CLINICAL REVIEW

Efficacy of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors for Prevention of Stroke

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OBJECTIVE: **To determine if 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are effective in preventing fatal and nonfatal strokes in patients at increased risk of coronary artery disease.**

DESIGN: **Meta-analysis of randomized controlled trials. Clinical trials were identified by a computerized search of MEDLINE (1983 to June 1996), by an assessment of the bibliographies of published studies, meta-analyses and reviews, and by contacting pharmaceutical companies that manufacture statins. Trials were included in the analysis if their patients were randomly allocated to a statin or placebo group, and reported data on stroke events. Thirteen of 28 clinical trials were selected for review. Data were extracted for details of study design, patient characteristics, interventions, duration of therapy, cholesterol measurements, and the number of fatal and nonfatal stroke events in each arm of therapy. Missing data on stroke events were obtained by contacting the investigators of the clinical trials.**

MAIN RESULTS: **Among 19,921 randomized patients, the rate of total stroke in the placebo group was 2.38% (90% nonfatal and 10% fatal). In contrast, patients who received statins had a 1.67% stroke rate. Using an exact stratified analysis, the pooled odds ratio (OR) for total stroke was 0.70 (95% confidence interval [CI] 0.57, 0.86; p = .0005). The pooled OR for nonfatal stroke was 0.64 (95% CI 0.51, 0.79; p = .00001), and the pooled OR for fatal stroke was 1.25 (95% CI 0.71, 2.24; p = .4973). In separate analyses, reductions in total and nonfatal stroke risk were found to be significant only for trials of secondary coronary disease prevention. Regression analysis showed no statistical association between the magnitude of cholesterol reduction and the relative risk for any stroke outcome.**

CONCLUSIONS: **The available evidence clearly shows that HMG-CoA reductase inhibitors reduce the morbidity associated with strokes in patients at increased risk of cardiac events. Data from 13 placebo-controlled trials suggest that on average one stroke is prevented for every 143 patients treated with statins over a 4-year period.**

KEY WORDS: **cholesterol; HMG-CoA reductase inhibitors; meta-analysis; stroke prevention.**
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An increased serum cholesterol level has been implicated as a major risk factor for coronary artery disease, and lipid-lowering drugs are extensively used to modify this risk factor. The majority of the evidence has shown that lowering serum cholesterol reduces the risk of cardiac morbidity and mortality.[1] The effect of cholesterol reduction on stroke morbidity and mortality, however, has been less extensively studied and is controversial. Observational cohort studies have shown that stroke mortality is U-shaped; that is, at high cholesterol levels (>240 mg/dL) the risk of ischemic stroke is elevated, while at lower cholesterol levels (<200 mg/dL) the risk of hemorrhagic stroke is increased.[2,3] These observations suggest that the benefit from the reduction in cholesterol ceases at a cholesterol level around 200 mg/dL, and that further reduction in cholesterol may increase mortality from cerebral hemorrhages. It has been suggested that low cholesterol levels contribute to the weakening of the endothelium lining small cerebral arteries, thus predisposing patients to hemorrhagic strokes.[4,5]

Two prior meta-analyses using trials of diet, bile acid resins, fibric acid derivatives, and niacin have shown a nonsignificant decrease in the relative risk for nonfatal stroke, a nonsignificant increase in the relative risk for fatal stroke, and no effect on total stroke incidence.[6,7] Both analyses suggested that the inability to demonstrate a significant reduction in overall stroke rates was due to a degree of cholesterol reduction achieved in these trials (about 10%) that may have been inadequate to reverse established cerebrovascular disease and to an offset in the beneficial effects of cholesterol reduction by an increase in hemorrhagic stroke, which carries the higher case-fatality rate.

Since their publication, more than a dozen trials of cholesterol reduction using 3-hydroxy-3-methylglutaryl

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coenzyme A (HMG-CoA) reductase inhibitors have been conducted, demonstrating a total cholesterol reduction of about 20% over placebo. Although most trial's end points focused on coronary artery disease and total mortality risk reduction, several trials were also designed to measure the effect of cholesterol reduction on early carotid atherosclerosis.[8–11] These trials, the Asymptomatic Carotid Artery Prevention Study (ACAPS),[8] the Kupio Atherosclerosis Prevention Study (KAPS),[9] the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries trial (PLAC-II),[10] and the Carotid Atherosclerosis Italian Ultrasound Study (CAIUS),[11] demonstrated a reduction in the rate of progression of carotid artery disease. Further, a pooled analysis of four pravastatin trials,[12] which included two of the above trials,[9,10] demonstrated with borderline significance (p = .054) a decrease in total stroke risk.

In view of the greater cholesterol-lowering ability of statins as compared with earlier cholesterol-lowering agents and their increased effects in slowing the progression of carotid artery lesions, we conducted a meta-analysis of all randomized trials that used statins and provided stroke data, to determine if statins, as a class, are effective in preventing stroke events in patients at an increased risk of coronary artery disease. Because prior meta-analyses had shown an opposite trend between fatal and nonfatal stroke events,[6,7] we studied both outcomes individually by contacting each study site to obtain further, unpublished data.

METHODS

Acquisition of Trials

The medical literature was searched to obtain all trials that used HMG-CoA reductase inhibitors to lower serum cholesterol and measured their effects on total mortality or cardiovascular end points. Our search strategy was conducted in two stages. First, we performed a MEDLINE search from 1983 to June 1996 using single word combinations: *pravastatin and trial*, *simvastatin and trial*, *lovastatin and trial*, and *fluvastatin and trial*. Each abstract obtained from the search was independently reviewed and assessed by three authors (NS, DMT, and DP) for any indication that total mortality or cardiovascular end points were measured. Any reference designated as relevant by at least one author was obtained in full-length form.

Second, the bibliographies of the retrieved full-length studies were independently reviewed by two authors (NS and DP) to identify any other potentially relevant studies not retrieved in the first stage. Any reference identified as potentially relevant by either reviewer was retrieved in full length and its bibliography reviewed. This review process was repeated for every new article retrieved until all possible references were obtained. In addition, we contacted two pharmaceutical firms (Merck and Bristol-Meyers) to obtain their lists of references on HMG-CoA reductase inhibitor trials and of any studies relevant to stroke reduction. All references obtained were included in the second search stage.

Eligibility Criteria

All trials identified by our search strategy that included data on total mortality or cardiovascular events were applied to predetermined inclusion criteria that were agreed to by discussion and consensus among three of the authors (SW, SJM, and NS). To be included into the meta-analysis, trials had to be randomized and placebo controlled. Each trial must have used an HMG-CoA reductase inhibitor and reported or made any mention of collecting stroke data or other cerebrovascular end point. We excluded trials that used multi-interventional therapies when the effect from statins could not be separated out.

Data Extraction

Data were extracted independently from the eligible trials by two authors (DMT and DP) using a standard data collection form. A third author (NS) reviewed the two sets of forms, and disagreements were resolved by discussion and consensus.

Data were extracted for author, year of trial publication, number of patients enrolled in each arm of therapy, the percentage of males enrolled, the percentage of patients that had a prior myocardial infarction, initial and final cholesterol measurements on each arm of therapy including low-density lipoprotein (LDL) and high-density lipoprotein (HDL), type and dosage of interventions used, duration of trial, details of eligibility criteria for admission into the trial, and the number of fatal and nonfatal stroke events on each arm of therapy. When reported, the specific type of stroke event (hemorrhagic, embolic, or thrombotic) was recorded. The reviewers also computed the net percentage of change in cholesterol level for the treatment group relative to the control group, calculated as follows: net % change = % change in cholesterol level on treatment − % change in cholesterol level on placebo. The percentage of change in cholesterol for either group was calculated as: % change = (initial cholesterol level − final cholesterol level)/initial cholesterol level. We also extracted data for coronary events, defined as the number of nonfatal myocardial infarctions plus the number of deaths from coronary heart disease.

When eligible trials did not provide sufficient information to completely determine the number of fatal, nonfatal, or total strokes in each arm of therapy, we contacted the investigators to obtain missing information.

Statistical Methods

We used Meta-Analyst, Version 0.98 (New England Medical Center, Boston, Mass, 1994) software to compute odds ratios (ORs) and 95% confidence intervals (CIs) for individual trials on fatal, nonfatal, and total stroke outcomes. To avoid undefined ORs and variance terms, the

program added 0.5 to all cells within a study when a 0 cell was present. The program also used Woolf's method to compute 95% CIs.[13]

STATXACT, Version 3.0.2 (Cytel Software Corp, Cambridge, Mass, 1996) was used to compute a conditional maximum likelihood pooled odds ratio estimate (CMLE), 95% CIs, and an exact test of homogeneity for all trials combined. We also computed a Mantel-Haenszel pooled OR estimate and a Breslow-Day χ^2 test of homogeneity. Because the pooled results and tests of homogeneity for each outcome were similar for both methods, only the exact CMLE estimates and exact tests of homogeneity are reported.

We also performed subgroup analyses to observe the relative risks of stroke outcomes in primary and secondary coronary prevention trials. To compare the differences in results between primary and secondary prevention trials, a χ^2 test for between-group heterogeneity was used.[14]

BMDP (1R and 9R) statistical software, Version 7.0 (BMDP Statistical Software Inc, Los Angeles, Calif, 1992), was used to perform weighted univariate linear regressions. We used the natural log of the ORs for individual trials for fatal, nonfatal, and total stroke outcomes as the dependent variables, and the initial total and LDL cholesterol levels and the net percentage decrease in total and LDL cholesterol levels as the independent variables. Trials were weighted by the inverse of their variance. To observe the relation of the relative OR and absolute risk reduction for stroke across the range of baseline cardiac event rates for the included trials, we performed weighted univariate regressions for all three stroke outcomes. Standard errors for the β values (meta-regression coefficients) were corrected by dividing their reported standard errors by the square root of the residual mean square.[14] We performed a retrospective meta-analysis for coronary events using Meta-Analyst (Version 0.98) software to compute a pooled Mantel-Haenszel risk ratio and 95% CIs.

RESULTS

Literature Search and Eligibility Criteria

Our MEDLINE search identified 251 references that were reviewed in abstract form. Of these, eight trials,[10,15–21] five reviews and meta-analyses,[22–26] and 16 additional references,[27–42] were obtained in full-length form. The bibliographies from these 29 references were reviewed to obtain other potentially relevant articles. The second stage of our review identified another 19 clinical trials,[8,9,43–59] 18 meta-analyses and reviews,[6,7,12,60–74] seven abstracts,[75–81] and 20 additional references.[2,82–100]

A total of 27 trials that included data on total mortality or cardiovascular events were identified by our search strategy and applied to our predetermined eligibility criteria. Twelve of these trials randomized their patients to receive either statin monotherapy or placebo and reported or made mention of collecting data on stroke events,[8–10,15–19,43–46] thereby meeting our inclusion criteria. Of the 15 excluded trials,[20,21,47–59] 3 trials used a statin but did not report or make mention of collecting any stroke data,[21,52,58] and 9 studies did not use a statin.[49–51,53–57,59] We excluded three trials because statins were used concomitantly with other lipid lowering agents,[20,47,48] hence, the effect of monotherapy on stroke reduction could not be ascertained. In addition, we later identified an abstract of a meta-analysis on HMG-CoA reductase inhibitors and stroke.[101] The abstract identified one new clinical trial[11] and a previously excluded trial that met our inclusion criteria.[52]

Of the 14 eligible trials,[8–11,15–19,43–46,52] 9 trials had missing data on stroke events.[10,11,16–19,44,46,52] We were able to obtain the complete information on stroke events in eight [10,11,16–18,44,46,52] of the nine trials. The Expanded Clinical Evaluation of Lovastatin Study (EXCEL) had one stroke event[19] but despite contacting the authors, we were not able to learn the treatment group in which it had occurred, and the trial was excluded. Our meta-analysis was, therefore, based on the complete evidence (both fatal and nonfatal stroke events) obtained from 13 randomized placebo-controlled trials.[8–11,15–18,43–46,52]

Study Characteristics and Methodologic Issues

Study characteristics of the 13 included trials are outlined in Tables 1 and 2. Four trials were classified as primary coronary prevention studies.[8,9,11,15] The West of Scotland Prevention Trial (WOSCOP) enrolled patients with an LDL cholesterol level above 155 mg/dL who had no prior history of myocardial infarction and no serious electrocardiogram abnormalities or concurrent illnesses.[15] The ACAPS,[8] KAPS,[9] and CAIUS[11] trials enrolled hypercholesterolemic patients with early carotid artery disease diagnosed by B-mode ultrasonography. Patients with a prior history of myocardial infarction, angina, stroke, or transient ischemic attack were excluded from the ACAPS trial,[8] while patients in the CAIUS trial were reported to be free of symptoms or signs of coronary artery disease.[11] The population-based KAPS trial included about 8% of patients with a prior history of myocardial infarction.

Of the nine secondary coronary prevention trials, four trials, the Monitored Atherosclerosis Regression Study (MARS),[17] the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries Trial (PLAC-I),[18] the Regression Growth Evaluation Statin Study (REGRESS),[44] and the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT),[52] were quantitative angiographic trials that enrolled patients with hypercholesterolemia and angiographically documented coronary atherosclerosis. One, the Lovastatin Restenosis (LR) Trial,[16] was an angiography study evaluating the effect of lovastatin on restenosis rates after coronary angioplasty. At baseline, both groups had mean total cholesterol levels under 210 mg/dL. The PLAC-II trial was a carotid ultrasonographic study that enrolled hypercholesterolemic patients who had a prior history of myocardial infarction or documented evidence of coronary artery disease by angiography.[10] In addition, patients were

Table 1. Study Characteristics of Included Trials*

Trial Year	Patients Randomized, *n*	Study Focus	Proportion Enrolled with Myocardial Infarction, %	Drug Intervention	Daily Dose, mg/d	Mean Length of Follow-up, years
ACAPS[8] 1994	461	Primary prevention	0	Lovastatin	10–40†	3.0
KAPS[9] 1995	447	Primary prevention	8	Pravastatin	40	3.0
PLAC-II[10] 1995	151	Secondary prevention	63	Pravastatin	10–40†	3.0
CAIUS[11] 1996	305	Primary prevention	0	Pravastatin	40	3.0
WOSCOP[15] 1995	6,595	Primary prevention	0	Pravastatin	40	4.9
LR[16] 1994	404	Secondary prevention	25	Lovastatin	80	0.5
MARS[17] 1993	270	Secondary prevention	60	Lovastatin	80	2.2
PLAC-I[18] 1995	408	Secondary prevention	43	Pravastatin	40	3.0
4S[43] 1994	4,444	Secondary prevention	63	Simvastatin	10–40†	5.4‡
REGRESS[44] 1995	884	Secondary prevention	47	Pravastatin	40	2.0
PMSG[45] 1993	1,062	Secondary prevention	35	Pravastatin	20–40	0.5
CARE[46] 1996	4,159	Secondary prevention	100	Pravastatin	40	5.0‡
CCAIT[52] 1994	331	Secondary prevention	54	Lovastatin	20–80†	2.0

**ACAPS indicates Asymptomatic Carotid Artery Progression Study; KAPS, Kuopio Atherosclerosis Prevention Study; PLAC-II, Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries; CAIUS, Carotid Atherosclerosis Italian Ultrasound Study; WOSCOP, West of Scotland Coronary Prevention Study; LR, Lovastatin Restenosis Trial; MARS, Monitored Atherosclerosis Regression Study; PLAC-I, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries Trial; CARE, Cholesterol and Recurrent Events Trial; 4S, Scandinavian Simvastatin Survival Study; REGRESS, Regression Growth Evaluation Statin Study; PMSG, Pravastatin Multinational Study Group for Cardiac Risk Patients; CCAIT, Canadian Coronary Atherosclerosis Intervention Trial.*

†*Range of dosages reported in trial to maintain target cholesterol levels in study participants.*

‡*Length of follow-up reported as median.*

required to have one carotid artery lesion by B-mode ultrasonography at baseline. The Scandinavian Simvastatin Survival Study (4S) enrolled hypercholesterolemic patients with a prior history of angina pectoris or myocardial infarction,[43] and the Pravastatin Multinational Study Group (PMSG) enrolled hypercholesterolemic patients with two or more additional risk factors for coronary artery disease.[45] Thirty-five percent of patients reported a history of previous myocardial infarction, and 40% reported a history of angina pectoris. Finally, the Cholesterol and Recurrent Events (CARE) trial enrolled patients who had experienced myocardial infarction 3 to 20 months previously and had total cholesterol levels of less than 240 mg/dL.[46]

All 13 trials were conducted in double-blind fashion. Twelve of 13 trials randomized their patients to receive either statin monotherapy or placebo. One trial, ACAPS,[8]

Table 2. Subject Characteristics and Cholesterol Changes by Trial

Trial*	Mean Age, years	Proportion of Male Patients Enrolled, %	Baseline Total Cholesterol, mg/dL	Baseline LDL Cholesterol, mg/dL	Total Cholesterol Change,† %	LDL Cholesterol Change,† %
ACAPS[8]	62	51	236	156	−15	−21
KAPS[9]	57	100	259	189	−22	−32
PLAC-II[10]	62	85	235	166	−21	−29
CAIUS[11]	55	53	261	181	−18	−24
WOSCOP[15]	55	100	272	192	−20	−26
LR[16]	62	72	203	128	IR	−36
MARS[17]	58	91	235	166	−30	−37
PLAC-I[18]	57	78	231	164	−21	−29
4S[43]	59	82	261	188	−26	−36
REGRESS[44]	56	100	234	166	−19	−26
PMSG[45]	55	77	265	180	−18	−26
CARE[46]	59	86	209	139	−20	−28
CCAIT[52]	53	81	250	173	−20	−28

**Abbreviations are defined in the first footnote to Table 1.*

†*Percentage reduction from baseline in treated patients compared with controls. A negative change implies a greater cholesterol reduction from baseline on statin therapy as compared to control; LDL indicates low-density lipoprotein; IR, insufficient information reported to permit calculation.*

randomized patients to four groups: lovastatin and warfarin; lovastatin and warfarin placebo; lovastatin placebo and warfarin, and lovastatin placebo and warfarin placebo. In this study, we only analyzed data comparing the lovastatin and warfarin placebo group to the lovastatin placebo and warfarin placebo group. Of the 13 trials, 11 were multicenter studies. Four were conducted solely in the United States, [8,16–18] one from 80 centers in the United States and Canada,[46] one from the five countries in Scandinavia,[43] one from The Netherlands,[44] one from Scotland,[15] one from Canada,[52] one from Italy,[11] and one from eight countries—Australia, Belgium, Finland, Germany, Israel, The Netherlands, Sweden, and the United Kingdom.[45] PLAC-II was a single-center study from the United States,[10] and KAPS was a population-based single-center study that enrolled patients from a geographically defined area in Eastern Finland.[9]

A total of 19,921 patients were enrolled in the trials: 9,973 in the statin group and 9,948 in the placebo group. Individual trial sizes varied, and enrollments ranged from 151 patients[10] to 6,595 patients.[15] Four trials used lovastatin,[8,16,17,52] eight used pravastatin,[9–11,15,18,44–46] and one used simvastatin,[43] for the groups allocated to statin treatment. No eligible trial used fluvastatin. Trial duration ranged from 6 months[16,45] to 5.4 years,[43] with a weighted total mean duration of 4.3 years.

On average, patients enrolled in these trials were of middle age. The weighted overall mean age was 57.2 years. Mean age at entry ranged from 53 years[52] to 62 years.[8,10,16] The percentage of male subjects ranged from 51%[8] to 100%.[9,15,44] The percentage of patients that were male from the 13 trials combined was 88.4% (17,613 patients).

Mean baseline total cholesterol levels were close to

Table 3. Stroke Events and Odds Ratios of Stroke Events in Included Trials

Trial*	Treatment	Total Patients, *N*	Stroke Events†, *n*			Odds Ratio (95% Confidence Interval)‡,§		
			Total, *n*	Nonfatal, *n*	Fatal, *n*	Total Stroke	Nonfatal Stroke	Fatal Stroke
ACAPS[8]	Lovastatin	231	0	0	0	0.33	1.00	0.33
	Placebo	230	1	0	1	(0.01, 8.15)	(0.02, 50.39)	(0.01, 8.15)
KAPS[9]	Pravastatin	224	2	2	0	0.49	0.66	0.33
	Placebo	223	4	3	1	(0.09, 2.72)	(0.11, 3.99)	(0.01, 8.15)
PLAC-II[10]	Pravastatin	75	1	1	0	0.33	0.33	1.01
	Placebo	76	3	3	0	(0.03, 3.23)	(0.03, 3.23)	(0.02, 51.73)
CAIUS[11]	Pravastatin	151	0	0	0	1.02	1.02	1.02
	Placebo	154	0	0	0	(0.02, 51.72)	(0.02, 51.72)	(0.02, 51.72)
WOSCOP[15]	Pravastatin	3,302	46	40	6	0.90	0.85	1.50
	Placebo	3,293	51	47	4	(0.60, 1.34)	(0.55, 1.29)	(0.42, 5.31)
LR[16]	Lovastatin	203	0	0	0	0.33	0.33	0.99
	Placebo	201	1	1	0	(0.01, 8.11)	(0.01, 8.11)	(0.02, 50.14)
MARS[17]	Lovastatin	134	0	0	0	0.11	0.11	1.01
	Placebo	136	4	4	0	(0.01, 2.05)	(0.01, 2.05)	(0.02, 51.52)
PLAC-I[18]	Pravastatin	206	0	0	0	0.19	0.19	0.98
	Placebo	202	2	2	0	(0.01, 4.07)	(0.01, 4.07)	(0.02, 49.66)
4S[43]	Simvastatin	2,221	61	47	14	0.70	0.63	1.17
	Placebo	2,223	86	74	12	(0.50, 0.98)	(0.43, 0.91)	(0.54, 2.53)
REGRESS[44]	Pravastatin	450	2	2	0	0.48	0.48	0.96
	Placebo	434	4	4	0	(0.09, 2.63)	(0.09, 2.63)	(0.02, 48.71)
PMSG[45]	Pravastatin	530	0	0	0	0.14	0.14	1.00
	Placebo	532	3	3	0	(0.01, 2.77)	(0.01, 2.77)	(0.02, 50.68)
CARE[46]	Pravastatin	2,081	54	44	10	0.68	0.60	1.67
	Placebo	2,078	78	72	6	(0.48, 0.97)	(0.41, 0.88)	(0.60, 4.60)
CCAIT[52]	Lovastatin	165	1	1	0	3.04	3.04	1.01
	Placebo	166	0	0	0	(0.12, 75.08)	(0.12, 75.08)	(0.02, 51.00)
Pooled results‖,¶	Statin	9,973	167	137	30	0.70	0.64	1.25
	Placebo	9,948	237	213	24	(0.57, 0.86)	(0.51, 0.79)	(0.71, 2.24)

*Abbreviations are defined in the first footnote to Table 1.

†Data on nonfatal and fatal stroke events that were incompletely or not reported were provided by the investigators of eight clinical trials.[10,11,16–18,44,46,52]

‡Value reflects the ratio of the odds of having a stroke event on statin therapy to the odds of having a stroke event on placebo therapy. OR < 1 implies that statin therapy is more effective than placebo. OR > 1 implies that statin therapy is less effective than placebo. OR = 1 implies equal effectiveness for both therapies.

§To avoid undefined odds ratios and variance terms, a value of 0.50 was added to each cell when any cell in the category contained 0.

‖Conditional maximum likelihood estimate of the common odds ratio with exact 95% confidence intervals.

¶P value of exact test for homogeneity: total, p = .5067; nonfatal, p = .5257; fatal, p = .6749.

desirable in the LR trial[16] and CARE trial[46] (203 and 209 mg/dL, respectively), mild to moderately elevated in five trials[8,10,17,18,44] (range, 231–236 mg/dL), and severely elevated in six trials[9,11,15,43,45,52] (range, 250–272 mg/dL). The mean net percentage of cholesterol reduction on statin therapy ranged from 15% to 30% for total cholesterol and 21% to 37% for LDL cholesterol. Overall, levels dropped by an average of 21% and 29% in total and LDL cholesterol, respectively, relative to the placebo treatment.

Meta-Analysis of Treatment Effect

Table 3 lists the number of total, nonfatal, and fatal strokes that occurred in each trial by treatment group, the odds ratio for each trial, and the pooled odds ratios for the trials combined for each outcome. Eleven of the 13 trials demonstrated more total stroke events in the placebo group compared with the statin therapy group. The CAIUS trial showed no stroke events on either arm of therapy,[11] while the CCAIT trial showed more total stroke events on statin therapy compared with placebo (one nonfatal stroke event on lovastatin).[52] Of the 11 trials that showed more total stroke events on placebo, the three largest trials had a greater number of fatal stroke events that occurred on statin therapy compared with placebo therapy.[15,43,46] One trial showed a favorable relation in both nonfatal and fatal stroke events on statin therapy,[9] while six trials demonstrated a favorable trend in nonfatal stroke events on therapy and no fatal strokes on either arm of therapy.[10,16–18,44,45]

There were 167 (1.67%) and 237 (2.38%) total stroke events among the 9,973 and 9,948 pathients in the treatment and placebo groups, respectively. Nonfatal stroke events occurred in 137 (1.37%) of the statin group and 213 (2.14%) of the placebo group; and fatal stroke events occurred in 30 (0.30%) of the statin and 24 (0.24%) of the placebo group. Hence, among the placebo-treated patients, 90% of all strokes were nonfatal and 10% were fatal. Among the statin-treated group, 82% of all strokes were nonfatal and 18% were fatal.

For all three outcomes, the test of homogeneity was highly insignificant (Table 3). This reflects the fact that the individual trials' ORs differed from each other by chance alone, and therefore made it appropriate to pool the individual trial results to estimate for a common treatment effect.

For total stroke outcome, individual trial ORs ranged from 0.11,[17] to 3.04.[52] Statistical significance was achieved in two of the 13 trials.[43,46] The pooled OR for total stroke was 0.70 (95% CI 0.57, 0.86; $p = .0005$). For the nonfatal stroke outcome, individual trial ORs ranged from 0.11,[17] to 3.04,[52] and achieved statistical significance in the same two trials.[43,46] The pooled OR for nonfatal stroke was 0.64 (95% CI 0.51, 0.79; $p = .00001$). For the fatal stroke outcome, individual ORs ranged from 0.33,[8,9] to 1.67.[46] In the three largest trials, WOSCOP,[15] 4S,[43] and CARE,[46] all ORs were substantially greater than 1.00 (1.50, 1.17, and 1.67, respectively). None of the 13 individual trials, however, achieved statistical significance for fatal strokes. The pooled OR for fatal stroke was 1.25 (95% CI 0.71, 2.24; $p = .4973$).

Subgroup and Regression Analysis

In separate analyses, reductions in total and nonfatal stroke risk were found to be significant only for trials of secondary coronary disease prevention (Table 4). Although the observed relative risk reduction for secondary prevention trials was over twice that for primary prevention trials for the outcome of total and nonfatal stroke, the χ^2 tests of homogeneity between categories were not significant. Although no excess stroke mortality was observed in the primary prevention trials, trials of secondary prevention demonstrated a nonsignificant 34% increase in fatal stroke risk (24 strokes on statins vs 18 on placebo).

We did not find a strong or significant univariate association between the relative odds of stroke (total, fatal, or nonfatal) and the mean initial cholesterol level or mean net cholesterol reduction across these trials (Table 5). Also, we did not find a significant association between the relative ORs for all stroke outcomes and the baseline risk for cardiac events (Table 6). In contrast, the association between absolute risk reduction for total and nonfatal stroke outcomes was strong and significant for an increase in baseline risk for cardiac events in these trials. As in our subgroup analysis, a positive trend in fatal

Table 4. Subgroup Analysis of Lipid-Lowering Trials Included in the Meta-Analysis*,†

Category	Number of Studies	Subjects Randomized, *n*	Odds Ratio (95% Confidence Interval)		
			Total Stroke	Nonfatal Stroke	Fatal Stroke
Primary prevention[8,9,11,15]	4	7,808	0.85 (0.57, 1.28)	0.84 (0.54, 1.29)	1.00 (0.27, 3.73)
Secondary prevention[10,16–18,43–46,52]	9	12,113	0.65 (0.51, 0.82)	0.57 (0.44, 0.75)	1.34 (0.69, 2.62)

**Conditional maximum likelihood estimate of the common odds ratio with exact 95% confidence intervals.*

†The p *value for treatment effect. Primary prevention: total,* p = *.4803; nonfatal,* p = *.4545; fatal,* p = *1.0000. Secondary prevention: total,* p = *.0003; nonfatal,* p = *.00001; fatal,* p = *.4396. The* p *value for exact test of homogeneity within category. Primary prevention: total,* p = *.6818; nonfatal,* p = *1.0000; fatal,* p = *.2269. Secondary prevention: total,* p = *.4665; nonfatal,* p = *.5781; fatal,* p = *.7496. The* p *value for* χ^2 *test of homogeneity between categories (primary vs secondary prevention): total,* p > *.25; nonfatal,* p > *.10; fatal,* p > *.50.*

Table 5. Univariate Analysis of the Relation of Cholesterol Level and Percentage Change in Cholesterol Level to the Odds Ratio of Stroke in Cholesterol-Lowering Trials*

Independent Variable	Dependent Variable	Correlation Coefficient *r*	Regression Coefficient β	*p* Value
Baseline total cholesterol, mg/dL	Fatal stroke	−.2495	−.0035	.7340
	Nonfatal stroke	.3960	.0042	.3126
	Total stroke	.3186	.0032	.4010
Baseline LDL cholesterol, mg/dL	Fatal stroke	−.2572	−.0040	.7260
	Nonfatal stroke	.3524	.0042	.3682
	Total stroke	.2801	.0032	.5754
Total cholesterol change, %	Fatal stroke	−.0364	−.0038	.9600
	Nonfatal stroke	−.2181	−.0206	.5824
	Total stroke	−.1501	−.0134	.6966
LDL cholesterol change, %	Fatal stroke	−.0913	−.0067	.9044
	Nonfatal stroke	−.2849	−.0184	.4716
	Total stroke	−.2164	−.0133	.5686

**Regression analyses on stroke outcomes were performed in the natural log scale (ln OR). Regression weights were computed for each trial by the inverse of the square of their standard errors.*

stroke events was found with baseline cardiac events, but was not significant.

Meta-Analysis of Cardiac Events

Of the 13 trials included, 11 provided adequate data to perform the meta-analysis on cardiac events.[8–11,15,18,43–46,52] There were 756 (7.84%) and 1,112 (11.67%) cardiac events that occur among the 9,636 and 9,611 patients in the treatment and placebo groups, respectively. The pooled risk ratio for cardiac events was 0.67 (95% CI 0.62, 0.73; $p < .00001$). No significant within-group heterogeneity was detected.

DISCUSSION

The totality of the evidence suggests that HMG-CoA reductase inhibitors, unlike previously studied cholesterol-lowering drugs,[6,7] lower total stroke risk. However, we found that the majority of the reduction lies in reducing nonfatal stroke events. We observed a small increase in risk for fatal stroke events; this was about 25% overall and 34% in trials of secondary prevention. This observation was nonsignificant with wide confidence intervals, which cannot exclude either a protective or deleterious effect from this class of drugs. In support of a deleterious effect is the hypothesis suggested from observational trials[2,3] and prior meta-analyses[6,7] that lowering cholesterol below 200 mg/dL may increase fatal strokes by weakening small cerebral vessels and cause hemorrhagic strokes. In support for either a null or beneficial effect, we did not find a strong or significant association between initial cholesterol level or the degree of cholesterol lowering and risk of fatal stroke.

This meta-analysis, like prior ones, suffers several limitations. With the exception of the 4S trial, which subclassified stroke among nonfatal events only, all other trials did not have any data on the pathology of stroke types for fatal and nonfatal events. Hemorrhagic strokes have a 30-day fatality rate of 40% to 50% as compared with 10% to 20% for ischemic strokes.[102] The much greater proportion of hemorrhagic strokes that are fatal as compared with ischemic strokes leads us to infer that it is possible

Table 6. Univariate Analysis of the Relation of Baseline Coronary Event Rate to the Odds Ratio and Risk Difference of Stroke in Cholesterol-Lowering Trials*

Outcome	Measure of Association†,‡	Correlation Coefficient *r*	Regression Coefficient *β*	*p* Value
Fatal stroke	Odds ratio	.2495	.0088	.7338
	Risk difference	.4768	.0125	.4716
Nonfatal stroke	Odds ratio	−.5486	−.0143	.2302
	Risk difference	−.7607	−.0946	.0140
Total stroke	Odds ratio	−.3841	−.0096	.3844
	Risk Difference	−.6757	−.0848	.0366

**Risk differences for individual trials were computed using Meta-Analyst Version 0.98. To avoid undefined variance terms, a value of 0.5 was added to each cell when any cell contained 0.*

†*Regression of the odds ratios to baseline coronary event rates were performed using the natural log scale (ln OR). Risk difference was defined as the incidence rate difference for 1,000 patient-years. Baseline coronary event rates were computed as the number of coronary events on placebo treatment per 1,000 patient-years.*

‡*Regression weights were computed for each trial by the inverse of the square of their standard errors.*

that the majority of fatal stroke events were hemorrhagic in nature, while most of the nonfatal stroke events were ischemic.[6,7] This assumption may be erroneous because most strokes are ischemic in absolute number (approximately 85% of total strokes); therefore, the majority of fatal strokes still may represent large ischemic events.[103] Although our meta-analysis failed to demonstrate a beneficial effect of statins on fatal stroke risk, we observed a modest and significant decrease in the relative risk of nonfatal stroke (OR = 0.64). For a null effect, that is, an equal risk of fatal stroke on statin and placebo, we postulate that statins' benefit on ischemic events is offset by an increase in fatality due to hemorrhage. Although there is a greater chance of having a nonfatal stroke event from small vessel disease as compared with large vessel disease, the majority of nonfatal events are from large vessel ischemia (emboli or thrombotic).[104] We suspect that statins are beneficial in preventing ischemic processes in all types of cerebrovascular disease. However, their effect may be more beneficial for small vessel disease than for large vessel disease as their tiny caliber would make hemostatic and vascular wall changes more pronounced. Therefore, our data could suggest that statins prevent nonfatal stroke events by lowering the incidence of small vessel thrombotic stroke (lacunes) more than the potentially lethal cardioembolic or large vessel infarcts. Cholesterol lowering may have a greater effect on small vessels to prevent lacunar infarcts, just as the effect of cholesterol lowering can more profoundly cause arterial rupture in these small vessels by weakening the intimal lining.[105]

Our overall case-fatality rate for stroke was 13%, whereas that seen in general stroke populations is about 30%.[106,107] The lower fatality rate in our study is expected, as the study population was younger, healthier, and predominantly white. As 40% of our patients were in primary prevention studies (which excluded coronary artery disease, myocardial infarction, and stroke), they were generally a healthy group. Stroke mortality rises exponentially with age and doubles every 10 years.[108] Our average age was young (57.2 years), whereas the majority of strokes occur in people over age 65. Race is also important in stroke mortality. African Americans have a twofold higher mortality than their white counterparts.[109,110] Although we did not study the data on race, over 11,000 patients in this meta-analysis were Scandinavian or Scottish and presumably unrepresentative of the African-American population.

Some of the observed effects of statins in reducing stroke events may reflect their non-lipid-lowering properties. Statins have antithrombotic effects on endothelial function, plaque stability, and thrombus formation.[111] Statins also cause platelet inhibition and facilitate fibrinolysis. These effects could also explain the lowered incidence of nonfatal stroke by preventing ischemia, however, causing fatal strokes by facilitating bleeding.

Our results are concordant with the four meta-analyses published after our search was concluded.[112–115] All four studies showed statistically significant reductions in total stroke risk. The two that were able to discriminate fatal from nonfatal strokes,[113,114] as we did, found a significant reduction in nonfatal stroke risk and a nonsignificant increase in fatal stroke events on statins. Two of these four overviews also conducted separate meta-analyses for trials of primary and secondary coronary disease prevention.[112,113] They found, as we did, a significant reduction in total and nonfatal stroke risk only for trials of secondary coronary disease prevention. Although the studies included in our meta-analysis were similar to the others,[112–115] two randomized controlled trials using statins[21,58] were excluded from analysis on the basis that they did not report stroke data. Two of the four recent meta-analyses[113,114] included data on the Multicenter Anti-Atheroma Study (MAAS),[21] while no data were available for the other excluded trial.[58] The MAAS study was an angiographic trial of 381 patients assigned to simvastatin or placebo for 4 years.[21] The trial demonstrated no fatal stroke events on either arm of therapy, two nonfatal strokes on placebo, and one nonfatal stroke on simvastatin. Recalculating the meta-analysis by including the MAAS data, we found exactly the same summary point estimates and confidence limits for both fatal and nonfatal stroke outcomes (fatal stroke, OR 1.25; 95% CI 0.71, 2.24; nonfatal stroke, OR 0.64; 95% CI 0.51, 0.79). The Sahni et al. trial was an angiography study that evaluated the effect of lovastatin on restenosis rates after coronary angioplasty.[58] This trial included 157 patients followed for an average duration of 4 months. Although no stroke data were reported in their publication, it is doubtful that their results would appreciably alter our overall summary estimates.

In this meta-analysis, the aggregation of summary statistics from a wide diversity of patients to arrive at a point estimate of relative risk may obscure the ability to determine whom this type of therapy is most or least likely to benefit. Although we did find that the relative risk reduction in nonfatal stroke from secondary prevention trials may be more than twice that of primary prevention trials, this difference was not significant and had overlapping confidence intervals. While the relative risk of stroke did not show a significant relation to baseline cardiac risk, our weighted linear regression model did support a significant trend between the absolute risk reduction and baseline risk for cardiac events. This relation implies that while the relative benefit may be similar between primary and secondary prevention, patients with a greater background risk of cardiovascular events, such as those with established coronary artery disease or with multiple risk factors, will benefit the most in stroke reduction from statin therapy.

Our meta-analysis did not find that the initial and net percentage of change in cholesterol levels obtained on statin therapy were significantly correlated with the relative risk reduction for fatal or nonfatal stroke. Our findings therefore imply that the relative benefit is fairly uniform for a magnitude of total cholesterol change within a 15% to 30% range, as well as a starting total cholesterol level of 200 to 300 mg/dL as observed in the included trials. Also, any potential deleterious effects of cholesterol

reduction cannot be attributed to the observed magnitude of cholesterol change or range of baseline cholesterol values. Regardless of the reduction in serum cholesterol, our observations could support a therapeutic effect on ischemia and a deleterious effect to promote hemorrhage due to the non-lipid-related properties of the statins. Alternatively, it is possible that the initial mean cholesterol levels were too high or that the cholesterol reductions were too small to detect an increase in fatal stroke risk. Perhaps, consistent with some observational studies, hemorrhagic stroke risk may become pronounced at cholesterol levels less than or equal to 160 mg/dL.[2,3]

Obtaining individual patient data may then be useful in assessing the relative risk of fatal stroke at very low cholesterol levels and at very high cholesterol reductions. However, it is probable that with only 54 fatal events in nearly 20,000 patients, this question could not be answered due to the rarity of these events. In fact, to detect an absolute risk difference in fatal stroke of 0.06% between treatment and placebo groups, as found in our meta-analysis, would require 121,402 patients in each group to be 80% certain of showing a significant difference between the groups at the $p = .05$ level.[116] It is doubtful that such a trial would be considered in the future.

With such a small difference in absolute risk, if a 25% increase in relative risk of fatal stroke does exist, what would the risk-benefit ratio be, assuming a 36% decrease in nonfatal stroke risk observed in these trials, and how will these results be placed in view of the much larger protective effect of statins on cardiac risk? Our data suggest that for every 10,000 patients treated per year with statins, we can expect to prevent 91 myocardial infarctions and 18 nonfatal strokes and to cause one fatal stroke.

In summary, we believe the best available evidence supports the use of statins to prevent the morbidity associated with stroke. However, its ability to affect mortality rates, either beneficially or deleteriously, is uncertain owing to the low event rates found in these clinical trials of cardiovascular disease prevention. Further research will need to focus on defining the etiology of strokes observed in patients on statin medications to better understand the impact of lipid-lowering therapy on cerebrovascular diseases. For the present, we conclude that the benefits of statins on coronary morbidity and mortality far outweigh their impact on stroke events. We estimate that, on average, one cardiac event is prevented for every 26 patients treated, and one stroke is prevented for every 143 patients treated with statins over a 4-year period.

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