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Cholesterol-Lowering Interventions and Stroke

Insights From a Meta-Analysis of Randomized Controlled Trials

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Objectives This meta-analysis was performed to determine the effects of various cholesterol-lowering treatments on the risk of stroke and its relationship with the extent of cholesterol lowering.

Background Statins reduce the incidence of stroke, and it has been proposed that such effect is independent of cholesterol lowering and is explained by alternative mechanisms.

Methods We performed a meta-analysis of randomized trials of cholesterol-lowering treatments in cardiovascular disease reporting on stroke, involving 266,973 patients investigated and a cumulative 946,582 person-years of exposure, and a meta-regression analysis of the extent of stroke reduction as a function of changes in total cholesterol.

Results The odds ratio (OR) for the incidence of stroke in actively treated groups versus controls was 0.88 (95% confidence interval: 0.83 to 0.94, $p < 0.001$). No treatment affected fatal strokes. Whereas statins decreased the risk of total stroke significantly (OR: 0.85, 95% confidence interval: 0.78 to 0.92; $p < 0.001$), the benefit of non-statin interventions was smaller and not statistically significant (diet OR: 0.92, fibrates OR: 0.98, other treatments OR: 0.81). We found a significant relationship between percent reduction of total (and low-density lipoprotein) cholesterol and percent reduction of total strokes ($p = 0.0017$), with each 1% reduction of total cholesterol predicting a 0.8% relative risk reduction of stroke. We found no significant association between stroke reduction and changes of high-density lipoprotein cholesterol levels, and inconsistent associations with reduction of triglycerides.

Conclusions Among cholesterol-lowering treatments, statins are the most effective at decreasing the risk of total stroke, but their benefit is proportional to the percent reduction of total cholesterol and low-density lipoprotein cholesterol. No lipid-lowering intervention was associated with a reduction of fatal stroke. (J Am Coll Cardiol 2010;55:198–211) © 2010 by the American College of Cardiology Foundation

Ample epidemiological data suggest that hypercholesterolemia is a powerful risk factor for coronary heart disease (CHD) and nonfatal/fatal ischemic stroke (1,2). The relationship between serum cholesterol and stroke, currently 1 of the most common causes of death and long-term severe disability, has been in the past controversial (3,4). Recently, the Cholesterol Treatment Trialists meta-analysis of 14 statin trials, including >8,000 deaths, determined that a 38 mg/dl reduction in low-density lipoprotein cholesterol (LDL-C) reduced the risk of total stroke by 17% (5). Although different cholesterol-lowering drugs or nonpharmacological treatments significantly reduce morbidity from CHD (6–14), thus proving a causal role for cholesterol in coronary events, it has been maintained that among cholesterol-lowering interventions, only statins protect against stroke (9,14–19), thus arguing for the clinical relevance of statin properties unrelated to cholesterol lowering ("pleiotropic") on this clinical outcome.

To avoid type II error due to the small sample size of clinical trials testing cholesterol-lowering interventions different from statins, we here report on a meta-analysis of the effect of all cholesterol-lowering interventions on the occurrence of different types of strokes, specifically on fatal and nonfatal strokes, the types of strokes more frequently defined in clinical trials and of substantial clinical relevance, and a meta-regression of the relationship between the extent of cholesterol lowering (total cholesterol [TC] being the lipid data always reported in the various trials) and the extent of stroke reduction, including a total of 78 trials and 266,973 patients, with a mean follow-up of 3.5 years and a cumulative exposure of 946,582 person-years. We specifically sought to answer these questions: 1) Is the effect of cholesterol-lowering agents on the incidence of stroke restricted to statins, or is it also shared by other agents or nonpharmacological strategies? 2) Is there a different effect of cholesterol-lowering interventions on fatal and nonfatal

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strokes? 3) Is the reduction of stroke, if found, proportional to the extent of blood lipids (TC, high-density lipoprotein cholesterol [HDL-C], and LDL-C) reduction?

Methods

Literature search and data abstraction. We retrieved all randomized clinical trials (RCTs) reporting on cholesterol-lowering interventions and stroke published until April 2009. (Search criteria and methods for data abstraction are detailed in the Online Appendix.)

Statistical methods. Estimates of the average effect and 95% confidence intervals (CIs) of statins, fibrates, and other cholesterol-lowering interventions on serum lipids were calculated with a random-effect assumption, according to the Mantel-Haenszel method (20,21). However, a preliminary Q test (22) for homogeneity was performed, and no material evidence for heterogeneity was found.

Individual odds ratios (ORs) were estimated as the cross-product of cell counts in the corresponding 2 × 2 table, with variance of natural logarithm (ln) of OR equal to the sum of the reciprocal cell counts. For trials with no events, a pseudocount of 0.5 was added to each cell for these calculations (20,21).

Sensitivity analyses were carried out to assess the strength of the association between effects of statins on the events of interest and explanatory variables, such as baseline characteristics of patients. Relative risk (RR) instead of OR was used to assess the effect of the interventions on the risk of stroke according to the risk of death of the population recruited in each trial. This risk was estimated according to the rate of death observed in the control group of each study.

To further explore the relationship of cholesterol reduction and total stroke, a meta-regression by using inverse variance-weighted linear regression was performed (23). The dependent variable in the model was the logarithm RR for total stroke as the dependent variable against the variables discussed earlier, and weights in each study were the reciprocals of the variances for the logarithm RR for stroke (24). In each trial, the percent reduction in total serum cholesterol levels (%ΔTC) was calculated by subtracting end-study (or mean in-study) TC from baseline TC in treated and control groups:

$$\%\Delta TC = \frac{TCf - TCb}{TCb} \times 100$$

where TCf was end-study (or mean in-study) total serum cholesterol, and TCb was baseline total serum cholesterol.

When not reported, the mean duration of follow-up (FUmean) was calculated as follows:

$$FUmean = \frac{AP \times FUmax + DP \times \frac{FUmax}{2}}{TP}$$

where TP was the total number of patients, AP was the number of patients alive, DP the number of subjects deceased during the study, and FUmax the maximum follow-up.

Statistical testing for efficacy was conducted at a 2-tailed α-level of 0.05. As to the homogeneity tests, an α-level of 0.10 was chosen. All analyses were performed using the SAS software version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Abbreviations and Acronyms

CHD = coronary heart disease
CI = confidence interval
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
OR = odds ratio
RCT = randomized clinical trial
RR = relative risk
TC = total cholesterol

Results

Overall, 78 trials tested the efficacy of cholesterol-lowering interventions on total, fatal, or nonfatal stroke, involving 266,973 patients, with a cumulative exposure of 946,582 person-years (mean follow-up of 3.5 years). Four studies randomly allocated patients to multiple arms of treatment; for this reason, data from their control groups were used twice in the analysis, and the total number of trials included was raised to 82.

A total of 49 RCTs tested the efficacy of statins. The other 33 trials used other lipid-lowering interventions: 13 studies tested fibrates, 7 trials tested dietary interventions, 12 studies tested other drugs, and 1 study tested surgery.

As to total stroke, 76 trials evaluated the effect of lowering cholesterol levels in 251,476 subjects on total stroke, thus raising the total number of trials included in the analysis to 80. The occurrence of fatal stroke was reported in 62 RCTs, and 2 actively treated groups were compared with a single control group in 4 studies, thus raising the total number of RCTs to 66. The occurrence of nonfatal stroke was reported in 41 RCTs, and 2 actively treated groups were compared with a single control group in 3 studies. (Details on such trials from which data abstraction was obtained are given in the Online Appendix.)

Tables 1 and 2 show the main characteristics of the RCTs included in the analysis. Patients included in the selected RCTs had a mean age of 61 years, and the male/female ratio was 0.61. Smokers, diabetic patients, and hypertensive patients were 20% (71 trials), 21% (70 trials), and 47% (64 trials), respectively. Twenty-seven percent (66 trials) and 3.4% (35 trials) of patients had a history either of myocardial infarction or stroke, respectively. Mean pre-treatment level of total serum cholesterol was 224 mg/dl as an average of the active and control groups.

Effect of cholesterol-lowering interventions on fatal events. Table 3 and Figure 1A present the main results for total stroke. Information about total stroke was available for 123,293 patients allocated to an active cholesterol-lowering treatment and 131,219 controls. Overall, 2,993 subjects (2.4%) suffered a stroke in the treated group as compared with 3,724 (2.8%) in the control group. Cholesterol-