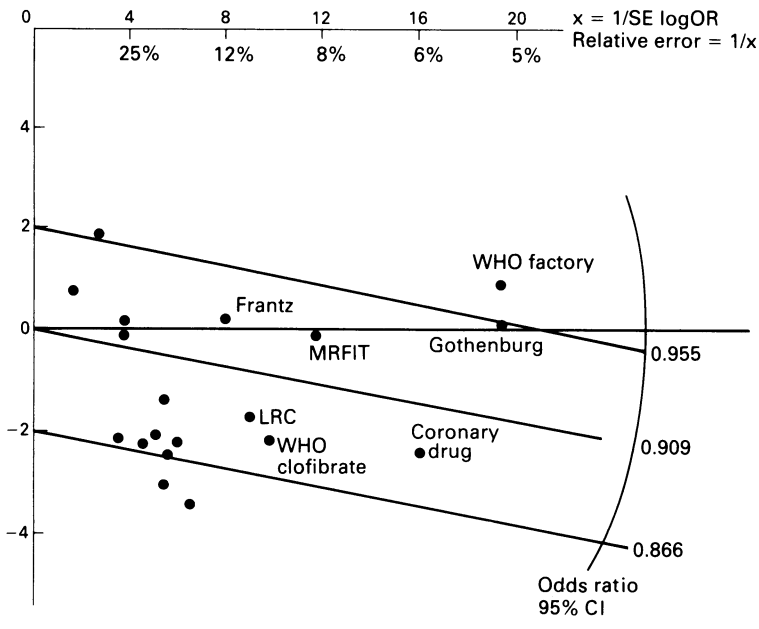


*Figure 1 Galbraith plot of log OR (vertical axis) for coronary heart disease incidence with adjustment for trial size (horizontal axis). Small studies lie to the left whereas larger studies to the right will influence the regression line to a greater degree. The regression line slope indicates the odds ratio measured on the circular scale. The normal variation lies within ± 2SD. Points lying outside this range represent heterogeneous studies with results that are significantly different from the other studies.*

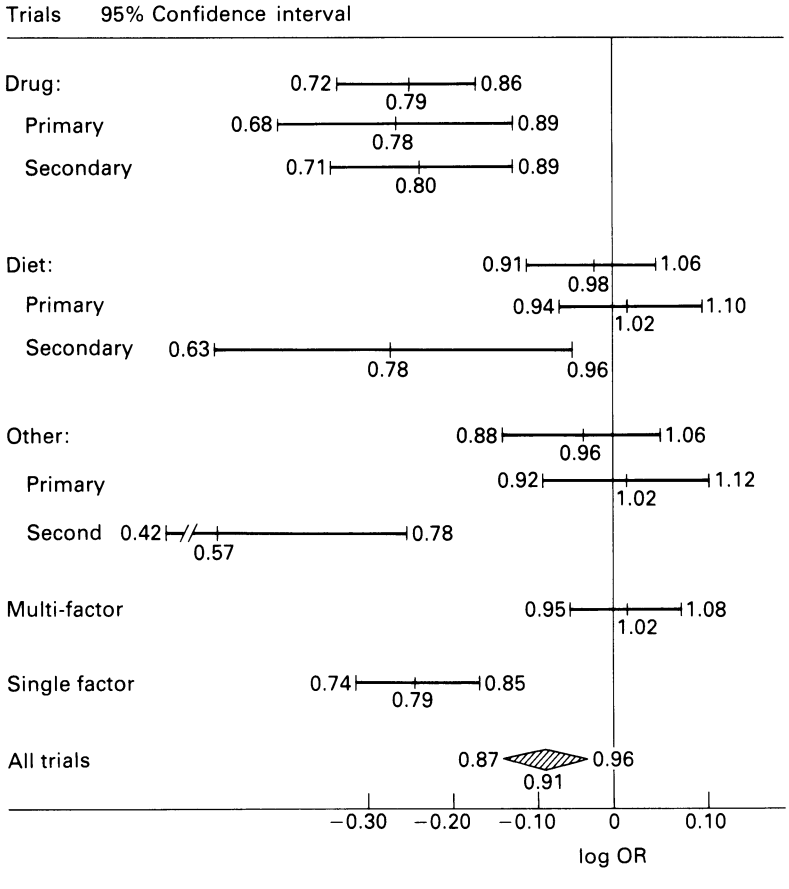


*Figure 2 Comparison of the OR for the incidence of coronary heart disease in different trial types.*

parison of the slope of single factor and multi-factor trials shows a tendency to heterogeneity (slope (single) = −0·0217 and slope (multi) = +0·0001; NS). Figure 5 shows that it may be possible to draw a line with a positive slope within the given confidence interval; however, the magnitude of positivity can only be small.

The $\chi^2$ error terms for the models with linear fit give $\chi^2_{20} = 27{\cdot}8$ for total mortality (NS) and $\chi^2_{17} = 23{\cdot}2$ for coronary heart disease incidence (NS)—that is, there is no significant heterogeneity after allowing for differences in cholesterol reduction. Thus comparisons between single groups of trials are valid once there has been a proper adjustment for cholesterol reduction.

Figures 6 and 7 show similar graphs for absolute change in cholesterol (mg/dl). Each 1 mg/dl reduction in cholesterol is associated with 1·1% reduction in coronary heart disease incidence. For total mortality the slope is −0·38%. So a reduction in cholesterol from 7 mmol/l to 6 mmol/l in a population should reduce the incidence of coronary heart disease by about 42% and total mortality by about 12%.

But the cholesterol benefit ratio is also dependent on the baseline cholesterol concentration in a trial. The benefit ratio for coronary heart disease is only about 1·2 when cholesterol is below 5·0 mmol/l at baseline.

## Discussion

The results from single factor and multifactorial trials and from trials of primary and secondary prevention tend to be different. With adjustments for cholesterol reduction, however, this heterogeneity vanishes. The coronary heart disease cholesterol benefit ratio was estimated to be 2·5 when all 19 randomised trials with available information were included. Thus there are two major considerations in trials of the impact of plasma cholesterol reduction: to what degree was plasma cholesterol concentration lowered and what was the statistical power of the study.

The relation of plasma cholesterol reduction and total or non-cardiac mortality has been much discussed.[8-15] The disappointing results in terms of total mortality must be considered in the context of the very modest reduction in plasma cholesterol. The 5% reduction in cholesterol that is generally achieved in these trials should reduce total mortality by about 4% according to fig 3. A single trial to detect a between group difference of 4% in total mortality with the given absolute risk in the trials I have included would need at least 200 000 participants per group—far greater than the numbers available in this meta-analysis. Hence, part of the controversy may be attributable to lack of statistical power to give precise statements about a beneficial or harmful effect on total mortality with regard to cholesterol reduction. For overall coronary heart disease incidence, however, the power is more than adequate with the included trials to detect an expected coronary heart disease risk reduction of about 13%.

*Table 3 Reduction in cholesterol (%) in various types of trial*

| Type of trial | Reduction in cholesterol (%) |
|---|---|
| Single factor | 10·8 |
| Multi-factor | 0·7 |
| Primary preventive | 3·4 |
| Secondary preventive | 10·9 |
| Diet intervention | 3·2 |
| Non-diet intervention | 5·7 |

The dose response relation between total mortality and cholesterol reduction is negative—that is, if anything, large reductions in plasma cholesterol are associated with larger reductions in total mortality than smaller reductions in plasma cholesterol. Consistent with this are the poor results from the trials with a small reduction in plasma cholesterol such as the primary preventive trial in Gothenburg, the WHO factory study, and the MRFIT trial, all multi-factor primary preventive trials.

I concluded that previous randomised trials when taken together show that reducing plasma cholesterol has a beneficial effect on non-fatal and fatal coronary heart disease events combined. In fact, this is very encouraging given the modest reductions in plasma cholesterol most of the trials achieved. The reductions in plasma cholesterol were, however, too low for their effect on total mortality to be discernible in trials of the size carried out so far.

To obtain a reduction in total mortality in a single trial of practical size, plasma cholesterol must be reduced by more than 5–10%. In several recent secondary prevention studies (see Brown *et al* pages 48–53), use of combinations of lipid lowering drugs produced much greater reductions in LDL cholesterol. HMG CoA reductase inhibitors in combination with resins reliably reduce total (35%) and LDL cholesterol (45%).[35] The large trials of such drugs that are underway should show

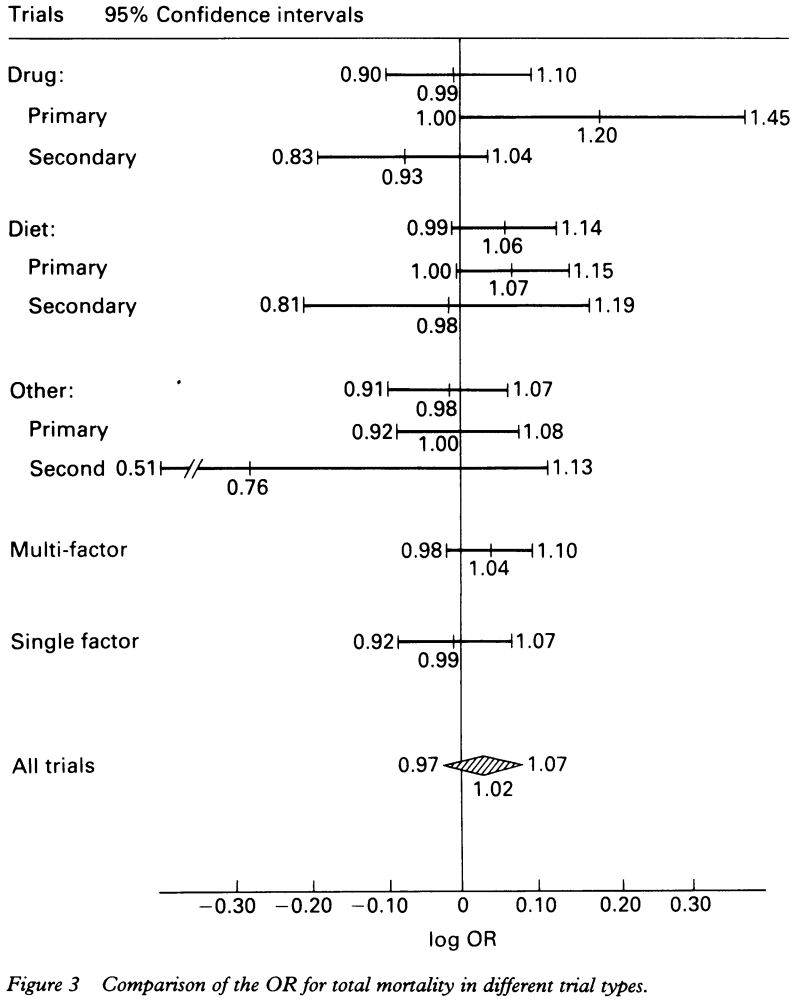


*Figure 3 Comparison of the OR for total mortality in different trial types.*

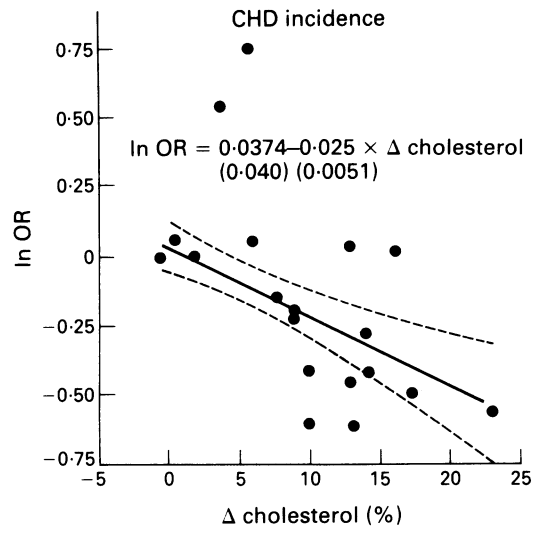


*Figure 4 Relation between log OR for coronary heart disease incidence and percentage change in plasma cholesterol.*

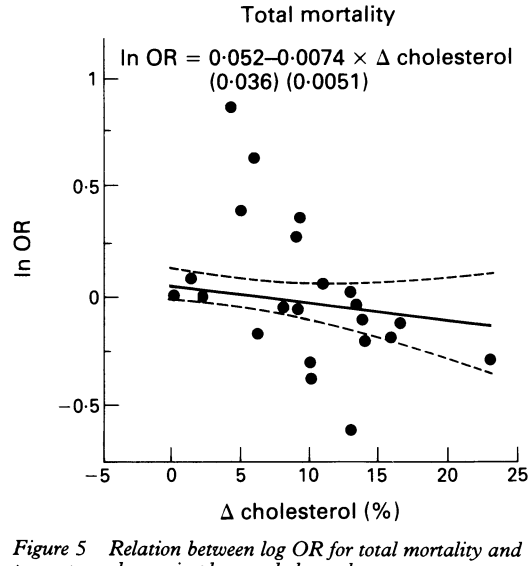


*Figure 5 Relation between log OR for total mortality and percentage change in plasma cholesterol.*

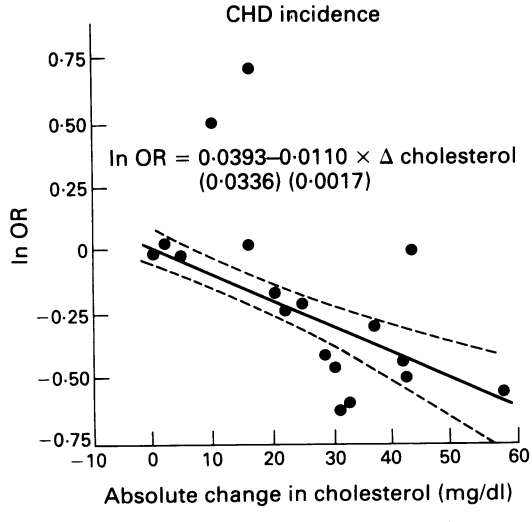


*Figure 6 Relation between log OR for coronary heart disease incidence and absolute change in plasma cholesterol.*

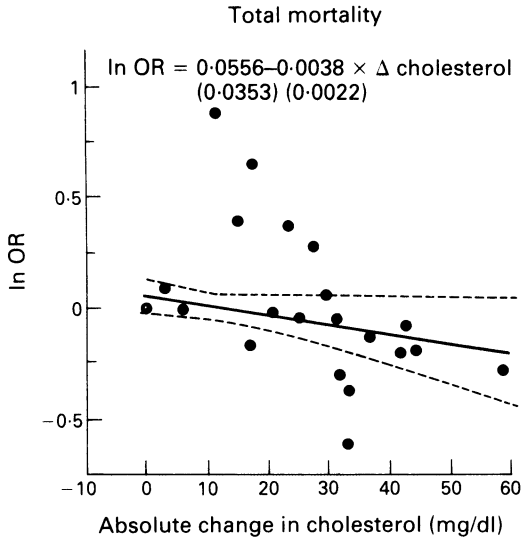


*Figure 7 Relation between log odds ratio for total mortality and absolute change in plasma cholesterol. Baseline mean cholesterol concentration in the Frantz trial was not available.*

more favourable results on total mortality, provided that the regression lines I have presented reflect the true underlying mechanisms. But most people at low or medium risk of developing coronary heart disease do not require HMG co-reductase inhibitors, For these groups non-pharmacological interventions such as giving up smoking, taking regular exercise, and eating a prudent diet remain the most appropriate approach.


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