An Analysis of Randomized Trials Evaluating the Effect of Cholesterol Reduction on Total Mortality and Coronary Heart Disease Incidence

Ingar Holme, PhD

The primary aim of this study was to estimate the relation between cholesterol reduction and total mortality and coronary heart disease (CHD) incidence. Secondarily, the clinical issues of whether the efficacy of cholesterol lowering is dependent on the treatment modality, presence of CHD at baseline, or the simultaneous introduction of other interventions was explored. All randomized clinical intervention trials of cholesterol reduction were used in an overview analysis of total mortality rate and CHD incidence; analysis was performed with weighted linear regression. The trials include those that used primary and secondary intervention, diet and drugs, and single or multifactor design. Nineteen trials were analyzed for total mortality, and of the 19, 16 were analyzed for CHD incidence rate. Net difference in cholesterol change between study groups was used as the independent variable, and the three previously mentioned dichotomous design characteristics were used as additional independent variables. For every 1% reduction in cholesterol, an estimated 2.5% reduction in CHD incidence is indicated (95% CI: 1.1, 3.9). With regard to CHD drug trials tended toward better efficiency in cholesterol lowering than did dietary trials. With regard to total mortality, this efficiency was higher in secondary than in primary preventive trials. The efficiency was also somewhat dependent on the baseline cholesterol level. This study shows that cholesterol reduction is effective in lowering CHD incidence, but cholesterol reduction must be at least 8–9% to be effective in lowering total mortality. (Circulation 1990;82:1916–1924)

In the prevention of early occurrence of coronary heart disease (CHD), various strategies have been implemented based on the three most important coronary risk factors, that is, total cholesterol, blood pressure, and cigarette smoking. The evidence of cholesterol lowering as an efficient method of CHD risk reduction has been tested through a series of intervention trials. These include single and multifactor trials, and primary and secondary diet and drug trials.1-19

Two overview analyses have evaluated the effects of cholesterol lowering in clinical trials.20,21 They show that for every 1% cholesterol reduction a 2% CHD risk reduction is achieved. This 1:2 ratio is subsequently referred to as “the cholesterol benefit ratio.” These reviews generally exclude multifactor trials or analyze them separately, and they do not address the question of whether the effect of cholesterol lowering is dependent on design characteristics such as primary and secondary or diet and drug intervention.

The primary aim of this study was to estimate the relation between cholesterol reduction and total mortality and CHD incidence. Secondarily, the clinical issues of whether the efficacy of cholesterol lowering is dependent on the treatment modality, presence of CHD at baseline, or the simultaneous introduction of other interventions was explored. These questions are addressed through an overview analysis of all randomized controlled clinical trials involving designed cholesterol lowering. Total mortality and CHD incidence are the only end points under investigation. Trials with angiographic end points will not be discussed.

Methods

The criteria for inclusion of trials in this overview were 1) designed cholesterol lowering, 2) randomized design, and 3) total mortality or CHD incidence reported as end points. The criteria for exclusion of

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Received June 13, 1989; revision accepted July 10, 1990.
trial end points were 1) termination of trial or trial subgroups because of unforeseen side effects, and 2) data gathered after end of planned trial duration.

Nineteen randomized cholesterol-lowering trials with CHD incidence or total mortality as end points fulfill the inclusion requirements, and they are listed in Table 1.

The trials include both untreated and placebo-treated control groups with open and blinded design. They vary with respect to drugs or diet, primary or secondary intervention, single or multifactor intervention, follow-up period (from 2 to 10 years), age span, and sample sizes (from less than 100 to 50,000). The coronary risk at entry also varies widely between the trials. Because of this heterogeneity, which cannot be totally controlled by statistical modeling, a major random component is bound to be present in such an overview analysis. In the analysis, all trials are equally handled disregarding differences in quality of methods and conduct.

The multifactor trial by Miettinen et al.22 was both a diet and a drug trial in which some intervention group patients received a dietary regimen alone, and others received a drug regimen in addition. For this reason, the trial has been excluded from the analyses. Its inclusion would not have influenced global results noticeably because it reported only a few events.

A particular problem with respect to inclusion and exclusion is present for the Coronary Drug Project,7 which had to discontinue three of its six trial regimens before the scheduled completion of the project. This was due to an excess in fatal complications in the actively treated groups compared with the placebo-treated group. A further technical complication from a statistical point of view is the problem of treating five actively treated groups against only one matching placebo-treated group. All odds ratio statistics for those five trial arms would be dependent and would seriously complicate the overview analysis (see below). The decision was made to exclude the three discontinued groups and only include the pooled results from the niacin- and the clofibrate-treated groups and compare that with the placebo-treated group. It is realized that this procedure probably biases the overview results somewhat by showing a greater benefit from cholesterol lowering on total mortality. However, the alternative of collapsing all treatment arms results in one treatment group would probably also have a biasing effect in the other direction because of the frequent overestimation of effects seen in trials stopped prematurely.

In the Scottish Research Committee Study,6 the data from both blinded and open phases has been included.

The end points used are total mortality and CHD incidence. The definitions of CHD may vary, but fatal and nonfatal acute myocardial infarction including sudden deaths as reported in each trial have been adopted without adjustments. Three trials have not reported CHD incidence data,4,9,15 and they will only be included in the analysis of total mortality. In the trial by Rose et al.,14 probable infarctions are not included as a CHD end point. The morbidity data from the Multiple Risk Factor Intervention Trial (MRFIT) trial23 has been included using electrocardiographic criteria.

Some trials have produced long-term follow-up information after completion of the scheduled trial
period, for instance, the Coronary Drug Project\textsuperscript{24} or the Oslo Study.\textsuperscript{25} It was decided not to include the additional end points in these studies. An argument about increased precision is surely relevant. However, the validity of such data is harder to judge in the context of the relation to cholesterol reduction because the cholesterol difference between treatment groups are no longer fully controlled as in the trial itself.

In all trials, intention-to-treat analysis data have been used whenever a choice appeared. The small trial of Acheson and Hutchinson\textsuperscript{4} has only published on treatment data but is included in this overview. The WHO multiple risk factor trial\textsuperscript{3} used factories as units of randomization, but the odds ratio (OR) for that trial will be treated in the same way as the other person-based randomized trials.

The calculations of net difference in cholesterol levels between treatment groups were reported differently in the various trials. Sometimes percent average differences between baseline and postrandom follow-up values of cholesterol in each group were computed, and then the absolute differences between the groups based on these averages were calculated. In other (most) trials, the difference was calculated as the percent net difference between average postrandom value in each group. The difference between the two methods should be small because of randomization.

**Statistical Analysis**

Each trial was used as a unit for statistical analysis. OR for treatment versus control group was calculated. To obtain an adjusted OR for the entire set of trials, pooling of the various trials by ignoring the independent variables was performed with the Mantel-Haenszel method in the Peto framework with observed and expected cases.\textsuperscript{26} To determine which trials dominate the overview analysis, a radial plot of standardized logOR according to a method of Galbraith\textsuperscript{27} was used (Figure 1). In a radial plot, a regression line through the origin will pass through the global point estimated at the radial segment. The line will be dominated by points with high \( x \) values, that is, high precision. The use of logOR instead of OR overcomes some problems with the interpretation along the OR scale. First, the length of its confidence interval is dependent on the level of OR. This means that with a given sample size a confidence interval around an estimated OR of 1.5, for instance, will be much wider than a confidence interval around an OR of 0.67. This is not the case with a confidence interval of logOR. Second, confidence intervals will be preferably symmetrical on both sides along a logOR scale but not on an OR scale. Third, a unit of change in logOR will give the same percent change at any point of OR. This will not be the case if OR changed.

The logarithm of OR was used as the dependent variable in various weighted linear regression models given below with percent net difference in cholesterol between the treatment groups as one independent variable. The weight used for each trial was the variance of OR, suggested by the fact that the overview logOR can be written as a weighted average of each trial’s logOR where the weights are (relative) variances of OR.\textsuperscript{28} Design characteristics such as single-factor or multifactor, primary or secondary prevention, and diet or drug were defined by three separate dichotomized independent covariates. Interaction terms between cholesterol and the three design variables were defined by multiplying percent cholesterol difference with each binary variable.

The criteria for classifying the various trials with respect to the design characteristics were as follows. Trials aiming at changing other CHD risk factor levels in addition to cholesterol are classified as multifactor trials, whereas trials with cholesterol-lowering alone are classified as single-factor trials. Trials including patients without known cardiovascular disease at baseline are classified as primary preventive trials, whereas all others are classified as secondary preventive trials (mostly on infarction patient populations). Cholesterol reduction by diet alone or by drug (possibly with addition of diet in both treatment groups) distinguishes the diet or drug values.

Average baseline cholesterol (mg/dl), male gender (1–0), and average age at entry (years) were three other independent variables used in some supplementary analyses.

The strategy of analysis was first to search for interactions between cholesterol reduction and each design characteristic. If interactions were not present, this indicates that none of the design characteristics had any modifying effect on the logOR cholesterol relation.

![Figure 1. Radial plot of CHD odds ratio (OR) for all trials from Table 2. Each point has unit standard error in the y-axis direction. OR for each trial is found by extrapolating a line from origin to the global estimate on the circular scale.](image-url)
An example of a model for testing interaction between single-factor or multifactor intervention on the cholesterol and CHD relation is

$$\log \text{OR} = \beta_0 + \beta_1 \Delta \text{cho}l + \beta_2 \Delta \text{cho}l \cdot \text{SM} + \epsilon$$

Usually, a linear term with SM (single-factor or multifactor intervention) would also be included in such a model, but the question raised and the appropriateness of two regression lines (SM=0 or 1) starting at the same point on the y axis makes it undesirable to add such a term. The model fit was not improved by such an addition.

The null hypothesis to be tested first would be $$H_0: \beta_1=0$$. Here, \( \Delta \text{cho}l \) equals percent net difference in cholesterol between treatment groups. SM is 1 for single-factor and 2 for multifactor trials; \( \epsilon \) is an error term. Similarly, the term DD (diet or drug) would be 1 for diet and 2 for drug, whereas the term PS (primary or secondary intervention) would be 1 for primary and 2 for secondary prevention trials. The software package GLIM29 was a practical tool for the analysis.

One would think that if there is no net difference in cholesterol between treatment groups logOR should be zero (neglecting multifactor intervention effects). Therefore, \( \beta_1 \) ought to be zero, a hypothesis that will be tested separately after assessing the final model. If the hypothesis is well accepted, the omission of \( \beta_1 \) seems natural.

The interpretation of the slope \( \beta_1 \) in case of \( \beta_2=0 \) is that it expresses the benefit ratio of cholesterol reduction. That is for every 1% net reduction in cholesterol between treatment groups, a risk reduction of \( \beta_1 \) multiplied by 100% occurs, ignoring the influence of the design variables. The Lipids Research Clinics Program, for instance, claimed \( \beta_1 \times 100\% = 2.0\% \) unadjusted.20

In a supplementary analysis, the ratio logOR/\( \Delta \text{cho}l \) was calculated from each trial and regressed (weighted as before) against the three supplementary baseline variables.

Tests of significance are performed with \( \chi^2 \) tests. A \( \chi^2 \) statistic of residuals between observed and expected cases is computed for the model under the alternative and under the null hypothesis. The difference between the two is the \( \chi^2 \) test statistic for the null hypothesis. Adequacy of model fit was judged by comparing the \( \chi^2 \) residual squared differences between observed and expected end points according to the model with its degrees of freedom, with the realization that these should be about equal in case of a good model fit.

Results

Table 2 presents number of deaths and CHD end points in the various trials of the overview analysis as well as OR and 95% confidence intervals and percent net difference in cholesterol between treatment groups. Total mortality is increased by intervention by about 4±3% compared with control \((p>0.10)\). Likewise, CHD incidence is reduced by about 10±2.5% \((p<0.001)\). This corresponds to a weighted average net difference in cholesterol of 5–6%; that is, the 1:2 CHD benefit ratio of cholesterol reduction is confirmed across all trials. However, the \( \chi^2 \) residual for a model with the constant term alone is far above the number of degrees of freedom \((p<0.01)\), indicating heterogeneity across trials for the CHD end point.

To determine which trials dominate the overview, a radial plot of standardized CHD logOR by its precision measured by \( x=1/SE \) logOR was developed (Figure 1). The larger the \( x \), the greater the dominance of the drawn regression line through origin and global estimate on the radial segment. Each estimate has unit standard error on the y axis. Six trials in the figure dominate the regression line because of their high precision, and their influence somewhat reduces the beneficial effects of cholesterol lowering compared with the trend in the other trials.

Relation to the Degree of Cholesterol Reduction

Total mortality. Even if cholesterol reduction could not be shown to significantly reduce total mortality in all trials combined, Figure 2 shows that it is associated with a weak downward trend in total mortality. The figure suggests that the treatments used in these trials may have a small adverse effect on mortality when cholesterol levels are not reduced and that cholesterol lowering appears to offset this effect.

Table 3 shows the regression coefficients with standard errors and \( \chi^2 \) error term for the models that test interaction between cholesterol reduction and design characteristics with respect to total mortality. Model 1 presents estimated coefficients for percent net difference in cholesterol without interaction terms, and models 2, 3, and 4 give the cholesterol interaction coefficient for each particular design characteristic. The fit was not quite good for models 1 and 2, indicating that some important, unexplained variation is omitted. The question of a different efficacy of cholesterol lowering by diet or drugs is not supported by the data in model 2, which shows no sign of an interaction effect. However, in model 3, the interaction term for primary or secondary intervention is of borderline significance \((Z=1.97, p=0.05)\), and the model fits very well with its degrees of freedom. This indicates that secondary preventive trials have shown a stronger relation between total mortality reduction and cholesterol lowering than have primary preventive trials, an observation not unexpected when one considers the dominance of CHD deaths in secondary preventive trials.

Single-factor or multifactor trials could not be shown to have different regression slopes because the interaction term in model 4 was not significant \((Z=1.34, \text{NS})\). With regard to the effect of cholesterol lowering on total mortality, multifactor trials showed a weak tendency to be more efficient than
Table 2.  Number of Deaths and Instances of Coronary Heart Disease, Odds Ratios and 95% Confidence Intervals, and Percent Difference in Cholesterol Levels Between Treatment Groups

<table>
<thead>
<tr>
<th>Study</th>
<th>$n$</th>
<th>Death T/C</th>
<th>CHD T/C</th>
<th>CHD OR</th>
<th>95% CL</th>
<th>CHD OR</th>
<th>95% CL</th>
<th>%ΔChol</th>
<th>Z logOR</th>
<th>logOR±SE logOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRFIT</td>
<td>6,428/6,438</td>
<td>265/267</td>
<td>277/280</td>
<td>1.021</td>
<td>1.217</td>
<td>0.990</td>
<td>1.173</td>
<td>2</td>
<td>-0.12</td>
<td>-0.01±0.087</td>
</tr>
<tr>
<td>Hjermann et al</td>
<td>604/628</td>
<td>16/24</td>
<td>19/36</td>
<td>0.693</td>
<td>1.289</td>
<td>0.534</td>
<td>0.951</td>
<td>10</td>
<td>-2.13</td>
<td>-0.627±0.294</td>
</tr>
<tr>
<td>WHO fact</td>
<td>24,615/25,169</td>
<td>997/924</td>
<td>773/756</td>
<td>1.103</td>
<td>1.213</td>
<td>1.047</td>
<td>1.156</td>
<td>1</td>
<td>0.91</td>
<td>0.046±0.051</td>
</tr>
<tr>
<td>Acheson &amp; Hutchinson</td>
<td>47/48</td>
<td>23/20</td>
<td>...</td>
<td>1.174</td>
<td>2.987</td>
<td>...</td>
<td>...</td>
<td>9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Carlson et al</td>
<td>279/279</td>
<td>24/26</td>
<td>41/62</td>
<td>0.923</td>
<td>1.950</td>
<td>0.603</td>
<td>0.979</td>
<td>17</td>
<td>-2.05</td>
<td>-0.506±0.247</td>
</tr>
<tr>
<td>RC of Scottish Society</td>
<td>264/273</td>
<td>34/38</td>
<td>59/76</td>
<td>0.934</td>
<td>1.520</td>
<td>0.778</td>
<td>1.131</td>
<td>14</td>
<td>-1.31</td>
<td>-0.251±0.191</td>
</tr>
<tr>
<td>Coronary Drug Project</td>
<td>2,222/2,789</td>
<td>554/709</td>
<td>596/839</td>
<td>0.981</td>
<td>1.108</td>
<td>0.892</td>
<td>0.990</td>
<td>8</td>
<td>-2.15</td>
<td>-0.114±0.053</td>
</tr>
<tr>
<td>Newcastle upon Tyne</td>
<td>244/253</td>
<td>27/48</td>
<td>55/89</td>
<td>0.583</td>
<td>0.883</td>
<td>0.646</td>
<td>0.897</td>
<td>13</td>
<td>-2.60</td>
<td>-0.437±0.168</td>
</tr>
<tr>
<td>Dorr et al</td>
<td>1,149/1,129</td>
<td>37/48</td>
<td>...</td>
<td>0.751</td>
<td>1.158</td>
<td>...</td>
<td>...</td>
<td>10</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dayton et al</td>
<td>424/422</td>
<td>174/177</td>
<td>60/88</td>
<td>0.978</td>
<td>1.267</td>
<td>0.682</td>
<td>0.941</td>
<td>13</td>
<td>-2.34</td>
<td>-0.383±0.164</td>
</tr>
<tr>
<td>Leren</td>
<td>206/206</td>
<td>44/51</td>
<td>61/81</td>
<td>0.764</td>
<td>1.237</td>
<td>0.755</td>
<td>1.049</td>
<td>14</td>
<td>-1.68</td>
<td>-0.281±0.167</td>
</tr>
<tr>
<td>MRC12</td>
<td>199/194</td>
<td>28/32</td>
<td>40/39</td>
<td>0.853</td>
<td>1.437</td>
<td>1.000</td>
<td>1.553</td>
<td>16</td>
<td>0</td>
<td>0.000±0.225</td>
</tr>
<tr>
<td>MRC13</td>
<td>123/129</td>
<td>20/24</td>
<td>43/44</td>
<td>0.874</td>
<td>1.627</td>
<td>1.038</td>
<td>1.560</td>
<td>6</td>
<td>0.18</td>
<td>0.037±0.208</td>
</tr>
<tr>
<td>Rose et al</td>
<td>54/26</td>
<td>6/1</td>
<td>13/4</td>
<td>2.890</td>
<td>12.669*</td>
<td>1.744</td>
<td>4.097</td>
<td>4</td>
<td>1.28</td>
<td>0.556±0.436</td>
</tr>
<tr>
<td>Woodhill et al</td>
<td>231/237</td>
<td>39/28</td>
<td>...</td>
<td>1.429</td>
<td>2.553</td>
<td>...</td>
<td>...</td>
<td>5</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LRC-CPPT</td>
<td>1,906/1,900</td>
<td>68/71</td>
<td>155/187</td>
<td>0.955</td>
<td>1.337</td>
<td>0.811</td>
<td>1.022</td>
<td>9</td>
<td>-1.78</td>
<td>-0.210±0.118</td>
</tr>
<tr>
<td>WHO (clofibrate)</td>
<td>5,331/5,296</td>
<td>128/87</td>
<td>167/208</td>
<td>1.462</td>
<td>1.921</td>
<td>0.791</td>
<td>0.977</td>
<td>9</td>
<td>-2.18</td>
<td>-0.235±0.108</td>
</tr>
<tr>
<td>Frick et al16</td>
<td>2,051/2,030</td>
<td>45/42</td>
<td>56/83</td>
<td>1.060</td>
<td>1.624</td>
<td>0.658</td>
<td>0.936</td>
<td>10</td>
<td>-2.33</td>
<td>-0.419±0.180</td>
</tr>
<tr>
<td>Frantz et al</td>
<td>4,922/4,853</td>
<td>268/256</td>
<td>134/129</td>
<td>1.034</td>
<td>1.233</td>
<td>1.304</td>
<td>1.304</td>
<td>13</td>
<td>0.20</td>
<td>0.025±0.123</td>
</tr>
<tr>
<td>Total</td>
<td>1.037</td>
<td>1.096</td>
<td>0.981</td>
<td>0.858</td>
<td></td>
<td>0.905</td>
<td>0.954</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Uncertain due to small numbers.

logOR±SE logOR and Z score added for CHD.

CHD, coronary heart disease; OR, odds ratio.

single factor trials, but model fit is also somewhat poorer in this case.

CHD incidence. Figure 3 displays the relation between CHD logOR and percent net difference in cholesterol reduction. The estimated $\beta_3$ term of the linear model with net cholesterol difference alone is 0.061±0.052 (NS). Table 4 shows the model estimates with and without interaction terms for CHD incidence. The coefficient for cholesterol difference between treatment groups is highly significant in model 1 ($Z=4.1, p<0.001$), but the model fit is not quite satisfactory. For all trials combined, a benefit ratio of cholesterol lowering is estimated to be 1:2.5 with 95% confidence interval ranging from 1.1 to 3.9. In model 2, the fit is better, and the interaction term for diet and drug terms approaches statistical significance ($Z=1.74, p=0.08$). This may indicate that drug trials are more efficient than dietary trials in reducing CHD incidence by cholesterol lowering. Unlike the reduction of total mortality, reduction of CHD inci-
dence by cholesterol lowering does not seem to differ between primary and secondary trials. Also, single-factor and multifactor trials did not differ significantly in this respect.

A supplementary analysis was performed to search for possible covariates to the variation in the cholesterol benefit ratio. This was achieved by regressing the ratio (weighted) between CHD logOR and ΔChol in each trial against the variables of baseline cholesterol level, baseline age, and whether the trial was conducted in male patients (see Table 1). Figure 4 presents a plot of the relation to baseline cholesterol. The Y variable, which should be an estimate of $\beta_1$, shows a clear downward trend in reducing CHD incidence by starting with an increased level of cholesterol, that is, an increasing efficiency of cholesterol lowering ($p<0.001$). Table 5 gives details of the equations for each of the three independent variables. Neither age nor all-male trials showed a significant relation to the cholesterol benefit ratio.

**Discussion**

Between-trial comparisons will always suffer from a series of methodological shortcomings due to differences in protocols, quality of conduct, incomplete reporting, and so on. Despite these limitations, the overview analysis showed that a substantial amount of the heterogeneity in the trial outcomes on CHD was attributable to the cholesterol reduction attained by their participants. The model fits indicated also that the remaining variability could be attributable to chance. In fact, the weighted regression line had an intercept close to zero, which is consistent with the hypothesis of no CHD risk reduction if not preceded by a cholesterol reduction.

The LRC-CPPT reported that for every 1% cholesterol reduction one should expect a 2% CHD risk reduction. This was evident from an overview analysis of long-term epidemiological follow-up studies, between-trial comparisons, and for various end points in that trial. Epidemiological follow-up studies usually operate with a single baseline measurement of cholesterol. Therefore, the slope of the regression should be multiplied by $1/r$ due to measurement errors, individual short-term variations, and so on, where $r$ is the correlation coefficient between two independent cholesterol readings (taken for the same individual some time apart). For cholesterol, $r$ is approximately 0.70, so the ratio of 1:2 should be 1:3 as reported by MacMahon et al. The crude estimate of the CHD benefit ratio in this overview was 1:2.5 with a 95% confidence interval ranging from 1.1 to 3.9. The breadth of this interval reflects the major impact of uncontrolled variability in this type of analysis. However, the supplementary analyses showed that the efficiency of CHD preven-

**FIGURE 2.** Plot of log odds ratio (OR) of total mortality by percent net difference in cholesterol (ΔCHOL) with weighted regression line. All trials.

**Table 3.** Estimated Regression Coefficients (SE) for Total Mortality in Four Models for Testing Interaction Between Cholesterol Reduction and Design Characteristics Including All Trials With Model $\chi^2$ Residual and Degrees of Freedom

<table>
<thead>
<tr>
<th>Model</th>
<th>Constant $\beta_0$</th>
<th>$\Delta$Chol $\beta_1$</th>
<th>$\Delta$Chol · DD $\beta_2$</th>
<th>$\Delta$Chol · PS $\beta_3$</th>
<th>$\Delta$Chol · SM $\beta_4$</th>
<th>$\chi^2$</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.105 (0.048)</td>
<td>-0.011 (0.006)</td>
<td></td>
<td></td>
<td></td>
<td>20.1</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>0.106 (0.050)</td>
<td>-0.008 (0.013)</td>
<td>-0.002 (0.008)</td>
<td></td>
<td></td>
<td>20.0</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>0.104 (0.045)</td>
<td>+0.010 (0.012)</td>
<td>-0.014 (0.007)</td>
<td></td>
<td></td>
<td>16.2</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>0.157 (0.061)</td>
<td>+0.027 (0.029)</td>
<td></td>
<td>-0.043 (0.032)</td>
<td></td>
<td>18.0</td>
<td>16</td>
</tr>
</tbody>
</table>

DD, drug/diet; PS, primary/secondary preventive; SM, single-factor/multifactor trials.
tion by cholesterol lowering could be dependent on the baseline level of cholesterol. At 240 mg/dl cholesterol, the estimate of $\beta_1$ was 0.0068 but was $-0.036$ at 280 mg/dl cholesterol. These estimates still have wide confidence intervals and should be interpreted with care. The relation to age at baseline was nonexistent within the age span observed; that is, cholesterol lowering did not seem to be less efficient in reducing CHD incidence in higher than in lower age groups. A weak tendency for all-male trials to show a more efficient relation between cholesterol lowering and CHD prevention than the trials with both sexes could be seen, but this issue cannot be answered with these data.

A word of caution should be given because these discussions are only relevant for small and moderate cholesterol reductions starting from (mostly) elevated levels in a rather short-term perspective. The $1:2.5$ ratio will hardly be valid for drastic cholesterol reductions (above 20%) in the “normal” population. Also, preferential publication of positive trial results is a problem inherent in such a discussion.

The data indicate that cholesterol lowering by drugs more effectively reduced CHD incidence than did that by diet. Strong contributors to that indication are the dominant Frantz and MRFIT trial results. Also, drug trials are performed more often in patients at high risk of CHD than are dietary trials that “should” provide a better reduction CHD incidence. Any significant effect on total mortality, however, could not be traced.

Primary or secondary preventive trials did not significantly differ with respect to the efficiency of cholesterol lowering on CHD incidence. This is consistent with the notion that the distinction between primary and secondary intervention is rather artificial. What is really aimed at in these trials is a reduction in the progression or a regression of atherosclerosis in these patients, and average degree of atherosclerosis was probably not much different for patients in the two types of trials.

Single-factor and multifactor trials also show some slight tendency toward a difference in cholesterol-reduction slopes; that is, multifactor trials are more

![Graph](image-url)

**Figure 3.** Plot of log odds ratio (OR) of coronary heart disease (CHD) incidence according to percent net difference in cholesterol ($\Delta$CHOL) with weighted regression line. All trials with CHD incidence data included ($n=16$).

<table>
<thead>
<tr>
<th>Model</th>
<th>$\beta_0$</th>
<th>$\Delta$Chol</th>
<th>$\Delta$Chol · DD</th>
<th>$\Delta$Chol · PS</th>
<th>$\Delta$Chol · SM</th>
<th>$\chi^2$</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.061 (0.052)</td>
<td>$-0.025$ (0.006)</td>
<td>$\beta_2$</td>
<td>$\beta_2$</td>
<td>0.003 (0.008)</td>
<td>$0.040$ (0.027)</td>
<td>14.5</td>
</tr>
<tr>
<td>2</td>
<td>0.065 (0.048)</td>
<td>$-0.005$ (0.013)</td>
<td>$-0.012$ (0.007)</td>
<td>14.0</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.063 (0.053)</td>
<td>$-0.029$ (0.014)</td>
<td>16.8</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.110 (0.059)</td>
<td>$-0.011$ (0.025)</td>
<td>14.5</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DD, drug/diet; PS, primary/secondary preventive; SM, single-factor/multifactor trials.
effective than single-factor trials with regard to cholesterol reduction. However, statistical significance was not reached on a conventional level.

A finding in this study was that total mortality logOR was lower in secondary than in primary preventive trials, adjusting for cholesterol reduction, but this was not seen for the CHD end point. Patients in secondary prevention trials have a much higher probability of dying from CHD than those in primary preventive trials. Thus, for total mortality, there is a built-in “advantage” for secondary prevention trials of cholesterol lowering, assuming that non-CHD end points do not counterbalance the beneficial effects more in secondary than in primary prevention.

The history of cholesterol-lowering trials have shown that they have not been without specific excess hazards on the part of the participating patients. The most dramatic side effect was seen in the WHO clofibrate trial where total mortality was increased by 35% in the treated compared with the control group. The global estimate from all trials of logOR in total mortality was positive despite an overall 6% cholesterol reduction across trials. The adjusted analysis showed that total mortality logOR was significantly above zero without cholesterol reduction. Thus, to be of benefit, cholesterol lowering should have been at least 8–9% to outweigh the hazards involved, assuming that the hazards are not dose-response dependent of the cholesterol-lowering drug regimen. Hopefully, the future experience with new drugs and strategies will show improvements.

Summary Conclusions

The 1:2 benefit ratio of percent cholesterol lowering on CHD incidence may be a slight underestimate according to this across-trial overview analysis that adjusted for design characteristics. Cholesterol lowering seems equally effective in primary and secondary trials but is possibly more effective in drug than in dietary trials with CHD as an end point.

What was gained by cholesterol lowering with respect to CHD risk reduction was mostly lost on other fatal end points so that at least 8–9% chole-

![Figure 4](image_url)

**FIGURE 4.** Plot of coronary heart disease (CHD) cholesterol benefit ratio (logOR/Δchol) by baseline cholesterol level (chol). All trials with CHD end point except Frantz et al19 are included (n=15).

**TABLE 5.** Regression Equations (Weighted by Reciprocal of logOR Variance) Between Cholesterol Benefit Ratio (logOR/ΔChol) and Three Independent Variables: Trials with Coronary Heart Disease End Points, Excluding the Frantz et al19 Trial

<table>
<thead>
<tr>
<th>Model</th>
<th>Constant (γ0)</th>
<th>Baseline cholesterol (γ1)</th>
<th>Baseline age (γ2)</th>
<th>Male trial (γ3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.264 (0.055)</td>
<td>-0.00107 (0.00022)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-0.012 (0.065)</td>
<td></td>
<td></td>
<td>-0.00019 (0.0013)</td>
</tr>
<tr>
<td>3</td>
<td>-0.021 (0.032)</td>
<td></td>
<td></td>
<td>0.024 (0.033)</td>
</tr>
</tbody>
</table>

*p<0.001
terol reduction had to take place before an associated reduction of total mortality was indicated.

Acknowledgments

I thank professors Paul Leren and Knut Westlund and Dr. Ingvar Hjermann for helpful suggestions and advice during the preparation of this paper. Also, I thank the reviewers and editors of Circulation for their valuable help in preparing this manuscript.

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Key Words • total mortality • coronary heart disease • cholesterol • clinical trials
An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence.

I Holme

Circulation. 1990;82:1916-1924
doi: 10.1161/01.CIR.82.6.1916

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