The Relationship Between Reduction in Low-Density Lipoprotein Cholesterol by Statins and Reduction in Risk of Cardiovascular Outcomes: An Updated Meta-Analysis

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ABSTRACT

Background: In 2005, the Cholesterol Treatment Trialists' Collaboration (CTTC) quantified the relationship between reduction in low-density lipoprotein cholesterol (LDL-C) achieved by statin treatment and reduction in cardiovascular risk. Since this publication, several large statin trials have been reported.

Objective: The objective of our analysis was to extend the CTTC results by including active-controlled trials and other trials published since 2005.

Methods: A literature search in English (1966–December 2008) was undertaken of MEDLINE, EMBASE, Derwent drug file databases, and the Cochrane library using standard MESH terms (*cardiovascular disease, death, fatal outcome, pravastatin, simvastatin, atorvastatin, rosuvastatin, fluvastatin, lovastatin,* and *hydroxymethylglutaryl coenzyme A reductase inhibitors*) to identify randomized trials of statins (placebo controlled, active controlled, or usual care) that reported clinical outcomes, enrolled >1000 subjects, and followed them up for ≥1 year. Random effects meta-regression was used to analyze the relationship between absolute changes in LDL-C and risk for cardiovascular events.

Results: Twenty-five trials were included in a primary analysis involving 155,613 subjects. 6321 vascular deaths, 23,791 major vascular events, 11,357 major coronary events, and 4717 strokes. For every 25-mg/dL (0.65-mmol/L) reduction in LDL-C, the relative risk (95% CI) for various cardiovascular outcomes was as follows: vascular mortality, 0.89 (0.87–0.92); major vascular events, 0.86 (0.84–0.88); major coronary events, 0.84 (0.82–0.86); and stroke, 0.90 (0.86–0.94).

Conclusions: Based on meta-regression analysis of these trials, there was a significant positive relationship between reduction in LDL-C and reduction in the risk for major cardiovascular events. These results support and extend the findings of the CTTC. (*Clin Ther.* 2009;31:236–244) © 2009 Excerpta Medica Inc.

Key words: LDL-C, cardiovascular risk, Cholesterol Treatment Trialists' Collaboration, meta-regression analysis.

INTRODUCTION

There is now strong evidence that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce the risk of coronary heart disease and cerebrovascular disease in both the primary and secondary preventive settings.[1–4] A key mechanism by which statins achieve this is a reduction in serum low-density lipoprotein cholesterol (LDL-C).

Meta-analyses of individual patient data from 14 randomized, placebo-controlled trials of statins were undertaken by the Cholesterol Treatment Trialists' Collaboration (CTTC).[5] The objective was to quantify the relationship between reduction in LDL-C and reduction in cardiovascular risk following treatment with statins. These analyses weighted each trial using the inverse variance of the relative risk (RR) and found RR reductions of −23% and −21% per 1.0-mmol/L reduction in

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LDL-C for major coronary and vascular events, respectively.[5]

Since the publication of the CTTC analyses in September 2005, the results of 8 large statin trials have been reported. The objective of our analyses was to extend the CTTC results by including active-controlled trials and other trials published since 2005.

METHODS

A literature search in English (1966–December 2008) was undertaken of MEDLINE, EMBASE, Derwent drug file databases, and the Cochrane library using standard MESH terms (*cardiovascular disease, death, fatal outcome, pravastatin, simvastatin, atorvastatin, rosuvastatin, fluvastatin, lovastatin,* and *hydroxymethylglutaryl coenzyme A reductase inhibitors,* combined with Boolean operators) to identify randomized trials of statins (placebo controlled, active controlled, or usual care) that reported clinical outcomes, enrolled >1000 subjects, and followed them up for ≥1 year.

Random-effects meta-regression techniques were applied to the mean absolute changes in LDL-C at 1 year and the RR of cardiovascular end points (vascular mortality, major coronary events [defined as nonfatal myocardial infarction or coronary heart disease death], major vascular events [defined as major coronary event, fatal or nonfatal stroke, or coronary revascularization], and fatal and nonfatal stroke). The log RR of an event was regressed against the mean reduction in LDL-C between statins (atorvastatin, simvastatin, pravastatin, and rosuvastatin) and their comparator (placebo, usual care, or active statin comparator). Each study was weighted using the inverse-variance of the log RR to account for the precision of the RR estimate from each trial.[6] The r^2 statistic, which provides an estimate of the proportion of heterogeneity explained by reductions in LDL-C, was also calculated.

The definitions of cardiovascular end points were consistent with those used by the CTTC, as was the adoption of mean LDL-C reduction at 1 year.[5]

RESULTS

Summary data (number of events, total number of participants in each arm, mean reduction in LDL-C, and population characteristics) were available for 26 trials (**Table**) of which 25 were used in the primary analysis.[1–3, 7–29] The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study[15] was excluded. The CORONA study randomized 5011 subjects aged ≥60 years with symptomatic, ischemic, systolic heart failure to 10 mg of rosuvastatin daily or placebo. At 3 months, levels of LDL-C had declined from 137 mg/dL (3.5 mmol/L) at baseline to 76 mg/dL (2.0 mmol/L) in the rosuvastatin group, but did not change significantly in the placebo group, in which levels were 136 mg/dL (3.5 mmol/L) and 138 mg/dL (3.6 mmol/L), respectively ($P < 0.001$). However, after a median follow-up of 32.8 months, there was no significant difference between the 2 groups in terms of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke (hazard ratio, 0.92; 95% CI, 0.83–1.02; $P = 0.12$). In our primary analysis, we excluded the CORONA study because it specifically targeted subjects with heart failure, a distinct disease subgroup. Data from the CORONA study was included in a secondary analysis.

Eleven of the 25 trials included in our analyses were either newly identified since the CTTC publication or included an active comparator. All trials included in our analyses had independent review board/ethics committee approval and consent and were of high quality.[30] This provided a total of 155,613 individuals and a median follow-up of 4.2 years. The mean absolute reduction in LDL-C at 1 year ranged from 13.5 to 73.1 mg/dL (0.35–1.89 mmol/L) and there were 6321 vascular deaths, 23,791 major vascular events, 11,357 major coronary events, and 4717 fatal and nonfatal strokes.

For every 25-mg/dL (0.65-mmol/L) reduction in LDL-C, the proportional reduction, RR (95% CI and r^2 statistic), for various cardiovascular events were as follows: vascular mortality, 11% (0.89 [0.87–0.92], $r^2 = 0.75$); major coronary events, 16% (0.84 [0.82–0.86], $r^2 = 0.87$) (**Figure 1**); major vascular events, 14% (0.86 [0.84–0.88], $r^2 = 0.84$) (**Figure 2**); and fatal and nonfatal stroke, 10% (0.90 [0.86–0.94], $r^2 = 0.47$). For every 1.0-mmol/L reduction in LDL-C, the equivalent proportional reduction figures were: 16%, 20%, 23%, and 15%, respectively.

In the secondary analysis, including the results from the CORONA study, for every 25-mg/dL (0.65-mmol/L) reduction in LDL-C, the proportional reduction, RR (95% CI and r^2 statistic), for various cardiovascular events were as follows: vascular mortality, 10%

Table. Baseline characteristics and summary of the results of randomized trials of statins (placebo controlled, active controlled, or usual care) that reported clinical outcomes, enrolled >1000 subjects, and followed up for ≥1 year.

Trial	Year	Mean Follow-Up, y	Treatment Comparison	Age Range, y	Gender (Female), No. (%)	Diabetes, No. (%)	Prevention Population	Mean LDL-C Reduction, mg/dL	RR			
									Major Coronary Event	Major Vascular Events	Vascular Mortality	Stroke
4S[1]	1994	5.2	S20-40 vs pbo	35-70	827 (19)	202 (15)	2°	-68.45	0.657	0.698	0.658	0.738
HPS[2]	2002	5.0	S40 vs pbo	40-80	5082 (25)	5963 (29)	Mixed	-49.88	0.740	0.757	0.833	0.765
CARDS[3]	2004	3.9	A10 vs pbo	40-75	909 (32)	2838 (100)	1°	-44.08	0.687	0.656	0.667	0.532
AFCAPS/ TexCAPS[7]	1998	5.3	L20-40 vs pbo	45-73	997 (15)	155 (2)	1°	-36.35	0.629	0.715	0.679	0.822
ALERT[8]	2003	5.1	F40 vs pbo	30-75	715 (34)	396 (19)	1°	-32.48	0.754	0.900	0.906	1.314
ALLHAT-LLT[9]	2002	4.8	P40 vs pbo	≥55	5051 (49)	3638 (35)	1°	-20.88	0.905	0.936	0.986	0.907
ALLIANCE[10]	2004	4.3	A10-80 vs UC	31-78	434 (18)	540 (21)	2°	-15.47	0.617	0.882	0.710	0.903
ASCOT-LLA[11]	2003	3.2	A10 vs pbo	40-79	1942 (19)	2527 (25)	1°	-41.38	0.646	0.703	0.898	0.732
ASPEN[12]	2006	4.0	A10 vs pbo	61*	811 (34)	2410 (100)	Diabetes	-40.99	0.834	0.887	1.017	0.886
A-Z[13]	2004	2.0	S80 vs pbo + S20	52-69†	1101 (24)	1059 (23)	2°-ACS	-14.31	0.862	0.878	0.757	0.788
CARE[14]	1996	4.8	P40 vs pbo	21-75	576 (14)	586 (14)	2°	-39.83	0.773	0.788	0.847	0.683
CORONA[15]	2007	2.7	R10 vs pbo	≥60	1180 (24)	1477 (30)	2°	-63.03	0.936	0.959	0.995	0.907
4D[16]	2005	4.0‡	A20 vs pbo	66*	578 (46)	1255 (100)	ESRD on haemodialysis	-41.76	0.811	0.935	0.939	1.378
GISSI[17]	2000	1.9	P20 vs no trt	19-90	587 (14)	582 (14)	2°	-13.53	0.841	0.907	0.769	1.050
GREACE[18]	2002	3.0	A10-80 vs UC	58*	344 (22)	313 (20)	2°	-73.09	0.461	0.472	0.526	0.529
IDEAL[19]	2005	4.0	A80 vs S20-40	61.8*	1701 (19)	1069 (12)	2°	-22.82	0.882	0.822	0.972	0.870
JUPITER[20]	2008	1.9‡	R20 vs pbo	60-71†	6801 (38)	NR	1°	-47.00	0.538	0.563	0.838	0.516
LIPID[21]	1998	5.6	P40 vs pbo	31-75	1516 (17)	782 (9)	2°	-39.83	0.778	0.824	0.763	0.827
LIPS[22]	2002	3.1	F80 vs pbo	18-80	271 (16)	202 (12)	2°	-35.58	0.808	0.811	0.535	NR
MEGA[23]	2006	5.3	P10-20 vs diet	58*	5356 (68)	1632 (21)	1°	-26.68	0.539	0.745	0.627	0.827
Post-CABG[24]	1997	4.2	L40-80 vs pbo	21-74	102 (8)	116 (9)	2°	-41.38	0.874	0.789	1.498	1.123
PROSPER[25]	2002	3.2	P40 vs pbo	70-82	3000 (52)	623 (11)	Mixed	-40.22	0.826	0.877	0.866	1.038
PROVE-IT[26]	2004	2.0	A80 vs P40	58*	911 (22)	734 (18)	2°-ACS	-30.94	0.843	0.893	0.774	1.086

(continued)

Table (continued).

Trial	Year	Mean Follow-Up, y	Treatment Comparison	Age Range, y	Gender (Female), No. (%)	Diabetes, No. (%)	Prevention Population	Mean LDL-C Reduction, mg/dL	RR Major Coronary Event	RR Major Vascular Events	RR Vascular Mortality	RR Stroke
SPARCL[27]	2006	4.9‡	A80 vs pbo	63*	1908 (40)	794 (17)	2°-prior stroke	-60.71	0.675	0.772	0.800	0.852
TNT[28]	2005	4.9‡	A80 vs A10	61*	1902 (19)	1501 (15)	2°	-24.75	0.790	0.756	0.781	0.757
WOSCOPS[29]	1995	4.8	P40 vs pbo	45-64	0	76 (1)	1°	-41.38	0.685	0.733	0.683	0.900

RR = relative risk; LDL-C = low-density lipoprotein cholesterol; 4S = Scandinavian Simvastatin Survival Study; S = simvastatin; S20-40 = simvastatin 20-40 mg; pbo = placebo; 2° = secondary prevention; HPS = Heart Protection Study; CARDS = Collaborative Atorvastatin Diabetes Study; A = atorvastatin; A10 = atorvastatin 10 mg; 1° = primary prevention; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; L = lovastatin; L20-40 = lovastatin 20-40 mg; ALERT = Assessment of Lescol in Renal Transplant; F = fluvastatin; F40 = fluvastatin 40 mg; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; P = pravastatin; P40 = pravastatin 40 mg; ALLIANCE = Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; UC = Usual Care; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-Dependent Diabetes Mellitus; A-Z = A to Z Trial; ACS = Acute Coronary Syndrome; CARE = Cholesterol And Recurrent Events; CORONA = Controlled Rosuvastatin Multinational Trial in Heart Failure; R = rosuvastatin; R10 = rosuvastatin 10 mg; 4D = German Diabetes and Dialysis Study; ESRD = end-stage renal disease; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; no trt = no treatment; GREACE = GREek Atorvastatin and Coronary-heart-disease Evaluation Study; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; JUPITER = Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; NR = not reported; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; LIPS = Lescol Intervention Prevention Study; MEGA = Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study); Post-CABG = Post-Coronary Artery Bypass Graft; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TNT = Treating to New Targets; WOSCOPS = West of Scotland Coronary Prevention Study.

*Mean age reported.

† 25th-75th Percentile reported.

‡ Median duration of follow-up reported.

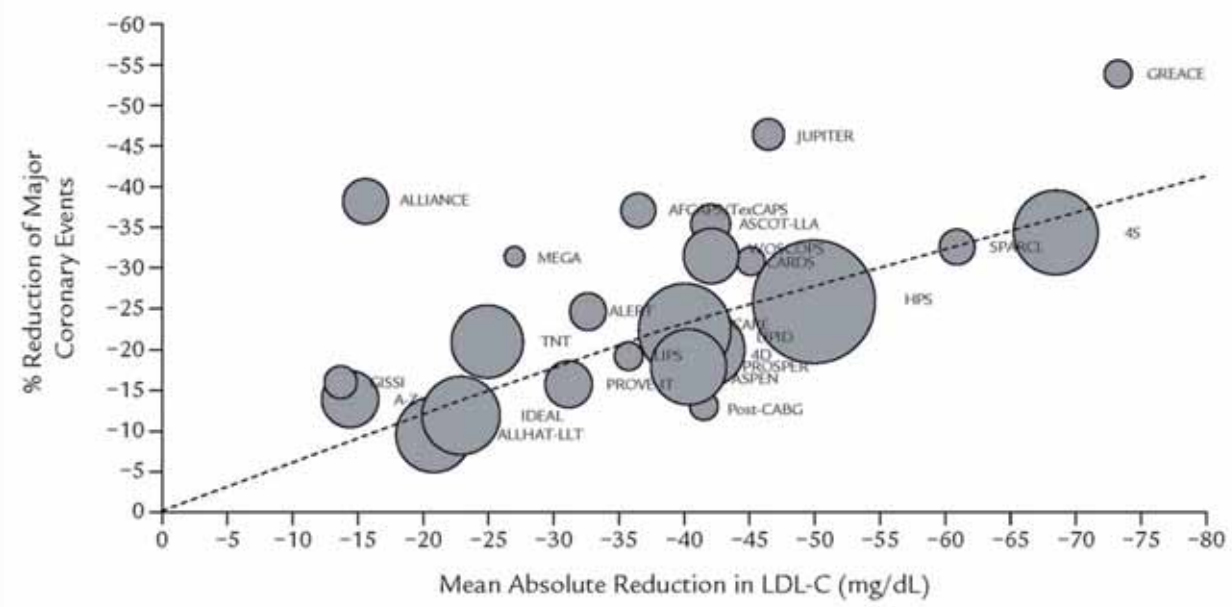

Figure 1. **Relationship between reduction in low-density lipoprotein cholesterol (LDL-C) and reduction in relative risk for major coronary events. A *major coronary event* was defined as nonfatal myocardial infarction– or coronary heart disease–related death. GREACE = GREek Atorvastatin and Coronary-heart-disease Evaluation Study[18]; JUPITER = Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin[20]; ALLIANCE = Aggressive Lipid-Lowering Initiation Abates New Cardiac Events[10]; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study[7]; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm[11]; 4S = Scandinavian Simvastatin Survival Study[1]; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels[27]; MEGA = Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study)[23]; WOSCOPS = West of Scotland Coronary Prevention Study[29]; CARDS = Collaborative Atorvastatin Diabetes Study[3]; HPS = Heart Protection Study[2]; ALERT = Assessment of Lescol in Renal Transplant[8]; CARE = Cholesterol And Recurrent Events[14]; TNT = Treating to New Targets[28]; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease[21]; LIPS = Lescol Intervention Prevention Study[22]; 4D = German Diabetes and Dialysis Study[16]; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk[25]; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-Dependent Diabetes Mellitus[12]; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico[17]; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction[26]; A-Z = A to Z Trial[13]; Post-CABG = Post-Coronary Artery Bypass Graft[24]; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering[19]; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.[9]**

(0.90 [0.87–0.94], r^2 = 0.56); major vascular events, 13% (0.87 [0.84–0.90], r^2 = 0.76); major coronary events, 15% (0.85 [0.82–0.88], r^2 = 0.76); and fatal and nonfatal stroke, 9% (0.91 [0.87–0.95], r^2 = 0.45).

The results were similar when the analyses were repeated with the trials stratified into primary and secondary prevention (data not shown).

DISCUSSION

The overarching differences between the individual statin trials relate to the types and doses of statin used, the effect of which would be differential reductions in LDL-C and, therefore, differing risks of clinical outcomes. By applying meta-regression techniques and using reported summary statistics from 25 large ran-

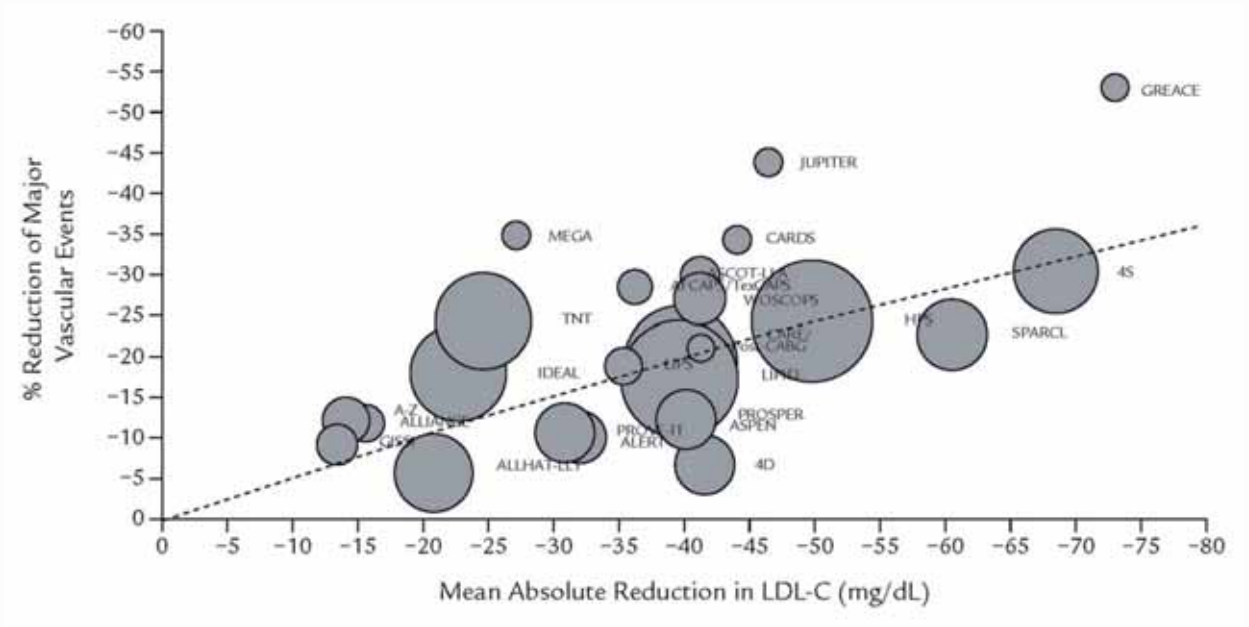

Figure 2. **Relationship between reduction in low-density lipoprotein cholesterol (LDL-C) and reduction in relative risk for major vascular events.** A *major vascular event* was defined as the combined outcome of major coronary event, nonfatal or fatal stroke, or coronary revascularization. GREACE = GREek Atorvastatin and Coronary heart-disease Evaluation Study[18]; JUPITER = Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin[20]; MEGA = Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study)[23]; CARDS = Collaborative Atorvastatin Diabetes Study[3]; 4S = Scandinavian Simvastatin Survival Study[1]; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm[11]; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study[7]; WOSCOPS = West of Scotland Coronary Prevention Study[29]; TNT = Treating to New Targets[28]; HPS = Heart Protection Study[2]; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels[27]; Post-CABG = Post-Coronary Artery Bypass Graft[24]; LIPS = Lescol Intervention Prevention Study[22]; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering[19]; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease[21]; A-Z = A to Z Trial[13]; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk[25]; ALLIANCE = Aggressive Lipid-Lowering Initiation Abates New Cardiac Events[10]; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus[12]; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction[26]; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico[17]; ALERT = Assessment of Lescol in Renal Transplant[8]; CARE = Cholesterol And Recurrent Events[14]; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[9]; 4D = German Diabetes and Dialysis Study.[16]

domized trials of statins, our results support the notion that the relationship between reduction in LDL-C and reductions in clinical events is approximately linear (at least over the range of reductions in LDL-C observed in the 25 trials). Every 25 mg/dL (0.65 mmol/L) reduction in LDL-C leads to a constant −14% and −16% reduction in major vascular and coronary events, respectively. The equivalent percentage reductions per 1.0 mmol/L reduction in LDL-C are −20% and −23%.

Meta-regression techniques investigate potential sources of heterogeneity between trials and thereby at-

tempt to explain differences in trial results. The main differences between our meta-regression and those of the CTTC were that 11 additional trials were included (4 of which contained an active-control arm) and that summary, rather than individual, data were used. Nevertheless, our findings were consistent with those observed in the CTTC for major vascular and major coronary events (–21% and –23% per 1.0 mmol/L reduction in LDL-C, respectively).

The main strength of our study was that we included all major large statin trials published prior to 2009, drawing on data from 155,613 subjects. Our study thus provides up-to-date and more precise estimates of the relationship between LDL-C and cardiovascular risk.

Limitations

As we were unable to obtain individual subject data, our analyses relied on the use of summary statistics reported in the publications for the individual trial reports. Therefore, we were unable to examine the effect of other covariates such as sex, age, and comorbidities. Furthermore, our findings only hold for the duration of the trials (median, 4.2 years) included in the analysis; it is unknown whether the approximate linear relationship exists beyond this time frame. Similarly, the linear relationship can only be considered applicable for the range of LDL-C reductions observed in the trials; namely, 13.5–73.1 mg/dL (0.35–1.89 mmol/L). Although no apparent differences were observed between primary and secondary prevention trials, the comparatively smaller number of primary prevention trials used in these analyses may have limited our ability to detect real differences between these particular patient populations. However, our findings are in alignment with those from the subgroup analyses conducted by the CCTC, which also indicated no differences between these patient populations.

CONCLUSIONS

A significant positive relationship between reduction in LDL-C and reduction in the risk of major cardiovascular events was observed in this meta-regression analysis. By including all active or placebo-controlled trials published prior to 2009, our results support and extend on the findings of the CTTC, which limited its analyses to placebo-controlled trials published prior to 2005.

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