OBJECTIVES

This study sought to determine whether statins reduce coronary heart disease (CHD) risk more than other interventions that also primarily lower low-density lipoprotein cholesterol (LDL-C).

BACKGROUND

Statins have anti-inflammatory, immunomodulatory, antithrombotic, vascular, and other non-LDL-C-lowering effects. It is unclear whether these pleiotropic effects contribute to cardiovascular risk reduction beyond that expected from LDL-C reduction alone.

METHODS

Trials published in English language journals were retrieved by searching Medline (1966 to October 2004), bibliographies, and the author's reference files. Randomized, placebo-controlled trials of interventions to primarily lower LDL-C of three or more years' duration in which clinical disease or death were primary outcomes were used. Information on sample size, treatment type and duration, participant characteristics at baseline, reduction in lipids, and outcome was independently abstracted by two authors (J.R. and N.M.) using a standardized protocol. Data from 5 diet, 3 bile acid sequestrant, 1 surgery, and 10 statin trials, with 81,859 participants, were included in the CHD meta-regression analysis.

RESULTS

The regression lines for non-statin and statin trials were similar and consistent with a one-to-one relationship between LDL-C lowering and CHD and stroke reduction over five years of treatment.

CONCLUSIONS

The pleiotropic effects of statins do not seem to contribute an additional cardiovascular risk reduction benefit beyond that expected from the degree of LDL-C lowering observed in other trials that primarily lowered LDL-C. (J Am Coll Cardiol 2005;46:1855–62) © 2005 by the American College of Cardiology Foundation

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Randomized, controlled trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, consistently demonstrate 25% to 40% reductions in cardiovascular events with 25% to 35% reductions in low-density lipoprotein cholesterol (LDL-C). Statins have effects other than LDL-C lowering, and some have suggested that these pleiotropic effects may provide a cardiovascular benefit beyond that expected from LDL-C lowering alone (1,2). The non–LDL-C-lowering effects of statins include other lipid (3,4), anti-inflammatory and immunomodulatory (5–10), antithrombotic (11,12), and vascular effects (13,14), which may vary by statin (15–19). This analysis explores whether statins, individually and as a class, reduce cardiovascular risk more than expected for the degree of LDL-C reduction when compared with non-statin approaches to lipid lowering.

METHODS

Data were abstracted from articles reporting the results of clinical trials evaluating the effect of LDL-C lowering on cardiovascular events. Articles were identified by a literature search of the Medline database (1966 to October 24, 2004), English language journals, a manual search of the author's reference files, and reference lists of original articles, reviews, and meta-analyses. The literature search identified 125 abstracts or full-text articles, which were reviewed to determine whether they met the criteria for inclusion (Fig. 1). Information on sample size, treatment type and duration, participant characteristics at baseline, reduction in lipids, and outcomes was independently abstracted by two authors (J.R. and N.M.) using a standardized protocol and reporting form. Disagreements were resolved by consensus. Authors were not contacted for additional study information.

For inclusion in the primary meta-analyses, a study must have met these criteria: 1) random, blinded (except for diet...
studies) allocation of study participants to treatment or control group; 2) a single predominantly LDL-C-lowering treatment was compared with placebo; 3) intervention duration of over two years; 4) primary outcomes of the trial were clinical events; and 5) non-fatal myocardial infarction (MI), coronary heart disease (CHD) death, and fatal and non-fatal ischemic stroke were primary or secondary outcomes.

Relative risk reductions and percent change in LDL-C were used. In the statin trials, relative risk reductions have been shown to be homogenous across studies of primary and secondary prevention populations with a range of baseline LDL-C levels, although absolute risk reductions vary substantially depending on baseline population risk (20,21). Similarly, percent change in LDL-C levels in these studies was homogeneous across a wide range of initial cholesterol levels.

Mean intent-to-treat LDL-C and total cholesterol levels were generally reported at only one time point during a trial. The mean percent LDL-C reduction was calculated from the LDL-C level in the intent-to-treat group compared with the level in the placebo after one or two years of follow-up, depending on the data reported. Because LDL-C was not reported for the diet trials, LDL-C reduction was estimated to be approximately 13% greater than the total cholesterol reduction based on more recent, large diet intervention trials (22,23) with similar percent total cholesterol reductions as the older diet trials.

Because relative risks were not consistently reported across studies, the study-specific relative risks and associated standard errors were estimated from the published total number of subjects and incident cases in the treatment and control groups for: 1) non-fatal MI and CHD death, and 2) fatal and non-fatal ischemic stroke. These end points were chosen as representative of hard cardiovascular end points. Coronary revascularization and unstable angina diagnoses were excluded because of greater temporal and regional variability in use and classification (24,25). With the exception of two trials (26,27), a diagnosis of definite or probable non-fatal MI or CHD death was based on protocol-defined criteria with blinded adjudication by an independent committee (28–40) or study investigators (41–44). The Scandinavian Simvastatin Survival Study (31) also included silent MIs. Because data for the separate hard CHD end points were not available for the Air Force/Texas Coronary Atherosclerosis Prevention Study (45), the primary end point was used, which included non-fatal and fatal MIs and unstable angina. Only the statin trials reported non-fatal and fatal stroke events, which were centrally adjudicated in a blinded fashion according to clinical and imaging criteria.

**Figure 1.** Flow diagram and trials excluded from the primary meta-analysis. CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; RCT = randomized controlled trial.

### Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
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<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>PROSPER</td>
<td>PROspective Study of Pravastatin in the Elderly at Risk</td>
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<tr>
<td>PROVE-IT</td>
<td>Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22</td>
</tr>
<tr>
<td>TNT</td>
<td>Treating to New Targets</td>
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**Statistical methods.** Separate meta-analyses were conducted to estimate the effects of: 1) LDL-C reduction from statins compared with non-statin interventions (diet, bile-acid sequestrant, and surgery) on the risk of non-fatal MI or CHD death, and 2) LDL-C reduction from statins on the risk of non-fatal and fatal stroke. A random effects model was used for the meta-analyses. The natural log-transformed relative risk was modeled as a linear function of the study-specific mean change in LDL cholesterol and mean length of follow-up. Gaussian errors were specified for the meta-analysis model as a combination of the within-study and between-study variation. The study-specific standard errors for the estimated relative risks were used to model the within-study variation. Between-study variation was estimated in the analysis. Bayesian methods were used to fit the random-effects meta-analysis models (46). The Bayesian approach was chosen over conventional, frequentist approaches because the former: 1) allows for the explicit quantification of prior knowledge and subsequent integration with new empirical data, 2) provides an estimate of the posterior distribution of all model parameters, and 3) yields summary statistics, such as the Bayes factor, which have natural, clinical interpretations (47,48). In contrast, a frequentist approach relies on asymptotic statistical theory to derive
only mean and variance estimates for the model parameters, which are not as informative as the posterior estimates from a Bayesian analysis. Furthermore, the p value, computed in frequentist approaches, is often misinterpreted in practice and problematic as an inferential tool. Note that the p value is defined as the probability of obtaining the observed data or more extreme, unobserved data given that the null hypothesis is true. However, what is often desired in practice is a measure of the probability that the null (or alternative) hypothesis is true given the observed data. The Bayes factor provides a way to measure this desired probability. Specifically, this analysis reports the Bayes factor as the probability of the published data under the alternative hypothesis relative to the probability under the null hypothesis. For this application, the null hypothesis was that the effect of LDL-C is the same between statin and non-statin trials versus the alternative hypothesis that the effect differs between the two. To obtain the relative probability of the alternative hypothesis given the data, one simply multiplies the Bayes factor by the prior odds that the alternative hypothesis is true. The prior odds represents one’s belief that the alternative is true before any new empirical data. In this analysis, a prior odds of unity is assumed to indicate no prior preference for the null or alternative hypothesis. Likewise, vague prior specifications were used for all regression parameters in the Bayesian analyses. The models were fit with the WinBUGS statistical software (49), and the methods of Chib (50) were used to compute the Bayes factor.

The final regression results were examined for evidence of a one-to-one relationship between LDL-C reduction and percent CHD risk reduction, as suggested in the literature (51). Sensitivity analyses evaluated whether statin trials that did not meet the inclusion criteria and were of at least two years’ duration showed a similar relationship between LDL-C reduction and CHD death and non-fatal MI and stroke as the included trials (17,52–66). These trials included those trials without CHD as the primary end point (e.g., angiographic or ultrasound changes were primary end points) or active or usual care control groups with CHD and stroke end points. Studies of 2 or more years’ duration were included because the majority of the reduction in relative risk was achieved over 2.1 to 5 years of treatment, whereas after 1 year of treatment, less than one-third of the eventual risk reduction had been achieved (67).

RESULTS

Five trials of diet (26,41–44), 3 trials of bile acid sequestrants (27–29), 1 trial of surgery (30), and 10 trials of statin treatment (31,32,34,36,38–40,45,68,69) met the inclusion criteria and were included in the main analysis of the CHD data. Nine of the statin trials were included in the main analysis of the stroke data (31,32,39,40,45,69–72) (Table 1). The CHD analysis included 81,859 participants, and the stroke analysis included 70,300 participants from both primary and secondary prevention populations.

The Bayes factor comparing the estimated effect of LDL-C on MI or CHD death between the statin and non-statin trials was $7.3 \times 10^{-6}$. This Bayes factor is defined in the Statistical Methods section as the probability that the effect of LDL-C differs between statin and non-statin trials relative to the probability that the effect is the same, given the published data. Thus, the value of $7.3 \times 10^{-6}$ provides very strong evidence that there is no difference between the statin and non-statin trials included in our analysis, assuming a prior probability distribution that assigns equal weight to the two hypotheses. The estimated effect of LDL-C reduction on the five-year risk of CHD death or non-fatal MI for the combined statin and non-statin trials is plotted, along with the associated 95% probability interval (Fig. 2). The regression line for the statin and non-statin trials and the line corresponding to a one-to-one relationship between LDL-C reduction and CHD risk are not significantly different because the latter is contained within the 95% probability interval. The 95% confidence intervals of all individual diet, bile acid sequestrant, surgery, and statin trials also include the one-to-one line; trials of primary and secondary prevention populations did not differ.

The estimated effect of LDL-C reduction on the five-year risk of stroke is plotted in Figure 3. The 95% probability interval for the estimated regression line for the stroke data also contains the line representing a one-to-one relationship between LDL-C reduction and percent risk reduction. The 95% probability intervals for the individual statin trials with both primary and secondary prevention populations, with the exception of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) (69) study, also include the one-to-one line.

The sensitivity analysis of excluded statin trials of more than two years’ duration that did not have cardiovascular events as the primary end points, or that had had an active or usual-care control group, had a CHD regression line that did not significantly differ from the one-to-one line (not shown). Likewise, a significant difference from the one-to-one line was not observed for the stroke data from the excluded trials (52,53,55–57,60,61,63,65,66).

COMMENT

This meta-regression analysis found that the non-statin (diet, bile acid sequestrants, and ileal bypass surgery) and statin interventions seemed to reduce CHD risk in a similar manner, consistent with the one-to-one relationship with the degree of LDL-C lowering described by the National Cholesterol Education Program Adult Treatment Panel (51). These results provided no significant evidence to suggest the pleiotropic effects of statins, either as a class or individually, contributed additional CHD risk reduction beyond that expected from the degree of LDL-C lowering seen in the non-statin trials over approximately five years.

Both statins and diet have been shown to reduce inflammatory markers, although by varying degrees (73–75). It is unclear whether such changes are mediated through reduced
### Table 1. Characteristics of Randomized, Controlled Cholesterol-Lowering Trials Meeting Entry Criteria for Primary Meta-Regression Analyses

<table>
<thead>
<tr>
<th>Study/Type</th>
<th>Year</th>
<th>Intervention</th>
<th>Population</th>
<th>Total, n</th>
<th>Mean Follow-Up, yrs</th>
<th>Baseline LDL-C, Mean, mg/dl</th>
<th>LDL-C, % Reduction</th>
<th>Non-Fatal MI/CHD, Death, % Reduction (95% CI)</th>
<th>Stroke, % Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td></td>
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</tr>
<tr>
<td>London hospitals (41)</td>
<td>1965</td>
<td>Low-fat diet</td>
<td>CHD, men only</td>
<td>264</td>
<td>3</td>
<td>179*</td>
<td>11*</td>
<td>3 (−54 to 39)</td>
<td></td>
</tr>
<tr>
<td>Oslo (42)</td>
<td>1966</td>
<td>PUFA</td>
<td>CHD, men only</td>
<td>458</td>
<td>5</td>
<td>200*</td>
<td>16*</td>
<td>25 (−10 to 48)</td>
<td></td>
</tr>
<tr>
<td>MRC (43)</td>
<td>1968</td>
<td>Soy oil</td>
<td>CHD, men only</td>
<td>393</td>
<td>4</td>
<td>185*</td>
<td>18*</td>
<td>16 (−32 to 46)</td>
<td></td>
</tr>
<tr>
<td>Los Angeles (44)</td>
<td>1969</td>
<td>PUFA</td>
<td>High-risk primary, men only</td>
<td>846</td>
<td>5</td>
<td>158*</td>
<td>17*</td>
<td>17 (−29 to 46)</td>
<td></td>
</tr>
<tr>
<td>Sydney (26)</td>
<td>1978</td>
<td>PUFA</td>
<td>CHD, men only</td>
<td>458</td>
<td>5</td>
<td>192*</td>
<td>4*</td>
<td>−65 (−185 to 4)</td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td></td>
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<tr>
<td>Upjohn (27)</td>
<td>1978</td>
<td>Colestipol</td>
<td>Primary and CVD</td>
<td>2,278</td>
<td>3</td>
<td>214*</td>
<td>13*</td>
<td>38 (−11 to 65)</td>
<td></td>
</tr>
<tr>
<td>NHLBI (28)</td>
<td>1984</td>
<td>Cholestyramine</td>
<td>CHD</td>
<td>116</td>
<td>5</td>
<td>236</td>
<td>21</td>
<td>53 (−44 to 85)</td>
<td></td>
</tr>
<tr>
<td>LRC (29)</td>
<td>1984</td>
<td>Cholestyramine</td>
<td>Moderate-risk primary, men only</td>
<td>3,806</td>
<td>5</td>
<td>216</td>
<td>13</td>
<td>17 (−9 to 37)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POSCH (30)</td>
<td>1998</td>
<td>Ileal bypass</td>
<td>CHD</td>
<td>838</td>
<td>5</td>
<td>179</td>
<td>38</td>
<td>31 (−1 to 53)</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S (31)</td>
<td>1994</td>
<td>Simvastatin</td>
<td>CHD</td>
<td>4,444</td>
<td>5.4</td>
<td>188</td>
<td>35</td>
<td>31 (21 to 39)</td>
<td>29 (2 to 48)</td>
</tr>
<tr>
<td>WOSCOPS (32)</td>
<td>1995</td>
<td>Pravastatin</td>
<td>High-risk primary, men only</td>
<td>6,595</td>
<td>4.9</td>
<td>192</td>
<td>26</td>
<td>30 (15 to 43)</td>
<td>10 (−34 to 40)</td>
</tr>
<tr>
<td>CARE (68,70)</td>
<td>1996</td>
<td>Pravastatin</td>
<td>CHD</td>
<td>4,159</td>
<td>5</td>
<td>139</td>
<td>28</td>
<td>23 (7 to 36)</td>
<td>32 (2 to 52)</td>
</tr>
<tr>
<td>LIPID (34,71)</td>
<td>1998</td>
<td>Pravastatin</td>
<td>CHD</td>
<td>9,014</td>
<td>6.1</td>
<td>150</td>
<td>25</td>
<td>22 (13 to 31)</td>
<td>17 (−2 to 33)</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS (45)</td>
<td>1998</td>
<td>Lovastatin</td>
<td>Moderate-risk primary</td>
<td>6,605</td>
<td>5.2</td>
<td>150</td>
<td>26.5</td>
<td>37 (20 to 50)</td>
<td>90 (−83 to 99)‡</td>
</tr>
<tr>
<td>HPS (36,72)</td>
<td>2002</td>
<td>Simvastatin</td>
<td>CHD, CVD, diabetes</td>
<td>20,536</td>
<td>5</td>
<td>131†</td>
<td>30</td>
<td>26 (19 to 32)</td>
<td>24 (14 to 33)</td>
</tr>
<tr>
<td>PROSPER (69)</td>
<td>2002</td>
<td>Pravastatin</td>
<td>Elderly, primary and CVD</td>
<td>5,804</td>
<td>3.2</td>
<td>147</td>
<td>27</td>
<td>17 (5 to 30)</td>
<td>−4 (−33 to 19)</td>
</tr>
<tr>
<td>ALERT (38)</td>
<td>2003</td>
<td>Fluvastatin</td>
<td>Renal transplant, primary, CHD and CVD</td>
<td>2,102</td>
<td>5.1</td>
<td>159</td>
<td>32</td>
<td>25 (−2 to 44)</td>
<td></td>
</tr>
<tr>
<td>ASCOT-LLA (39)</td>
<td>2003</td>
<td>Atorvastatin</td>
<td>High-risk primary, CVD</td>
<td>10,305</td>
<td>3.3</td>
<td>133</td>
<td>35</td>
<td>35 (17 to 50)</td>
<td>27 (4 to 45)</td>
</tr>
<tr>
<td>CARDS (40)</td>
<td>2004</td>
<td>Atorvastatin</td>
<td>Diabetes</td>
<td>2,838</td>
<td>3.9</td>
<td>117</td>
<td>40</td>
<td>35 (5 to 56)</td>
<td>41 (−2 to 66)</td>
</tr>
</tbody>
</table>

*LDL-C was not measured in these trials. LDL-C was estimated as approximately 68% of total cholesterol. LDL-C reduction was estimated as 14% greater than total cholesterol reduction. †Direct LDL-C measurement. LDL-C estimated by Friedewald equation, 150 to 155 mg/dl. ‡Stroke events in the treatment group /H11005 0; standard error was calculated using stroke events /H11005 0.5.

**Notes:**
- AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study;
- ALERT = Assessment of LEscol in Renal Transplantation;
- ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm;
- CARDS = Collaborative Atorvastatin Diabetes Study;
- CARE = Cholesterol and Recurrent Events study;
- CHD = coronary heart disease;
- CI = confidence interval;
- CVD = other cardiovascular disease such as stroke, transient ischemic attack, or peripheral arterial disease;
- HPS = Heart Protection Study;
- LDL-C = low-density lipoprotein cholesterol;
- LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease;
- LRC = Lipid Research Clinics;
- MI = myocardial infarction;
- MRC = Medical Research Council;
- NHLBI = National Heart, Lung, and Blood Institute;
- POSCH = Program on the Surgical Control of the Hyperlipidemias;
- primary = primary prevention, no known CHD, CVD, or diabetes;
- PROSPER = PROspective Study of Pravastatin in the Elderly at Risk;
- PUFA = polyunsaturated fatty acids;
- WOSCOPS = West of Scotland Coronary Prevention Study.
lipid levels or through direct anti-inflammatory actions. In trials of atorvastatin and pravastatin in patients with acute coronary syndromes, the degree of C-reactive protein reduction correlated poorly with the degree of LDL-C reduction for individual participants (76,77). In this analysis, which compared overall trial results, there seemed to be no significant difference between the individual statins, diet, and other non-statin interventions independent of LDL-C reduction, lending support to the concept that the anti-inflammatory effects described for statins may be the result of, rather than in addition to, LDL-C lowering. The direct corollary of such a relationship between LDL-C lowering and reduced inflammation suggests that inflammation may be a mechanism through which LDL-C promotes atherosclerosis rather than an independent effect. Indeed, experimental data support a direct causal relationship between LDL-C and inflammation. Statin-induced inhibition of cholesterol synthesis has been shown to disrupt lipid rafts in cell membranes, resulting in altered lymphocyte function (78). The alternative explanation that statins directly and independently lower both LDL-C and inflammatory markers has not been disproved by these data, but this analysis does show that statins seem to be no more effective in this regard than diet, bile acid sequestrants, or surgery.

The lack of correlation between LDL-C and a single measure of C-reactive protein reduction in individual acute coronary syndrome patients may be misleading. Intra-individual variation of C-reactive protein values varies by more than 40% to 60% in patients with stable ischemic heart disease (79). For acute coronary syndrome patients, recovery from the acute event, along with regression to the mean, is likely to add even greater measurement variability, thereby resulting in a lack of correlation with LDL-C levels. The finding that aggressive LDL-C reduction has been shown to stabilize and even regress atherosclerotic plaque in some but not all (80,81) patients suggests a unifying explanation for the lack of correlation between LDL-C and C-reactive protein. The lack of correlation between LDL-C and C-reactive protein levels may reflect plaque stabilization, or lack thereof, within the overall atherosclerotic milieu of the individual patient. That is, an LDL-C level <70 mg/dl may be sufficient to stabilize or regress plaque for one patient, but may not be sufficient for another patient because of cigarette smoking or poorly controlled diabetes or hypertension. Indeed, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial

Figure 2. Estimated change in the five-year relative risk of non-fatal myocardial infarction or CHD death associated with mean LDL-C reduction for the diet, bile-acid sequestrant, surgery, and statin trials (dashed line) along with the 95% probability interval (dotted line). The solid line has a slope = 1. The crude risk estimates from the individual studies are plotted along with their associated 95% confidence intervals. The Sydney (26) trial is not shown but was included in the analysis. Statin trials are designated by the boldface symbols. CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol. Study acronyms: MRC = Medical Research Council; LRC = Lipid Research Clinics; NHLBI = National Heart, Lung, and Blood Institute; POSCH = Program on the Surgical Control of the Hyperlipidemias; 4S = Scandinavian Simvastatin Survival Study; WOSCOPS = West of Scotland Coronary Prevention Study; CARE = Cholesterol and Recurrent Events study; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; AF/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS = Heart Protection Study; ALERT = Assessment of L’Ecole in Renal Transplantation; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study.

Figure 3. Estimated change in the five-year relative risk of stroke associated with mean LDL-C reduction for the statin trials’ (dashed line) along with the 95% probability interval (dotted line). The solid line has a slope = 1. The crude risk estimates from the individual studies are plotted along with their associated 95% confidence intervals. LDL-C = low-density lipoprotein cholesterol. Study acronyms: 4S = Scandinavian Simvastatin Survival Study; WOSCOPS = West of Scotland Coronary Prevention Study; CARE = Cholesterol and Recurrent Events study; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study. *Only statin trials reported stroke incidence.
Infarction-22 (PROVE-IT) trial, recurrent CHD event rates were lowest in patients with LDL-C levels <70 mg/dl and low C-reactive protein levels <1.0 mg/l (77).

Some have suggested that the pleiotropic effects of statins may play an important role in stabilizing vulnerable plaque and the very early reduction in CHD events in acute coronary syndrome trials (17,81–83). However, in the longer-term acute coronary syndrome trials, despite significant reductions in inflammatory markers, cumulative CHD risk reduction did not seem to exceed that expected from the one-to-one relationship between LDL-C lowering and CHD risk seen in trials of stable patients. In the PROVE-IT trial, the atorvastatin 80 mg group experienced an additional 18% reduction in CHD events over pravastatin 40 mg (17). This amount of CHD risk reduction is actually somewhat less than would be expected from a 31% lower LDL-C level in the atorvastatin group if a one-to-one relationship were present. Although the trial was only two years long, the benefit should begin approaching that seen by three to five years (67).

The recent Phase Z of the A to Z trial showed a non-significant 12% reduction in non-fatal MI and CHD death with a 14% greater reduction in LDL-C in the early treatment/simvastatin 40 to 80 mg group compared with the later treatment/simvastatin 20 mg group over two years (66). Although the PROVE-IT and A to Z trials suggest some attenuation of CHD risk reduction may occur with LDL-C lowering beyond 35%, results from the recent Treating to New Targets (TNT) trial (84) showed further reduction in CHD risk with more aggressive LDL-C reduction. The five-year TNT study enrolled 10,001 men and women with stable CHD who were randomized to atorvastatin 10 or 80 mg. Consistent with the findings of this analysis, the 24% lower LDL-C level in the atorvastatin 80 mg group (mean LDL-C level of 77 mg/dl) resulted in a significant 22% reduction in non-fatal MI and CHD death compared with the atorvastatin 10 mg group (mean LDL-C of 101 mg/dl). During the open-label lead-in period of the TNT trial, LDL-C was reduced by 35% by atorvastatin 10 mg. Therefore, the absolute LDL-C reduction in the atorvastatin 80 mg group of the TNT trial was approximately 59%. Because a previous trial of atorvastatin 10 mg showed a 34% reduction in non-fatal MI and CHD death with a 40% reduction in LDL-C after four years of treatment (40), the atorvastatin 80 mg treatment in the TNT trial may have lowered CHD risk by as much as 56% compared with placebo treatment. These findings seem to extend the one-to-one relationship between LDL-C and CHD risk reduction to more aggressive levels of LDL-C reduction. Further confirmation awaits the results of soon-to-be-completed large trials of aggressive LDL-C reduction (85,86).

This analysis also suggests that additive reductions in cardiovascular risk reduction should occur when newer non-statin agents that primarily lower LDL-C, such as ezetimibe, are added to statin therapy. Although no clinical outcomes data are yet available for ezetimibe, the cardiovascular risk reduction benefit with this agent would be expected to be in direct proportion to its degree of LDL-C reduction (18% to 20%) (87).

Because many epidemiologic studies have shown no relationship between total cholesterol level and stroke (88), some have speculated whether pleiotropic effects contribute to the reduction in stroke risk observed in the statin trials (89). However, in a meta-analysis of cohort studies by stroke type, a 1 mmol/l (about 28%) decrease in LDL-C was associated with a 15% reduction in ischemic stroke and a 19% increase in hemorrhagic stroke (90). A slightly greater benefit was shown in the accompanying meta-analysis of 58 randomized trials in which an approximately 20% lower ischemic stroke risk occurred with a 1 mmol/l reduction in LDL-C, similar to the results of this study. With the exception of the PROSPER trial, the confidence intervals for the non-fatal and fatal stroke end points included the one-to-one line. Several explanations for the lesser benefit for stroke, despite a 35% reduction in LDL-C, in the PROSPER trial have been forwarded, including a low stroke event rate in the trial (50% of expected rate) and short duration of the trial (three years) with stroke reduction from statins appearing after three years, whereas CHD risk reduction occurs earlier (69). The recent data from the TNT trial extends the one-to-one relationship between LDL-C and stroke to more aggressive LDL-C reduction, with a 25% reduction in fatal and non-fatal stroke in the atorvastatin 80 mg group (84). Because stroke data were not available from the non-statin trials, this analysis could not explore whether pleiotropic effects of statin treatment may be contributing to greater reductions in stroke risk than expected from other LDL-C lowering interventions.

Although emerging data suggest the anti-inflammatory, immunomodulatory, and vascular effects of statins may play a role in the progression of other chronic diseases such as diabetes mellitus (91) and rheumatoid arthritis (9), the present data do not seem to support a role for these effects in the clinical management of cardiovascular risk. The evidence to date supports statin choice guided by LDL-C lowering efficacy rather than non-lipid effects, as well as issues such as safety, drug interactions, and cost (92,93). The focus should remain on achieving LDL-C goals as recommended by current guidelines (51,94). Further research is needed before the choice of cholesterol-lowering therapy is influenced by effects other than the degree of LDL-C reduction.

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REFERENCES


