Differential Effects of Lipid-Lowering Therapies on Stroke Prevention

A Meta-analysis of Randomized Trials

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Background: Previous overviews suggested that hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins), but not other lipid-lowering therapy (LLT), may reduce stroke incidence in coronary patients.

Objective: To investigate the amplitude and sources of heterogeneity of LLT effects on stroke prevention.

Methods: We searched the literature from 1966 to 2001 and then conducted a meta-analysis including randomized trials of primary and secondary coronary heart disease prevention, testing statins, nonstatin drugs, diet, or other interventions and providing data on stroke incidence.

Results: The meta-analysis (38 trials, 83,161 patients, mean follow-up of 4.7 years) showed a significant relative risk reduction (RRR) of strokes by LLT of 17% (P<.001), without significant heterogeneity between trials and between subgroups according to either the type of prevention (primary or secondary) or the type of LLT. The most substantial effects were obtained, however, with statins (RRR, 26%). Effect model analysis showed that treatment benefit appeared constant whatever the risk of stroke, suggesting that LLT may be effective in a population with a higher risk of stroke. Weighted regression showed a significant correlation between RRR of stroke and total cholesterol levels (baseline, final, and change). Only final cholesterol allowed clear separation between benefit (RRR>0) and no effect (RRR<0) of LLT on stroke incidence, with a cutoff for benefit of 232 mg/dL (6.0 mmol/L).

Conclusion: Lipid-lowering therapy reduces stroke incidence in coronary patients, especially when total cholesterol level is lowered to less than 232 mg/dL (6.0 mmol/L), which explains the best results being obtained with statins.

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REDUCING STROKE incidence in industrialized countries is a major challenge, since stroke is the third leading cause of mortality after coronary heart disease and cancer, and the leading cause of disability. Although lowering blood cholesterol level decreases the risk of coronary heart disease, whether it decreases the risk of stroke remains unclear. To date, no large randomized trial with stroke as the primary end point has been completed to establish whether cholesterol reduction reduces stroke incidence. Indeed, primary end points in clinical trials using lipid-lowering therapies (LLTs) were usually coronary events and/or mortality. Previous overviews of these randomized trials had suggested that cholesterol lowering could be effective in reduction of stroke incidence. Particularly, only the newest class of cholesterol-lowering drug, the hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins), were efficient in stroke reduction in these meta-analyses. However, these overviews did not include 4 large randomized trials recently published: 2 trials testing fibrates and 2 trials testing statins. Moreover, why only statins and not the other LLT drugs or diets are successful in stroke prevention remains unresolved. It has been suggested that statins could prevent stroke by a mechanism other than cholesterol lowering. Indeed, in addition to their lipid-lowering effects, statins have been demonstrated to have a wide variety of effects, such as anti-inflammatory, antithrombotic, neuroprotective, and direct properties on endothelial cells and plaque stability, which may act on stroke prevention. However, fibrates have also been shown to improve endothelial function, to have anti-inflammatory effects, and to have favorable effects on several hemostatic variables.

We then conducted a new meta-analysis of all randomized clinical trials testing LLT in primary or secondary prevention of coronary events, and providing information on stroke.
METHODS

Our study used a meta-analysis of all published randomized trials that examined the cardiovascular effects of any LLT. We initially conducted a computerized PubMed search of the literature to identify all trials testing LLTs limited to English-language articles published between 1966 and 2001. In addition, we searched the reference lists of published trials testing statins, other cholesterol-lowering drugs, diets, and previously conducted overviews. Criteria for inclusion of trials in the meta-analysis were (1) randomized and controlled trials testing LLT vs placebo and (2) trials providing data on stroke incidence (fatal and/or nonfatal strokes). Strokes included ischemic and hemorrhagic strokes. Transient ischemic attacks were not considered because diagnostic criteria for such events were variable and not always reported in the trials. We included trials enrolling participants free of heart disease at baseline (primary prevention) and trials selecting participants with heart disease history (secondary prevention). We included trials with interventions in addition to lipid lowering (multiple intervention). We excluded crossover trials and short-term efficacy trials using serum cholesterol level as the primary end point. To ensure comparability of the included studies, we excluded 3 trials: 1 trial in which patients in both the control and intervention groups received simvastatin; 1 trial that was restricted to patients with previous stroke, with a small number of patients and a much higher risk of stroke than all other trials; and 1 trial because lovastatin was given at different dosages to patients and data were not provided for each group.

In the selected trials, we studied also the effect of LLT on myocardial infarction (MI) (fatal and nonfatal) and compared both effects on MI and stroke.

The pooled estimate of the overall relative risk (RR) was calculated by using, for each study, the inverse variance weighted RR. As is usual in meta-analysis, a χ² test for association on the pooled estimate of overall RR and a χ² test for homogeneity of RR between trials and between subgroups were performed. P values for significance were set at ,05 for χ² test for association and at ,10 for χ² test for homogeneity.

Means of age, follow-up, baseline and final total cholesterol levels, and total cholesterol reduction were expressed as arithmetic means weighted with the number of randomized patients in each trial. Baseline cholesterol level was defined as the average of total plasma cholesterol level.
in the control and treated groups before treatment. Final cholesterol level was defined as the average of the last value of total cholesterol provided in the treated group. The percentage of total cholesterol reduction (TCr) for each trial was calculated as the percentage of total cholesterol reduction during the study (variable delay according to available data for each study) between the treated (t) and control (c) groups:

$$TCr = TCr(t) - TCr(c).$$

We investigated relationships between annual stroke rate in the placebo and in the treated groups of trials testing LLTs in primary or secondary prevention, according to the “effect model” analysis described by Walter.24 Briefly, 3 possibilities can occur: (1) the effect model is multiplicative when the regression line slope is different from 1 and the 95% confidence interval (CI) of the intercept includes the origin, meaning that the relative risk reduction (RRR) is constant whatever the incidence of event in the placebo group; (2) the effect model is additive when the slope is close to 1 and the 95% CI of the intercept does not include the origin, meaning that absolute risk reduction is constant; and (3) the effect model is mixed when the slope is different from 1 and the 95% CI of the intercept does not include the origin; in this last case neither the RRR nor the absolute risk reduction is constant with the incidence of the disease in the placebo group. This method allows one to investigate whether the treatment effect is dependent on the baseline risk in the studied population, i.e., virtually the disease severity.

Finally, to test a dose-response relationship between the treatment effect on stroke incidence and its effect on cholesterol level, we used an inverse variance weighted linear regression between the percentage of total cholesterol reduction (TCr) for each trial and the relative risk (RR) of stroke. Analysis was performed with EasyMA software (Department of Clinical Pharmacology, Cardiological Hospital, Lyon, France; available at: http://www.spc.univ-lyon1.fr/~mcu/easyma/) and, for the regression, with STATISTICA 5.1 software (StatSoft, Tulsa, Okla.).

### RESULTS

**TRIAL CHARACTERISTICS**

We found 38 independent trials of LLT that fit our criteria (Table 1). All of these studies were primary (10 trials) or secondary (28 trials) coronary heart disease prevention trials. Interventions for lipid lowering were classified as follows: (1) statins, including 15 studies (8 with pravastatin sodium,26–31 3 with lovastatin,32–36 3 with simvastatin,37–40 and 1 with
atrovasatin calcium\textsuperscript{10}; (2) nonstatin drugs, including 13 trials (3 with clofibrate,\textsuperscript{39,41} 2 with cholestyramine resin,\textsuperscript{42-44} 3 with gemfibrozil,\textsuperscript{9,45,46} 1 with bezafibrate,\textsuperscript{8} 1 with colesterol hydrochloride,\textsuperscript{87} 1 with clofibrate plus niacin,\textsuperscript{48} and 1 trial testing clofibrate with or without niacin\textsuperscript{49} [see next sentence]); (3) diet, including 7 trials\textsuperscript{94,95,97-99}, and (4) 3 other interventions, including 1 trial testing LLT with various drugs vs placebo,\textsuperscript{30} 1 trial testing multifactorial advice (stop smoking and diet),\textsuperscript{27} and 1 trial testing ileal bypass.\textsuperscript{26} Two trials included 3 groups: the Coronary Drug Project (CDP) trial\textsuperscript{39} included 1 group treated with clofibrate alone, 1 group treated with niacin, and a placebo group; and the St Thomas' Atherosclerosis Regression Study trial\textsuperscript{44} randomized patients in 1 placebo group, 1 diet group, and 1 cholestyramine group. For the meta-analysis, each intervention group for these 2 trials was separately analyzed vs placebo.

Altogether, the data represented 83,161 patients (39,943 and 43,218 patients in the treatment and placebo groups, respectively), with 672 and 939 fatal and nonfatal strokes in the treatment and placebo groups, respectively. The average baseline total cholesterol level was 240 mg/dL (6.2 mmol/L), and the mean total cholesterol reduction in the treated group was 14.6%. This cholesterol reduction was dramatically higher than that in the placebo and LLT groups. The use of LLT did not significantly modify such incidence (RR, 1.16; 95% CI, 0.75-1.80).

The RRR of fatal and nonfatal MI by LLT was 22% (\textit{P} < .001; Figure 4). Given the annual incidence of stroke (0.8%) and MI (4.8%), and the overall RRR obtained with LLT on these 2 outcomes (17% and 22%, respectively), the calculated number of patients to be treated during 1 year (number needed to treat [NNT] = 1/[incidence \times RRR]) to avoid 1 stroke (NNT = 735) was dramatically lower than for MI (NNT = 95).

**EFFECT MODEL ANALYSIS**

To investigate whether the effect of LLTs on stroke risk reduction was related to the incidence of stroke in the studied population, we performed an effect model analysis with the use of the Walter weighted regression model,\textsuperscript{25} testing the relationship between the annual stroke rate in the placebo and LLT groups for each trial (Figure 5). The slope of the regression line was different from 1 (0.75; 95% CI, 0.64-0.87) and the 95% CI of the intercept included the origin (intercept, 0.000; 95% CI, 0.000-0.001), demonstrating that the effect model was multiplicative (see the “Methods” section). This result indicates that the RRR of stroke was constant whatever the incidence of event in the placebo group, and predicts that LLT effect on stroke incidence should be the same (in terms of RRR) in a population with a higher risk of stroke (ie, in stroke secondary prevention).

**RELATIONSHIP BETWEEN CHOLESTEROL AND STROKE INCIDENCE**

Our results showed that different classes of lipid-lowering drugs, statins and nonstatin drugs (but also other...
LLTs such as diet), did not have the same effect on stroke prevention (see Figure 2). Statins and nonstatin drugs also did not have the same efficacy on cholesterol lowering: statins induced an average total cholesterol reduction of 21.8% as opposed to only 8.3% with nonstatin drugs. We then studied the relationship between total cholesterol levels (baseline, final, and change) and stroke incidence reduction (RRR). The weighted linear correlation between these variables provided the following results (Table 2).

Stroke incidence RRR was significantly correlated with cholesterol reduction ($r = 0.46; P < .001$), baseline cholesterol level ($r = -0.47; P < .001$), and final cholesterol level ($r = -0.69; P < .001$). The threshold of cholesterol reduction to induce a beneficial effect on stroke incidence (RRR > 0) was around 2%. However, the strongest correlation was found between RRR and the final cholesterol level ($r = 0.48$). More importantly, the only final cholesterol level allowed a clear separation between absence and presence of stroke reduction (RRR > 0 and RRR < 0). The cut-off value of such final cholesterol level appeared around 232 mg/dL (6.0 mmol/L) (Figure 6A).

Results for the relationship between RRR for MI and cholesterol measures were different from those for stroke. The RRR of MI was significantly correlated with cholesterol reduction ($r = 0.50; P < .001$) and final cholesterol level ($r = -0.39; P < .001$) but not with baseline cholesterol level ($r = -0.03; P = .22$). The strongest correlation was found between RRR and cholesterol reduction and not final cholesterol level. Final cholesterol value did not allow the clear separation of treatment efficacy for MI that was observed with stroke, since RRR was positive for MI whatever the cholesterol level (Figure 6B).

Table 2. Relationships Between Relative Risk Reduction of Stroke or Myocardial Infarction and Cholesterol Measures

<table>
<thead>
<tr>
<th>Cholesterol Measure</th>
<th>RRR of Stroke</th>
<th></th>
<th>RRR of MI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$r^2$</td>
<td>$P$</td>
<td>$r$</td>
</tr>
<tr>
<td>Cholesterol reduction</td>
<td>0.46</td>
<td>0.21</td>
<td>&lt;.001</td>
<td>0.50</td>
</tr>
<tr>
<td>Baseline cholesterol level</td>
<td>-0.47</td>
<td>0.22</td>
<td>&lt;.001</td>
<td>-0.03</td>
</tr>
<tr>
<td>Final cholesterol level</td>
<td>-0.69</td>
<td>0.48</td>
<td>&lt;.001</td>
<td>-0.39</td>
</tr>
</tbody>
</table>

Abbreviations: MI, myocardial infarction; RRR, relative risk reduction.

The results of this meta-analysis provide strong evidence in favor of the potential of LLTs to prevent stroke. Such preventive effect appears related to efficacy of LLT to lower blood cholesterol levels, explaining why the most convincing results are obtained with statins. Indeed, optimal prevention appears to be obtained when cholesterol level is lowered to less than 232 mg/dL (6.0 mmol/L).

Our results confirm previous overviews, adding the new published trials MIRACL (Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering), SCAT (Simvastatin/Enalapril Coronary Atherosclerosis Trial), BIP (Bezafibrate Infarction Prevention Study), and VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial). The recently completed HPS (Heart Protection Study) provides similar results. However, all of these clinical trials included patients with or without coronary disease, and their main objective was not stroke reduction but death, cardiovascular death, and recurrence of MI. Stroke was included as a secondary end point. Therefore, no controlled trial had stroke prevention as a primary end point. Such trials are, however, ongoing and including a much more aged population at higher risk of stroke. This explains why all in trials in this overview incidence of stroke was very low, especially in the case of primary cardiovascular disease prevention, reducing the power of the comparison. Therefore, stroke reduction was significant only in cardiovascular secondary prevention (19%) and not in cardiovascular primary prevention (5%).

Similarly, no heterogeneity of LLT effect could be detected between the different types of treatments, but the greatest amplitude of stroke reduction was obtained with statins (RRR, 24%; $P < .001$; Figure 2). With the other treatment groups, the stroke reduction was nonsignificant: nonstatin drugs (RR, 0.93; 95% CI, 0.79-1.08), diet (RR, 0.60; 95% CI, 0.32-1.13), and other interventions (RR, 1.0; 95% CI, 0.62-1.60).
In cardiovascular secondary prevention trials, representing the subgroup providing the best estimation of treatment effect, statins reduced stroke incidence by 26% (P<.001). Moreover, the effect model predicted a constant RRR of stroke with LLT whatever the stroke incidence. This means that a 26% stroke reduction could be expected with statins in a population of patients with a history of stroke in which the annual incidence of stroke recurrence is much higher and estimated around 8%. Statins in such a population could then prevent 20 strokes for 1000 patients treated during 1 year. This is close to the benefit obtained with antithrombotic drugs in secondary prevention of stroke. If such a result is confirmed by further studies, this should place statins in the first line of treatment in stroke prevention.

The fact that the best effect was obtained with statins suggests 2 hypotheses: (1) statins have other properties in addition to cholesterol lowering that may explain their ability to prevent stroke; or (2) stroke prevention by LLT is related to cholesterol lowering, but nonstatin therapies are less efficient than statins in cholesterol lowering. To answer this question, we explored relationships between LLT effects on event prevention (MI and stroke) and blood lipid measures (total cholesterol levels and change during therapy).

The most meaningful result was the strong correlation between RRR of stroke and final cholesterol level. This correlation could separate beneficial (RRR>0) from nonbeneficial (RRR<0) effect of LLT on stroke incidence. The cutoff for RRR greater than 0 was around 232 mg/dL (6.0 mmol/L). An a posteriori meta-analysis confirmed this result: stroke incidence was significantly reduced by 19% in the 9 nonstatin trials in which the mean of final cholesterol level was lower than 232 mg/dL (6.0 mmol/L) (RR, 0.82; P=.045; data not shown). Furthermore, a recent subgroup analysis from the VA-HIT trial showed that gemfibrozil may be more effective to reduce stroke incidence in patients with low levels of high-density lipoprotein cholesterol and low levels of low-density lipoprotein cholesterol, ie, patients with low total cholesterol level.63 Altogether, these results suggest that the difference in stroke prevention observed between statins and nonstatin therapies may be due to difficulties to reach the final cholesterol level of 232 mg/dL (6.0 mmol/L) with nonstatin therapies.

The different relationships between RRR of stroke or MI prevention and cholesterol measures (see Table 2) may be explained, in part, by the differences existing in terms of impact of lipid metabolism as a risk factor on stroke and MI. Indeed, high cholesterol level is a stronger risk factor for stroke than for MI. Moreover, high-density lipoprotein cholesterol seems to be a stronger risk factor for stroke than total or low-density lipoprotein cholesterol. A meta-regression between cholesterol fractions and the RRR of stroke could not be performed because not all trials provided such data, and because the range of high-density lipoprotein and low-density lipoprotein cholesterol levels or change between trials was very low. An individual data analysis with these cholesterol measures should be of interest to investigate this question.

As in any meta-analysis, information bias cannot be totally avoided. Indeed, in some trials, mainly nonstatin trials, information on stroke in-
cidence was not complete. However, the amount of lacking information provided by these trials represents a very low percentage of the total number of included patients and does not significantly influence the overall result. In this meta-analysis, all strokes were considered, which probably underestimates the real impact of LLT. Indeed, LLT should mainly prevent ischemic strokes due to atherosclerosis. Available data from the studied trials did not allow separation of such strokes from other origins, especially cardioembolic strokes. Incidence of hemorrhagic strokes did not seem to be influenced by LLT. Since these strokes are most often fatal, this result could partly explain the apparent lack of effect of LLT on fatal strokes.

In conclusion, LLT appears to reduce stroke incidence in coronary patients. Such benefit appears to be related to blood cholesterol lowering, which explains why statin drugs provide the most consistent benefit among trials. If a similar stroke incidence reduction (observed in high-risk coronary patients) could be extended to a higher risk-stroke population, LLT will become essential drugs for secondary stroke prevention.

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