Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 55, No. 3, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.07.062

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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Manuscript received April 27, 2009; revised manuscript received July 20, 2009, accepted July 27, 2009.

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-

JACC Vol. 55, No. 3, 2010
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Table 1 Description of Trials Selected, Demographic Characteristics

Trial, Year of Publication	Design*	Follow-Up†	Total Patients	Total Stroke	Fatal Stroke	Nonfatal Stroke	Age, yrs (Mean)	SMK (%)	DM (%)	HBP (%)	PMI (%)	PST (%)
Oslo, 1966	D,op,SE	*5*	412	3	2	N/A	56.0	64.6	10.0	—	100	—
MRC, 1968	D,op,SE	4	393	2	2	0	—	82.5	0.0	13.0	100	—
LA, 1969	D,b,PS	*8*	846	38	12	26	65.5	66.4	—	—	20.1	12.5
Newcastle, 1971	F,b,SE	3.6	497	1	1	0	52.5	65.0	0.0	0.0	23.0	—
Scottish, 1971	F,b,SE	3.4	717	5	5	0	52.1	56.6	0.0	—	72.9	—
VA, 1974	F,b,SE	4.5	532	60	13	N/A	—	—	23.5	64.5	—	16.0
CDP, 1975	F O,b,SE	6.2	5,011	161	34	N/A	52.0	37.9	5.0	20.0	100.0	2.0
Dorr, 1978	O,b,PS	1.9	1,094	1	1	0	50.5	—	13.7	16.2	6.2	0.5
WHO, 1980	F,b,PR	5.3	10,627	N/A	25	31	45.9	56.0	0.0	0.0	0.0	0.0
McCaughan, 1981	O,b,PS	*1*	118	0	0	0	49.8	44.6	—	—	33.9	—
LRC-CPPT, 1984	O,b,PR	7.4	3,806	35	4	0	47.7	37.5	0.0	0.0	0.0	0.0
CLAS I, 1987	O,b,SE	*2*	188	0	0	0	54.2	0.0	0.0	0.0	—	—
Helsinki, 1987	F,b,PR	5	4,081	10	10	0	47.3	36.2	2.6	14.0	0.0	0.0
Stockholm, 1988	O,op,SE	*5*	555	11	6	5	59.8	67.3	3.3	36.0	100.0	—
Minnesota, 1989	D,b,PR	1.1	9,057	43	43	0	48.0	—	—	—	—	—
FATS, 1990	S O,b,SE	2.7	146	0	0	0	47.3	24.4	0.0	32.8	42.6	—
POSCH, 1990	B,op,SE	9.7	838	29	3	N/A	51.0	35.0	0.0	0.0	100.0	0.0
EXCEL, 1991	S,b,PS	*0.9*	8,245	11	1	N/A	55.8	18.3	1.1	39.6	—	3.9
Singh, 1992	D,b,SE	1	406	3	3	0	51.3	35.4	18.0	22.0	100.0	—
Frick, 1993	F,b,SE	*5*	628	2	2	0	48.6	38.8	—	—	9.0	—
MARS, 1993	S,b,SE	2.2	270	3	0	N/A	58.0	—	0.0	46.0	60.0	—
PMSG-CRP, 1993	S,b,SE	*0.5*	1,062	3	0	3	55.0	28.7	0.0	47.5	34.5	—
4S, 1994	S,b,SE	5.5	4,444	132	26	N/A	58.6	25.6	4.5	26.0	79.3	0.0
ACAPS, 1994	S,b,PR	2.8	919	5	2	3	61.7	11.9	2.3	28.8	0.0	0.0
CCAIT, 1994	S,b,SE	*2*	331	1	0	N/A	53.0	27.0	14.0	37.0	54.0	18.0
LR, 1994	S,b,SE	0.5	404	1	0	1	62.0	49.8	11.6	48.8	25.0	—
Lyon, 1994	D,b,SE	2.3	605	3	0	3	53.5	6.2	—	0.0	100.0	—
MAAS, 1994	S,b,SE	*4*	381	3	0	N/A	55.3	23.9	0.0	—	54.3	—
PLAC-I, 1994	S,b,SE	2.3	408	2	0	2	57.0	16.5	0.0	45.5	43.5	0.0
PLAC-II, 1994	S,b,SE	*3*	151	4	1	N/A	62.5	12.1	—	0.0	63.8	—
REGRESS, 1994	S,b,SE	*2*	884	2	0	2	56.2	27.7	0.1	27.8	47.4	—
KAPS, 1995	S,b,PS	*3*	447	6	1	5	57.4	26.2	2.5	33.1	7.6	—
CARE, 1996	S,b,SE	5	4,159	128	16	N/A	59.0	21.0	14.5	42.5	100	—
WOSCOPS, 1996	S,b,PR	4.9	6,595	97	10	N/A	55.2	44.0	1.0	15.5	0.0	0.0
CIS, 1997	S,b,SE	2.3	254	0	0	0	49.3	84.3	0.0	—	—	—
LOCAT, 1997	F,b,SE	2.5	395	0	0	0	59.2	—	0.0	40.0	55.2	—
PCABGT, 1997	S,op,SE	4.3	1,351	34	N/A	N/A	61.5	11.3	8.6	—	49.3	—
PREDICT, 1997	S,b,SE	*0.5*	695	1	1	0	58.3	33.7	7.2	30.7	37.1	1.9
AFCAPS, 1998	S,b,PR	5.2	6,605	31	N/A	N/A	58.0	12.4	2.4	21.9	0.0	0.0
LIPID, 1998	S,b,SE	6.1	9,014	373	49	N/A	61.5	9.6	8.7	41.7	63.8	4.1
Mas, 1999	O,b,SE	*0.5*	437	1	N/A	N/A	58.0	32.7	17.8	82.2	—	3.9
GISSI-P, 2000	S,op,SE	1.9	4,271	39	8	31	60.0	11.9	13.6	36.5	100.0	—
SCAT, 2000	S,b,SE	4.0	460	11	9	N/A	61.0	15.0	10.9	35.2	70.4	—
VA-HIT, 2000	F,b,SE	5.1	2,531	134	12	N/A	64.0	20.5	24.5	57.0	61.0	—
BCAPS, 2001	S,b,SE	*3*	793	8	N/A	N/A	61.8	30.8	3.0	12.1	—	—
BIP, 2001	F,b,SE	6.2	3,090	149	N/A	N/A	60.1	11.8	10.0	32.4	77.9	1.1
DAIS, 2001	F,b,SE	3.3	418	12	N/A	N/A	56.8	14.8	100.0	51.4	—	—
HATS, 2001	S,b,SE	*3*	160	4	0	4	53.0	24.0	16.0	49.0	55	—
ALLHAT-LLT, 2002	S,op,PR	4.8	10,355	440	109	N/A	66.4	23.2	35.1	100.0	0.0	0.0
FAST, 2002	S O,PR	*2*	246	0	0	0	66.3	61.2	24.2	39.1	—	—
GREACE, 2002	S,op,SE	3	1,600	26	1	N/A	58.5	—	19.6	42.9	81.2	—
HPS, 2002	S,b,SE	5	20,536	1,029	215	865	64.0	14.1	29.0	41.0	41.0	—
LEADER, 2002	F,b,SE	4.6	1,568	109	22	87	68.2	37.8	17.1	—	19.8	11.7
Liem, 2002	S,b,SE	1	540	3	3	0	60.5	—	—	—	100.0	—
LIPS, 2002	S,b,SE	3.9	1,677	3	3	N/A	60.0	26.6	12.1	38.6	44.4	2.6

Continued on next page

Table 1 Continued

Trial, Year of Publication	Design*	Follow-Up†	Total Patients	Total Stroke	Fatal Stroke	Nonfatal Stroke	Age, yrs (Mean)	SMK (%)	DM (%)	HBP (%)	PMI (%)	PST (%)
PROSPER, 2002	S,b,PS	3.2	5,804	266	36	235	75.4	26.8	10.7	61.9	13.4	—
ALERT, 2003	S,b,PS	5.1	2,102	104	31	N/A	50.0	18.5	18.8	74.9	3.1	5.8
ASCOT-LLA, 2003	S,b,PR	3.2	10,305	210	N/A	N/A	63.0	32.7	24.6	100.0	0.0	0.0
Mohler, 2003	S,b,SE	1	354	2	1	1	67.8	41.3	16.9	—	—	—
ALLIANCE, 2004	S,b,SE	4.3	2,442	74	N/A	N/A	61.2	19.5	22.1	—	57.8	6.6
ARBITER2, 2004	O,b,SE	*1*	167	1	N/A	N/A	67.5	10.2	27.5	74.9	49.7	—
Bae, 2004	S,b,SE	6	205	2	0	2	60.0	41.5	29.8	48.3	12.2	—
CARDS, 2004	S,b,PR	3.9	2,838	60	6	50	62.0	22.2	100.0	83.8	0.0	0.0
PCS, 2004	S,b,SE	5	120	7	N/A	N/A	59.6	67.5	17.5	59.2	—	—
4D, 2005	S,b,SE	4	1,255	103	40	65	65.7	8.6	100.0	—	17.6	—
FIELD, 2005	F,b,SE	*5*	9,795	333	N/A	N/A	62.2	9.4	100.0	56.6	5.0	3.5
Makuuchi, 2005	S,op,SE	4.5	303	6	1	N/A	58.9	41.9	33.3	51.5	62.0	—
Stone, 2005	S,b,SE	*1*	300	2	N/A	N/A	—	0.0	16.0	63.6	39.3	—
ASPEN primary, 2006	S,b,PR	4	1,905	56	N/A	N/A	60.5	13.2	100.0	52.3	0.0	0.0
ASPEN secondary, 2006	S,b,SE	4	505	16	N/A	N/A	63.2	9.7	100.0	65.5	78.2	—
SPARCL, 2006	S,b,SE	4.9	4,731	576	65	527	62.7	19.2	16.7	61.9	30.9	69.1
WHI-DM, 2006	D,op,PS	8.1	48,835	1,076	150	935	62.3	6.7	—	42.9	1.9	1.1
CORONA, 2007	S,b,SE	2.7	5,011	218	67	197	73.0	8.6	29.5	63.4	59.9	12.4
ARISE, 2008	O,b,SE	*2*	6,144	54	0	54	65.0	13.5	37.0	72.0	72.0	—
CCSPS, 2008	O,b,SE	4.5	4,870	N/A	25	N/A	58.9	34.5	12.5	55.5	100.0	—
GISSI-HF, 2008	S,b,SE	3.9	4,574	148	67	86	68.0	14.1	26.1	54.3	—	4.5
JUPITER, 2008	S,b,PR	1.9	17,802	97	N/A	88	66.0	15.8	0.0	57.3	0.0	0.0
OACIS lipid, 2008	S,op,SE	0.7	353	2	N/A	N/A	63.2	57.4	31.7	47.6	100.0	7.3

*Design: the first letter indicates the type of lipid lowering intervention (D = diet, S = statins, F = fibrates, O = other drugs, B = ileal bypass or other surgery); the second letter indicates the study design (op = open; b = blind); and the last letter indicates the clinical setting (PR = primary, SE = secondary, PS = primary and secondary). †Follow-up indicates mean duration (year); in its absence, the maximum follow-up duration is indicated in italics. For full details of trial references, see Online Table 1.

DM = diabetes mellitus; HBP = high blood pressure; N/A = not available; PMI = previous myocardial infarction; PST = previous stroke; SMK = smoking status.

lowering treatment decreased the risk of total stroke by 12% (95% CI: −17% to −6%; $p < 0.001$). The result of the heterogeneity test between studies was statistically significant ($p = 0.050$).

As to the efficacy of specific cholesterol-lowering interventions on total stroke, 148,296 patients were treated with statins or placebo and 106,216 subjects were treated with other interventions or placebo The effect of statins on the risk of total stroke was statistically significant, with a 15% decrease of the OR (95% CI: −22% to −8%; $p < 0.001$). The other cholesterol-lowering interventions did not decrease the risk of total stroke significantly, the OR varying from 0.81 for drugs other than statins and fibrates to 0.92 for the POSCH (Program on the Surgical Control of the Hyperlipidemias) study and diet trials. Compared with trials testing statins, those testing other cholesterol-lowering interventions were fewer and more likely to be conducted in primary prevention, and therefore observing a lower number of strokes. However, the lack of efficacy of the other interventions was mainly due to the lack of effect of fibrates in reducing the risk of total stroke (OR: 0.98, 95% CI: 0.86 to 1.12; p = NS), as confirmed by the nonsignificant result of the test of heterogeneity between trials when we excluded from the analysis trials testing fibrates, as well as by the wide overlap of the CI for studies testing statins and studies not testing fibrates.

Information on fatal stroke was available from 66 trials (Fig. 1B) for a total of 102,799 patients allocated to active cholesterol-lowering treatment and 110,822 controls. Lipid-lowering interventions did not decrease the risk of fatal stroke (OR: 0.99, 95% CI: 0.88 to 1.11; $p = 0.780$); the heterogeneity test between studies was not statistically significant. Similarly, neither statins (OR: 0.98, $p = 0.832$) nor other cholesterol-lowering interventions decreased the risk of fatal stroke.

Information on nonfatal stroke was available from 44 trials (Fig. 1C) for a total of 75,473 patients allocated to active cholesterol-lowering treatment and 85,074 controls. Cholesterol-lowering interventions decreased the risk of nonfatal stroke significantly, by 13% (95% CI: −19% to −6%; $p < 0.001$), and the heterogeneity test between studies was statistically significant ($p = 0.006$). Nonfatal stroke was indeed significantly reduced by statins (OR: 0.81, 95% CI: 0.74 to 0.89, $p < 0.001$), but not by the other cholesterol-lowering interventions.

We performed sensitivity analyses by assessing the efficacy of cholesterol-lowering treatments in various subgroups of trials (Online Table 3). We found no heterogeneity in the efficacy of cholesterol-lowering interventions across a number of characteristics of the studies, including study duration and year of publication, average age of the population recruited in the studies,

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Table 2 Description of Trials Selected, Lipid Parameters

Trial, Year of Publication	TC		TG		LDL-C		HDL-C		Non-HDL-C	
	mg/dl	Δ%	mg/dl	Δ%	mg/dl	Δ%	mg/dl	Δ%	mg/dl	Δ%
Oslo, 1966	296.0	13.9	—	—	—	—	—	—	—	—
MRC, 1968	272.5	13.2	—	—	—	—	—	—	—	—
LA, 1969	233.5	18.5	—	—	—	—	—	—	—	—
Newcastle, 1971	249.7	9.3	—	—	—	—	—	—	—	—
Scottish, 1971	272.2	8.6	—	—	—	—	—	—	—	—
VA, 1974	241.5	6.3	168.0	22.8	—	—	—	—	—	—
CDP, 1975	250.8	8.2	266.0	24.2	—	—	—	—	—	—
Dorr, 1978	307.5	9.5	252.0	1.8	—	—	—	—	—	—
WHO, 1980	248.0	9.1	—	—	—	—	—	—	—	—
McCaughan, 1981	305.7	8.0	232.2	—	—	—	—	—	—	—
LRC-CPPT, 1984	279.8	4.9	154.8	−3.8	204.9	7.7	44.4	2.5	235.4	9.5
CLAS I, 1987	244.5	22.3	152.5	18.7	170.0	37.9	44.2	34.7	200.4	34.9
Helsinki, 1987	269.8	10.0	176.0	35.4	188.7	10.7	47.4	11.2	222.4	14.5
Stockholm, 1988	248.3	13.0	208.6	19.0	160.6	—	47.9	—	200.4	—
Minnesota, 1989	207.0	13.8	116.5	11.2	—	—	—	—	—	—
FATS, 1990	266.7	24.4	212.4	33.3	183.2	31.1	37.9	19.2	228.8	31.5
POSCH, 1990	250.6	25.8	203.3	−15.7	178.4	35.5	40.2	7.2	210.5	32.1
EXCEL, 1991	257.9	23.7	155.5	17.8	179.8	32.4	45.0	6.0	212.9	30.0
Singh, 1992	227.0	5.9	173.4	9.0	168.6	6.8	43.5	9.5	183.5	9.8
Frick, 1993	270.1	8.5	183.3	38.5	188.1	7.1	46.3	8.6	223.8	12.0
MARS, 1993	231.6	30.4	159.4	25.5	152.7	37.4	42.7	5.7	188.9	38.6
PMSG-CRP, 1993	264.1	18.3	160.8	10.8	180.2	26.3	44.2	5.3	219.9	23.1
4S, 1994	260.4	26.0	132.9	17.0	188.0	36.0	45.5	7.0	215.0	32.7
ACAPS, 1994	235.3	14.6	139.7	11.6	155.6	21.5	52.0	4.8	183.4	20.0
CCAIT, 1994	249.5	19.6	195.0	11.9	172.5	27.4	41.3	4.3	208.2	24.0
LR, 1994	203.0	32.0	—	—	128.0	36.3	38.0	—	165.0	—
Lyon, 1994	250.4	0.3	183.8	17.8	174.9	2.0	45.0	−2.6	205.4	0.3
MAAS, 1994	246.8	22.7	167.0	17.6	170.9	31.4	42.7	9.1	204.1	29.1
PLAC-I, 1994	231.0	21.0	166.0	17.0	164.0	29.0	41.0	5.1	190.0	26.6
PLAC-II, 1994	234.9	21.6	171.1	1.9	165.9	29.6	41.4	−2.8	193.5	25.7
REGRESS, 1994	233.0	19.4	158.1	12.7	166.2	26.9	35.9	8.6	197.1	24.5
KAPS, 1995	258.7	22.4	150.4	11.7	189.2	32.7	46.3	0.0	212.4	27.3
CARE, 1996	209.0	20.0	155.5	14.0	139.0	28.0	39.0	5.0	170.0	25.9
WOSCOPS, 1996	272.0	20.0	163.0	12.0	192.0	26.0	44.0	5.0	228.0	24.6
CIS, 1997	241.9	28.5	—	28.0	166.0	35.0	44.0	6.1	197.9	36.3
LOCAT, 1997	199.9	10.6	145.3	40.6	139.6	9.8	31.5	14.1	168.4	15.2
PCABGT, 1997	226.8	18.0	159.9	8.9	155.5	25.6	39.3	4.7	187.6	22.7
PREDICT, 1997	229.5	17.9	139.5	18.7	156.0	24.5	47.0	6.4	182.5	24.3
AFCAPS, 1998	225.8	19.3	167.5	12.7	153.5	26.5	37.2	4.6	188.6	24.0
LIPID, 1998	218.0	18.0	140.0	11.0	150.0	25.0	36.0	5.0	182.0	22.5
Mas, 1999	255.1	16.9	190.3	22.8	198.4	25.1	39.8	74.7	215.3	34.0
GISSI-P, 2000	229.3	7.9	166.2	4.7	151.7	11.8	45.7	0.6	183.6	10.3
SCAT, 2000	200.0	24.1	160.2	20.9	129.8	34.2	37.9	4.1	162.2	30.7
VA-HIT, 2000	175.0	2.9	160.5	31.7	111.5	−0.8	32.0	3.1	143.0	4.2
BCAPS, 2001	236.2	13.0	102.5	—	161.2	23.0	53.2	—	183.0	—
BIP, 2001	212.5	4.7	145.0	25.2	148.5	5.2	34.6	14.5	177.9	8.4
DAIS, 2001	215.1	11.0	221.7	30.0	131.5	6.9	39.8	5.2	175.3	14.6
HATS, 2001	196.8	26.1	211.5	38.8	124.9	33.4	31.2	20.0	165.5	34.2
ALLHAT-LLT, 2002	223.7	10.4	151.7	5.7	145.5	15.1	47.5	5.5	176.2	14.7
FAST, 2002	253.6	23.6	145.8	19.8	167.5	23.8	56.9	−12.6	196.7	16.6
GREACE, 2002	256.0	32.0	181.0	28.0	179.5	41.0	39.0	5.0	217.0	38.5
HPS, 2002	227.8	20.3	185.8	14.3	131.3	29.4	40.9	2.8	186.9	25.4
LEADER, 2002	216.2	7.2	188.5	10.3	130.7	5.0	43.3	6.2	173.0	10.5
Liem, 2002	206.6	22.0	146.0	22.0	137.1	29.9	46.3	4.1	160.3	29.6

Continued on next page

Table 2 Continued

Trial, Year of Publication	TC		TG		LDL-C		HDL-C		Non-HDL-C	
	mg/dl	Δ%	mg/dl	Δ%	mg/dl	Δ%	mg/dl	Δ%	mg/dl	Δ%
LIPS, 2002	199.5	19.0	160.0	0.0	131.5	22.1	37.5	0.2	162.0	18.5
PROSPER, 2002	220.0	19.0	132.7	13.0	146.7	39.2	50.2	5.0	169.8	35.9
ALERT, 2003	249.1	19.2	194.7	6.0	158.3	32.0	52.2	1.0	196.9	24.2
ASCOT-LLA, 2003	211.6	21.8	146.5	15.8	132.8	31.8	50.6	1.8	161.0	29.2
Mohler, 2003	205.0	26.8	191.3	29.5	125.0	40.0	46.8	4.3	158.3	35.9
ALLIANCE, 2004	225.5	8.8	197.5	6.1	146.5	10.7	40.5	0.1	185.0	10.5
ARBITER2, 2004	157.5	−3.8	163.0	8.3	89.0	5.4	39.5	20.5	118.0	2.0
Bae, 2004	191.5	18.0	188.0	13.7	117.5	26.0	37.5	5.6	154.1	23.6
CARDS, 2004	206.8	26.0	171.7	19.0	117.0	40.0	54.3	1.0	152.5	35.5
PCS, 2004	200.3	8.5	142.9	5.6	128.5	11.9	43.2	1.1	157.2	11.1
4D, 2005	219.0	29.4	264.0	16.9	123.0	41.2	36.0	8.3	183.0	36.8
FIELD, 2005	194.4	6.8	153.6	23.6	118.5	5.6	42.5	0.9	151.9	8.9
Makuuchi, 2005	214.1	8.9	160.3	19.3	141.3	14.3	41.4	5.8	172.7	12.4
Stone, 2005	227.7	20.4	171.7	21.0	148.0	22.9	44.8	−2.3	182.9	25.7
ASPEN prim, 2006	195.0	18.4	144.8	12.0	114.0	30.0	47.5	2.3	147.5	25.2
ASPEN sec, 2006	189.5	18.0	149.3	21.2	112.5	26.4	43.0	2.6	146.5	23.9
SPARCL, 2006	211.9	28.5	143.7	23.9	133.2	41.2	50.0	2.2	161.9	38.1
WHI-DM, 2006	224.1	0.9	139.9	−0.2	133.8	2.2	59.3	−0.3	164.9	1.1
CORONA, 2007	206.8	32.5	177.0	23.6	136.5	46.0	47.5	4.2	159.3	43.6
ARISE, 2008	—	—	—	—	87.3	—	44.8	—	—	—
CCSPS, 2008	207.5	−13.5	164.0	−20.7	129.0	−20.2	46.0	−4.3	161.5	−18.5
GISSI-HF, 2008	193.5	17.0	143.5	5.6	118.0	27.1	47.5	0.0	146.0	22.6
JUPITER, 2008	185.5	31.6	118.0	16.1	108.0	50.0	49.0	0.0	136.5	42.9
OACIS lipid, 2008	220.0	—	117.0	—	148.0	15.8	48.5	—	171.5	

For full details of trial references, see Online Table 2.

Δ% = change (percent) in blood lipids due to the intervention: positive values are blood lipids reduction; HDL-C = mean treated/controlled high-density lipoprotein cholesterol at baseline; LDL-C = mean treated/controlled low-density lipoprotein cholesterol at baseline; non–HDL-C = mean treated/controlled non–high-density lipoprotein cholesterol at baseline; prim = primary; sec = secondary; TC = mean treated/controlled total blood cholesterol at baseline; TG = mean treated/controlled triglycerides at baseline.

prevalence of prior myocardial infarction, inclusion of patients with diabetes mellitus, heart failure, and baseline levels of TC, triglycerides, and HDL-C (Online Appendix).

We carried out a weighted linear regression of the log RR for total stroke against the percent of TC reduction as the explanatory variable (Fig. 2), which yielded the following equation:

$$\log_e(\text{total stroke RR}) = 0.00518 - 0.00793(\%\ \text{TC reduction})$$

The regression coefficient for percent TC reduction was significantly different from zero ($p = 0.0017$). This equation indicates that some benefit from cholesterol-lowering intervention on the risk of stroke can be expected when the percent reduction of serum cholesterol is >2% to 3%, the clinical benefit becoming statically significant (see the 95% confidence boundary detaching from the unity line in Fig. 2) when TC is reduced by ≈8%. Cholesterol reductions of 10%, 20%, and 30% yield 7.1%, 14.2%, and 20.8% reductions in the probability of stroke, respectively. In other words, the relative risk of stroke was significantly decreased by ≈0.8% for each 1% reduction of TC. However, the R^2 value of the weighted linear regression was only 0.1225, suggesting that, although statistically significant (and clinically relevant), the decrease of TC does not explain most of the variability in the incidence of stroke, which is clearly influenced by many other relevant factors.

Multivariable linear regression analysis of lipid variables in relation with stroke. We performed univariable and multivariable linear regression analyses having the relative risk of stroke and lipid variables as outcome and dependent variables, respectively (Tables 4 and 5). Although the relationship between TC at baseline and the risk of stroke disappeared in the fully adjusted multivariable models, a strong, inverse relationship was found between HDL-C measured at baseline on the one hand, and the change of relative risk of stroke on the other, at both the univariable and the multivariable analyses, indicating that the association between low levels of HDL-C and the risk of stroke was not eliminated by the interventions tested (Table 4).

The univariable analysis showed that a 10% reduction of total blood cholesterol (ΔTC, first row of Table 4) was significantly associated with 8% RR reduction of total stroke. Such relationship persisted when we adjusted the analysis for individual blood lipids measured at baseline, for all baseline lipids (Models 1, 2, and 3), and when we adjusted separately for changes of triglycerides and HDL-C (Models 5 and 6). Of note, a further adjustment by including statins as an independent variable made such a relationship disappear, thus con-

Table 3 Results, OR, and 95% CI for Total Stroke in Single Randomized Controlled Clinical Trials Testing Efficacy of Statins, Fibrates, and Other Interventions

	Trial	TC % Reduction Mean (SD)	Total Stroke All Trials		p Value Het-Within	p Value Het-Between	OR (95% CI) Treatment/Control
			Treated	Controls			
Trial							
Open	11	14.4 (9.0)*	715/29,758	953/39,508	0.605	0.023	0.97 (0.88–1.07)
Blind	67	17.2 (8.5)*	2,278/93,370	2,771/91,549	0.290		0.87 (0.81–0.93)
†	2	23.6 (0.8)	0/165	0/162			
Clinical setting							
Primary	13	18.3 (7.4)	486/37,355	598/37,240	0.296	0.007	0.80 (0.69–0.93)
Secondary	59	17.0 (8.9)‡	1,854/54,590	2,277/57,836	0.654		0.85 (0.80–0.91)
Primary and secondary	8	15.1 (8.1)	653/31,348	849/36,143	0.330		1.02 (0.88–1.18)
Follow-up, yrs							
≤2	23	18.4 (9.0)‡	115/29,217	152/24,076	0.885	0.132	0.72 (0.56–0.92)
3	14	21.5 (9.4)	118/5,610	161/5,601	0.724		0.78 (0.61–1.00)
4–5	29	15.7 (6.8)	1,776/47,897	2,029/47,914	0.057		0.91 (0.82–1.01)
6–10	14	13.2 (8.5)	984/40,569	1,382/53,628	0.316		0.92 (0.83–1.02)
Years of studies							
≤1980	9	10.6 (3.9)	127/4,461	236/7,830	0.192	0.139	1.00 (0.72–1.40)
1981–1990	9	16.3 (8.4)	67/9,474	61/9,367	1.000		1.09 (0.77–1.54)
1991–2000	27	18.2 (7.9)	456/30,658	574/25,694	0.959		0.79 (0.70–0.90)
>2000	35	18.1 (9.4)‡	2,343/78,700	2,853/88,328	0.020		0.89 (0.82–0.98)
Age, yrs							
<60	40	16.5 (8.0)	406/36,487	573/34,828	0.931	0.891	0.88 (0.77–1.01)
≥60	37	17.9 (9.3)‡	2,547/86,142	3,127/95,830	0.042		0.87 (0.81–0.95)
†	3	13.3 (7.1)	40/664	24/561			
MI, %							
No	10	17.7 (8.0)	464/32,649	577/32,562	0.146	0.107	0.78 (0.66–0.94)
≤50	26	16.8 (8.8)	1,655/47,991	2,040/57,616	0.098		0.94 (0.84–1.06)
>50	30	16.2 (9.2)‡	709/27,475	980/30,806	0.904		0.82 (0.74–0.91)
†	14	18.7 (7.5)	165/15,178	127/10,235			
Diabetes mellitus							
No	15	19.7 (8.7)	73/13,598	107/13,611	0.662	0.195	0.70 (0.52–0.96)
Yes	57	17.1 (8.3)‡	2,447/84,148	2,921/82,375	0.301		0.88 (0.82–0.94)
†	8	11.7 (8.7)	473/25,547	696/35,233			
Previous stroke, %							
No	13	19.2 (7.6)	534/35,497	670/35,404	0.259	0.030	0.78 (0.68–0.91)
≤5	12	12.6 (7.1)	997/43,542	1,352/51,714	0.565		0.97 (0.89–1.05)
>5	9	17.6 (9.7)*	573/8,962	609/8,954	0.041		0.99 (0.80–1.23)
†	46	17.5 (8.8)*	889/35,292	1,093/35,147			
Heart failure							
No	78	16.8 (8.5)‡	2,808/118,494	3,543/126,433	0.361	0.163	0.87 (0.82–0.93)
Yes	2	24.8 (11.0)	185/4,799	181/4,786	0.110		1.04 (0.74–1.46)
Death risk, control group§							
Low, <1%/yr	23	19.7 (7.6)	112/20,636	121/15,580	0.966	0.023	0.92 (0.70–1.20)
Mod, 1%–3.5%/yr	35	17.0 (8.9)‡	1,961/65,975	2,365/65,898	0.136		0.84 (0.78–0.91)
High, >3.5%/yr	19	14.7 (83)	483/16,652	591/19,955	0.507		1.00 (0.89–1.13)
†	3	12.0 (10.8)	437/20,030	647/29,786			
TC level, mg/dl							
≤200	12	15.7 (10.0)	372/20,099	433/20,077	0.194	0.812	0.84 (0.68–1.03)
201–250	44	17.8 (8.1)†	2,361/77,376	2,878/86,969	0.083		0.90 (0.83–0.98)
251–270	15	19.2 (9.0)	166/15,830	308/14,254	0.833		0.84 (0.69–1.02)
>270	8	10.8 (4.7)	73/6,910	72/6,853	0.899		1.00 (0.72–1.39)
†	1	*	21/3,078	33/3,066			

Continued on next page

Table 3 Continued

	Trial	TC % Reduction Mean (SD)	Total Stroke All Trials Treated	Total Stroke All Trials Controls	p Value Het-Within	p Value Het-Between	OR (95% CI) Treatment/Control
TC reduction, %							
<10	21	6.2 (3.5)	972/38,122	1,319/51,203	0.724	<0.001	0.98 (0.90–1.07)
10–20	29	16.5 (3.3)	884/38,148	954/38,081	0.696		0.93 (0.85–1.02)
>20	28	25.8 (4.1)	1,116/43,769	1,416/38,692	0.507		0.77 (0.71–0.84)
†	2	‡	21/3,254	35/3,243			
Triglycerides level, mg/dl							
<150	20	17.3 (7.8)*	1,400/57,160	1,768/66,884	0.143	0.599	0.88 (0.80–0.98)
150–169	23	16.0 (8.6)	652/34,813	730/29,843	0.668		0.89 (0.80–0.99)
≥170	29	17.5 (9.2)	899/26,487	1,164/29,658	0.241		0.91 (0.80–1.04)
†	8	17.7 (9.2)*	42/4,833	62/4,834			
Triglycerides reduction, %							
<10	15	11.6 (8.2)	897/36,216	1,101/45,973	0.879	0.001	1.01 (0.93–1.11)
10–20	29	19.2 (6.4)	1,251/61,250	1,539/56,128	0.096		0.82 (0.73–0.93)
>20	26	18.5 (9.8)	800/20,564	1,015/23,804	0.913		0.88 (0.80–0.97)
†	10	14.5 (7.8)‡	45/5,363	69/5,314			
HDL level, mg/dl							
<40	20	18.3 (9.6)	465/17,519	550/17,491	0.745	0.120	0.85 (0.75–0.96)
40–44	22	17.3 (7.9)*	823/34,838	998/29,810	0.661		0.82 (0.74–0.90)
≥45	27	18.5 (8.8)*	1,556/61,846	1,919/71,542	0.093		0.90 (0.81–0.99)
†	11	10.7 (3.7)	149/9,090	257/12,376			
Non–HDL-C level, mg/dl							
<160	13	17.7 (11.5)	495/22,984	579/22,937	0.165	0.805	0.83 (0.70–0.98)
160–189	30	16.9 (8.3)*	2,096/66,376	2,605/76,041	0.110		0.89 (0.81–0.97)
≥190	25	19.7 (7.5)	232/21,768	250/16,799	0.901		0.92 (0.76–1.10)
†	12	10.7 (3.7)*	170/12,168	290/15,442			
Non–HDL-C reduction, %							
<20	21	8.6 (6.8)	1,085/43,036	1,351/52,784	0.950	0.019	0.96 (0.89–1.04)
20–30	26	19.7 (2.1)	1,029/43,825	1,243/38,728	0.386		0.84 (0.76–0.92)
>30	17	27.1 (4.5)	700/23,211	827/23,213	0.088		0.81 (0.69–0.96)
†	16	12.5 (6.5)‡	179/13,221	303/16,494			

*Analysis comprises 1 trial in which the reduction in total cholesterol (TC) in % was not obtainable. †Group not included in the between-group heterogeneity (Het) test. ‡Analysis comprises 2 trials in which the reduction in TC in % was not obtainable. §For this subgroup analysis, relative risk has been calculated.

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; mod = moderate; OR = odds ratio.

firming the importance of serum cholesterol reduction in the reduction of the risk of stroke (data not shown). Not unexpectedly, the amount of benefit due to TC decrease was reduced to 5% when we adjusted the analysis for changes of triglycerides and HDL-C (Models 8 and 9), for the interrelation of these serum lipids.

The results of the analyses with the percent LDL-C change as the explanatory variable (Table 5) gave similar results. At the univariable analysis, a 10% LDL-C reduction was significantly associated with a 4% reduction of the RR of stroke. This relationship was not substantially modified when we adjusted it for blood lipids at baseline with and without percent changes of blood lipids during the follow-up (Models 1 to 9). While a relevant relationship was found between triglyceride changes and the risk of total stroke in some analyses, the association of changes in HDL-C with the risk of stroke was uncertain, namely, in the expected direction, but with no analysis being statistically significant.

Discussion

The main conclusions from this analysis of trials with cholesterol-lowering treatments and stroke are as follows. Lipid-lowering treatments reduce the cumulative incidence of stroke (total and nonfatal stroke) to a statistically significant—albeit quantitatively different—extent. The reduction of stroke by cholesterol-lowering treatments appears to be proportional to the percent of cholesterol lowering, with an adjusted 0.8% of RR reduction for any achieved 1% decrease in TC. Such benefit seems to be due mainly to the reduction of LDL-C. The relationships between baseline levels of HDL-C and triglycerides versus the risk of stroke are not abolished by the extent of cholesterol reduction. And finally, the effect of cholesterol-lowering interventions appears evident also for nonfatal strokes, while there is still at this moment substantial uncertainty—and actually no directional trend—for any favorable effect on fatal strokes.

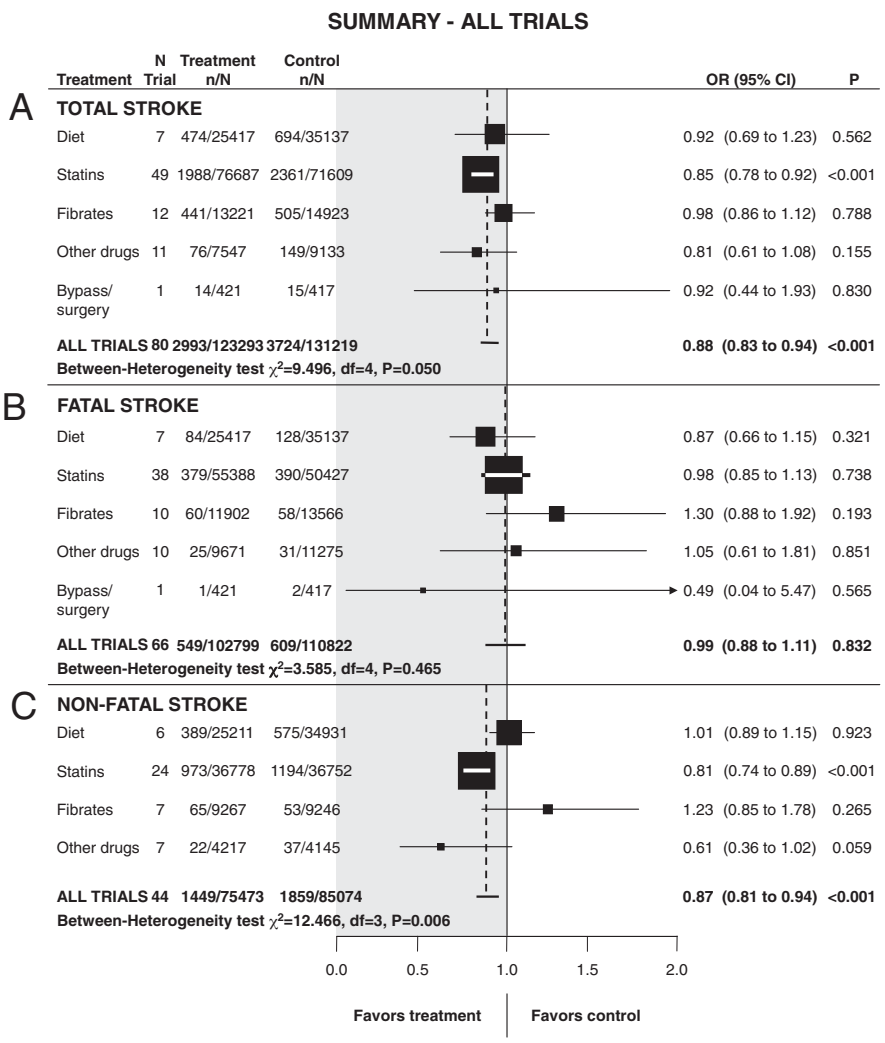

Figure 1 **Cumulative OR and 95% CI for Total, Fatal, and Nonfatal Stroke**

Cumulative odds ratios (ORs) and 95% confidence intervals (CIs) for the occurrence of total stroke **(A)**, fatal stroke **(B)**, and nonfatal stroke **(C)**, each also separated for statin trials and trials involving other interventions: diet, fibrates, "other drugs," and surgery. The OR of an event in the treatment group compared with that in the control group is plotted for each trial (the **black square** indicates area proportional to the amount of statistical information contributed by trial) along with its 95% CI **(horizontal line)**. The **black squares to the left of the solid vertical line** indicate benefit, which is significant at $p < 0.05$ only where the entire CI is to the left of the vertical line. The overall result of all trials (and 95% CI) is represented by a **vertical dashed line** (with a **horizontal line at the bottom of each panel** indicating its 95% CI). The OR and 95% CI are given to the right for each subcategory analyzed.

Such data are new in the context of the ongoing dispute on specific effects of statins—not related to the ability of these drugs to lower cholesterol—as causal in their beneficial effects on stroke.

Overall context for the main findings. Previous analysis of the MRFIT (Multiple Risk Factor Intervention Trial) concluded that there is a strong positive association of serum cholesterol levels with death from nonhemorrhagic stroke among middle-aged American men, overriding a smaller inverse relation between serum cholesterol and the risk of death from hemorrhagic stroke (25). The association between cholesterol and stroke, which is weaker than the association between cholesterol and myocardial infarction, had been disputed earlier for a number of reasons (4,26–28). Association studies can never—in general—prove causality, which may only derive from intervention trials demonstrating that cholesterol reduction leads to a reduction in stroke. Here, the evidence from nonstatin trials in previous literature was inconclusive, whereas statin trials showed such reduction (see the most recent meta-analysis of this kind [29]), leading one to postulate that noncholesterol-lowering properties of statins, generically termed "pleiotropic" effects, here play an important role. This conclusion might be biased, however, for a type II error because of the smaller sample size of nonstatin trials and the smaller extent of cholesterol reduction achieved in most nonstatin interven-

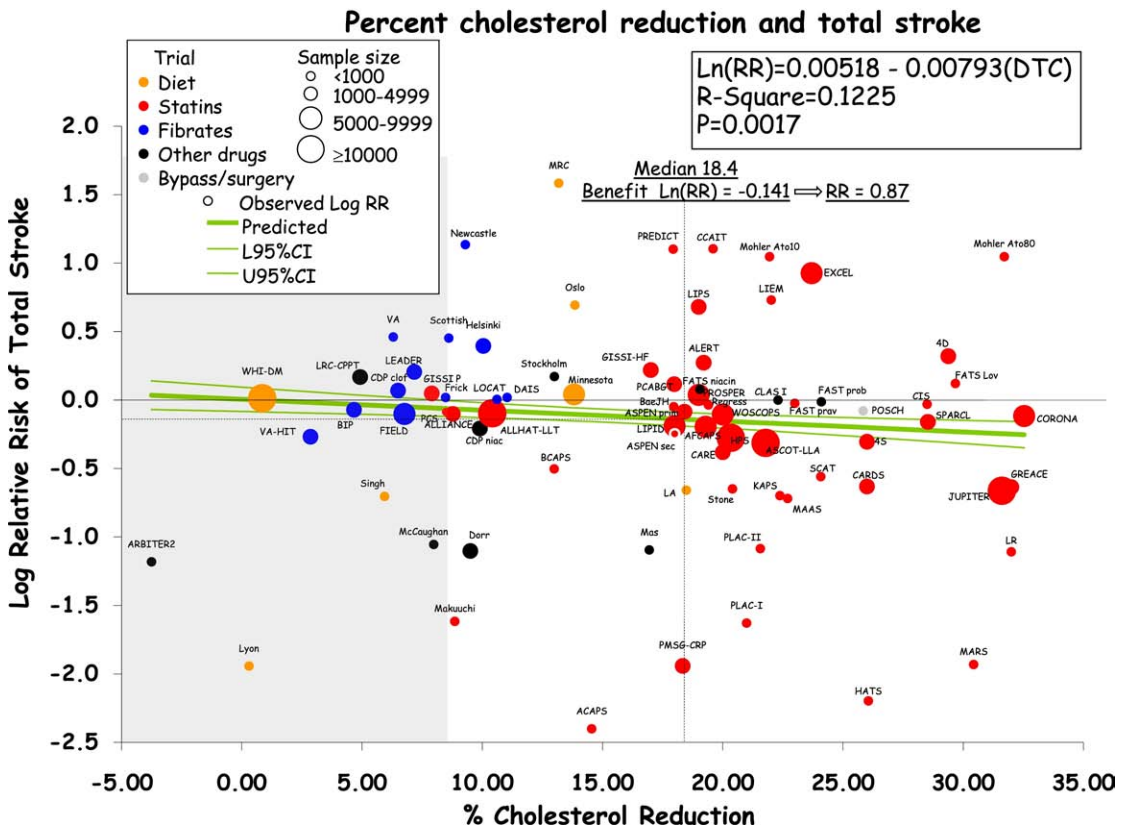

Figure 2 **Meta-Regression of Relationship Between Percent ΔTC Achieved in Cholesterol-Lowering Intervention Trials and RR of Stroke**

Meta-regression of the relationship between the percent change in total cholesterol (ΔTC) achieved in various cholesterol-lowering intervention trials (on the abscissa) and the relative risk (RR) of stroke (on the ordinate), on a logarithmic (ln) scale. The **single dots** represent individual trials as the primary source of data, where **orange dots** represent trials with diet, **red dots** represent trials with statins, **blue dots** represent trials with fibrates, **black dots** represent trials with other drugs, and **gray dots** represent trials with surgery. The size of the dot is proportional to the number of subjects involved in the trial. The regression line and its upper and lower 95% confidence limits are shown in **green**. Note that the vast majority of nonstatin trials achieved <8% reduction of total cholesterol (TC) (**shaded area** in the graph: its margin to the left indicates the point where the RR reduction becomes statistically significant, with 95% boundaries detaching from the unity line), whereas all statin trials achieved higher reductions in TC. The significance of the regression is indicated in the **upper left inset**. CI = confidence interval.

tions. Indeed, in our analysis, the number of patients involved in nonstatin cholesterol-lowering interventions was about one-fifth of patients involved in statin trials. That justifies the need of a cumulative meta-analysis of all trials to improve statistical inference. In our meta-analysis, including data from trials with 254,512 patients, 106,216 of whom were involved in nonstatin trials, the point estimate of the OR for statin trials with regard to stroke (0.85) is statistically heterogeneous from that of nonstatin interventions (heterogeneity test $p = 0.05$). However, such heterogeneity is attributable mostly to the effect of fibrates, which, conversely, are the weakest cholesterol-lowering interventions tested (Figs. 1 and 2). Lipid-lowering interventions different from statins, but successful in cholesterol lowering, had a 16% relative reduction of the risk of total stroke, with 95% CIs largely overlapping with those of statin trials (Fig. 1), a result compatible with the hypothesis that all sorts of cholesterol-lowering treatments can achieve some reduction in stroke. Nonstatin trials determined a much smaller reduction of serum cholesterol and included fewer subjects, cautioning about an overinterpretation of the nonstatistical significance of the stroke reduction here found.

Conversely, the results of the meta-regression of stroke reduction versus the change in TC achieved through the various interventions here demonstrate that the larger the extent of cholesterol reduction, the larger the protective effect on stroke, supporting the view that the 2 phenomena are linked. Here, we tried to run the same meta-regression distinguishing for the effects of statins, of fibrates (also possessing vasculoactive properties independent from their effects on lipids [30]), and of nonstatin, nonfibrate cholesterol-lowering interventions, or combining fibrates and nonstatin, nonfibrate cholesterol-lowering interventions, but the low number of stroke events accrued overall in these trials precluded meaningful statistical inference. The low R^2 test values in our regression analysis here, however, also suggest the large contribution of other factors in explaining the variability in the occurrence of stroke. As a

Table 4 Univariable and Multivariable Linear Regression for Effect of TC Percent Reduction on Total Stroke Reduction

	Model 0 Univariable	Model 1 Adjusted for Baseline TC	Model 2 Adjusted for Baseline TG	Model 3 Adjusted for Baseline HDL-C	Model 4 Adjusted for ΔLDL-C	Model 5 Adjusted for ΔTG	Model 6 Adjusted for ΔHDL-C	Model 7 Adjusted for Baseline TC, TG, HDL-C	Model 8* Adjusted for ΔLDL-C, ΔTG, ΔHDL-C	Model 9* Adjusted for Baseline TC, TG, HDL-C and ΔLDL-C, ΔTG, ΔHDL-C
No. of trials		78	71	67	—	70	64	65	64	63
No. of patients	248,063	248,063	244,532	226,589	—	243,875	224,835	225,927	224,835	224,579
R^2		0.112	0.115	0.150	—	0.145	0.117	0.218	0.162	0.258
ΔTC (n = 78)	−8% (0.002)	−8% (0.002)	−8% (0.002)	−6% (0.024)	—	−6% (0.031)	−7% (0.007)	−7% (0.010)	−5% (0.128)	−5% (0.099)
Baseline TC (n = 78)	+2% (0.276)	+1% (0.298)			—			0% (0.978)		−2% (0.397)
Baseline TG (n = 71)	+1% (0.519)		+1% (0.276)		—			+3% (0.032)		−3% (0.028)
Baseline HDL-C (n = 67)	+8% (0.021)			+5% (0.116)	—			+9% (0.024)		+11% (0.025)
ΔTG (n = 70)	−7% (0.015)				—	−4% (0.236)			−6% (0.078)	−4% (0.312)
ΔHDL-C (n = 64)	−4% (0.669)				—		+1% (0.896)		+5% (0.548)	+16% (0.112)

Values reported are relative risk changes per 10% change of blood lipids and p values (in parentheses). Baseline refers to blood lipid levels at baseline. Δ indicates percent variation of blood lipids due to the intervention. Italics denote percent changes (Δ%) over baseline values. *Adjusted for appropriate lipid parameters; for example, in Models 4, 8 and 9 the results for ΔTC (outcome variable) were not adjusted for ΔLDL.
Abbreviations as in Table 2.

caution, such R^2 values are obtained from a meta-regression analysis not using individual patient data, which might introduce an error tending to dilute the real strength of the underlying associations. Thus, our results in general are in agreement with the Cholesterol Treatment Trialists' meta-analysis of 14 statin trials concluding on a graded relationship between LDL-C lowering and a reduced risk of total stroke ("lower is better") (5), although our quantitative estimate of the relationship is less robust because it was not derived from a meta-analysis of individual patient data. Our study, however, also broadens the concept of the beneficial cholesterol lowering for stroke outside of specific effects attributable to statins.

Stroke reduction in relation to changes in various lipid subclasses. Results discussed so far pertain to the assessment of TC reduction versus the reduction of stroke. Total cholesterol was chosen because it is always reported in lipid-lowering trials. However, most of the effect of TC reduction is now thought to be mediated by LDL-C lowering. Of note, the multivariable linear regression analysis for the effect of LDL-C reduction on stroke was always significant even after adjustment for baseline total and LDL-C, baseline triglycerides, and HDL-C and for the reduction in such lipid parameters (Table 5, Model 9), indicating the strong relevance of LDL-C in driving the effect of various lipid-lowering treatments on stroke. Directionally similar reductions were also observed, however, for reduction in non–HDL-C and triglycerides, while the effects of HDL-C changes were—expectedly—in the opposite direction (Table 5), although generally no longer significant after multiple adjustments. These results also suggest that the negative prognostic impact on stroke of high triglycerides and low HDL-C is not eliminated by solely lowering LDL-C, implying the value of additive treatments that are effective on such parameters or of statins with beneficial effects on HDL-C.

Sensitivity analyses. We ran several sensitivity analyses to test whether results were heterogeneous according to several groupings. We found no heterogeneity in the efficacy of cholesterol-lowering interventions across study duration and year of publication, average age of the population recruited in the studies, prevalence of prior myocardial infarction, inclusion of patients with diabetes mellitus, heart failure, baseline levels of TC, triglycerides, and HDL-C. The low numbers of patients included in the trials recruiting patients with low (≤200 mg/dl) and high (>270 mg/dl) total serum cholesterol levels at baseline, as well as the large overlap of confidence intervals, allow neither confirmation nor exclusion of the existence of a linear relationship between baseline cholesterol levels and the effects of cholesterol-lowering interventions on stroke. However, no relationship could be found between baseline TC levels and the logarithm relative risk of total stroke by fitting a weighted linear regression.

In assessing the efficacy of cholesterol-lowering interventions according to the level of cardiovascular risk of the

Table 5 Univariable and Multivariable Linear Regression Analysis for the Effect of Non–HDL-C, LDL-C, HDL-C, and Triglycerides Percent Reduction on Total Stroke Percent Reduction

	Model 0 Univariable	Model 1 Adjusted for Baseline TC	Model 2 Adjusted for Baseline TG	Model 3 Adjusted for Baseline HDL-C	Model 4 Adjusted for ΔLDL-C	Model 5 Adjusted for ΔTG	Model 6 Adjusted for ΔHDL-C	Model 7 Adjusted for Baseline TC, TG, HDL-C	Model 8* Adjusted for ΔLDL-C, ΔTG, ΔHDL-C	Model 9* Adjusted for Baseline TC, TG, HDL-C and ΔLDL-C, ΔTG, ΔHDL-C
Effect of non–HDL-C reduction (%)										
No. of trials	64	64	>63	64	64	64	64	63	64	63
No. of patients	224,835	224,835	224,579	224,835	224,835	224,835	224,835	224,579	224,835	224,579
R^2	0.091	0.099	0.105	0.135	0.091	0.142	0.091	0.189	0.147	0.244
Δnon–HDL-C	−5% (0.016)	−5% (0.016)	−5% (0.011)	−4% (0.056)	−6% (0.644)	−3% (0.274)	−5% (0.018)	−4% (0.038)	−3% (0.257)	−3% (0.196)
Effect of LDL-C reduction (%)										
No. of trials	67	67	65	67		64	64	65	64	63
No. of patients	226,389	226,389	225,727	226,389		224,835	224,835	225,727	224,835	224,579
R^2	0.086	0.096	0.102	0.135		0.148	0.088	0.195	0.153	0.249
ΔLDL-C	−4% (0.016)	−4% (0.015)	−4% (0.012)	−3% (0.045)		−2% (0.200)	−4% (0.021)	−4% (0.026)	−2% (0.196)	−3% (0.148)
Effect of triglycerides reduction (%)										
No. of trials	70	70	69	65	64		64	64	64	63
No. of patients	243,875	243,875	243,619	225,390	224,835		224,835	225,134	224,835	224,579
R^2	0.084	0.085	0.107	0.011	0.148		0.129	0.181	0.153	0.249
ΔTG	−7% (0.015)	−7% (0.028)	−8% (0.008)	0.2% (0.985)	−6% (0.042)		−9% (0.004)	−7% (0.054)	−7% (0.036)	−5% (0.194)
Effect of HDL-C reduction (%)										
No. of trials	64	64	63	64	64	64		63	64	63
No. of patients	224,835	224,835	224,579	224,835	224,835	224,835		224,579	224,835	224,579
R^2	0.003	0.013	0.008	0.098	0.088	0.129		0.149	0.153	0.249
ΔHDL-C	−4% (0.669)	−4% (0.594)	−4% (0.605)	+10% (0.296)	−0.2% (0.984)	+5% (0.588)		+13% (0.207)	+5% (0.558)	+17% (0.096)

Values reported are relative risk changes per 10% change of blood lipids and p values (in parentheses). Δ indicates percent variation of blood lipids due to the intervention. Baseline refers to blood lipid levels at baseline. Italics denote percent changes (Δ%) over baseline values. *Adjusted for appropriate lipid parameters; for example, in Models 8 and 9, the results for Δnon–HDL-C (outcome variable) were not adjusted for ΔLDL-C.

Abbreviations as in Table 2.

patients recruited in the trials by stratifying studies according to the risk of death in the control group, we found a somewhat higher reduction of the risk of stroke in populations at moderate risk, compared with lower or higher risk of death. Significant heterogeneity in the results of trials was also found in assessing the efficacy of cholesterol-lowering interventions according to the study design (open or blinded studies), study setting (primary prevention, secondary prevention, and mixed studies), and the presence of a previous stroke. We acknowledge a limited power in such subgroup analysis. Dietary trials, for example, included fewer subjects, had a limited ability in reducing serum cholesterol, and were also—obviously—unblinded, which contributes to heterogeneities found. In most cases, such heterogeneities can be attributable to an unbalanced presence of statin trials in the various subgroups.

Cholesterol lowering and fatal strokes. We found inconclusive evidence for an effect of cholesterol-lowering treatments on fatal strokes. Actually, there was not even a trend in this direction. Although the possibility of a type II error in this context cannot be completely excluded because of the relatively small proportions of fatal as compared with nonfatal strokes, alternative explanations exist. One explanation is that hemorrhagic strokes, which are much more often associated with death than ischemic strokes (31,32), appear to be inversely related to TC (25,32), with the possible consequences that even a small trend toward an increased incidence of hemorrhagic strokes by cholesterol-lowering treatments may largely offset the effect of the reduction in the more frequent ischemic, more often nonfatal, strokes. This hypothesis is consistent with more recent results from intervention trials with statins in the HPS (Heart Protection Study) trial (33,34) and the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial (35). Our plan for analyzing this hypothesis in our study was hampered, however, by the very low number of trials reporting a precise diagnosis of stroke etiology, known to be difficult. Although an increase in hemorrhagic stroke has been only reported in the SPARCL trial (35), and not found when specifically sought in a short-term trial (36), this possibility cannot be dismissed looking at the cumulative evidence for fatal stroke in our analysis.

Study limitations. First, this is a meta-analysis based on published trials data, at variance from the Cholesterol Treatment Trialists meta-analysis (5), which included individual patient data but which only included statin trials (fewer than here) and many fewer patients and patient-year exposures. Some studies did not report on the mean follow-up, and most studies did not report on the drop-out of subjects at various times in the trial. Because of this, the computation of the mean follow-up based on our calculations (see the Methods section) is not adjusted for the subjects lost to follow-up or enrolled late in the trial. That would lead to some overestimation of the trial duration, the consequence of which would be some underestimation of the treatment effects. That would reinforce, rather than weaken, the overall message of this analysis on the effects of all cholesterol-lowering treatments on stroke. Second, the decision to include only trials longer than 6 months was arbitrary. Although dictated by the logical need for not including trials of short duration for treatments thought to affect the rates of stroke only chronically, and although few studies had duration close to 6 months, the average duration of statin trials was longer than that for nonstatin interventions, determining a potential bias in favor of the effects of statins. This bias, without an analysis based on individual patient data, could only partially be accounted for in our sensitivity analysis. Since, however, such a bias would have—if anything—diluted the effect of nonstatin interventions, it does not appear to appreciably hamper our here-suggested conclusion about the effects of nonstatin interventions on stroke. Third, most of our subgroup analyses are weak for the low number of trials in some subgroups and the nature of the analysis on cumulatively reported trial data. Therefore, all such analyses have to be taken judiciously and considered confirmatory at best.

Conclusions

Cholesterol lowering is associated with a significant reduction of stroke (total and nonfatal strokes), which appears to exist for both statin and nonstatin cholesterol-lowering interventions; there appears to be a proportionality between the reduction of cholesterol (mostly LDL-C) and the reduction of total stroke, with an estimate of 0.8% reduction in TC for a 1.0% reduction of the relative risk of stroke.

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Key Words: statins ■ HMG-CoA reductase inhibition ■ stroke ■ cholesterol ■ pleiotropic effects ■ neuroprotection.

APPENDIX

For a supplementary Methods section and Online Tables 1 to 3, please see online version of this article.