Lipoprotein Changes and Reduction in the Incidence of Major Coronary Heart Disease Events in the Scandinavian Simvastatin Survival Study (4S)

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Background—The Scandinavian Simvastatin Survival Study (4S) randomized 4444 patients with coronary heart disease (CHD) and serum cholesterol 5.5 to 8.0 mmol/L (213 to 310 mg/dL) with triglycerides ≤2.5 mmol/L (220 mg/dL) to simvastatin 20 to 40 mg or placebo once daily. Over the median follow-up period of 5.4 years, one or more major coronary events (MCEs) occurred in 622 (28%) of the 2223 patients in the placebo group and 431 (19%) of the 2221 patients in the simvastatin group (34% risk reduction, $P<.00001$). Simvastatin produced substantial changes in several lipoprotein components, which we have attempted to relate to the beneficial effects observed.

Methods and Results—The Cox proportional hazards model was used to assess the relationship between lipid values (baseline, year 1, and percent change from baseline at year 1) and MCEs. The reduction in MCEs within the simvastatin group was highly correlated with on-treatment levels and changes from baseline in total and LDL cholesterol, apolipoprotein B, and less so with HDL cholesterol, but there was no clear relationship with triglycerides. We estimate that each additional 1% reduction in LDL cholesterol reduces MCE risk by 1.7% (95% CI, 1.0% to 2.4%; $P<.00001$).

Conclusions—These analyses suggest that the beneficial effect of simvastatin in individual patients in 4S was determined mainly by the magnitude of the change in LDL cholesterol, and they are consistent with current guidelines that emphasize aggressive reduction of this lipid in CHD patients. (***Circulation.*** **1998;97:1453-1460.)**

Key Words: coronary disease ■ lipoproteins ■ cholesterol ■ simvastatin

The 4S[1,2] randomly allocated 4444 patients with CHD and total cholesterol 5.5 to 8.0 mmol/L (213 to 310 mg/dL) to double-blind therapy with placebo or simvastatin for 4.9 to 6.3 years. Simvastatin reduced coronary mortality by 42% ($P<.00001$), thus reducing all-cause mortality by 30% ($P=.0003$), and reduced the incidence of MCEs (CHD death and nonfatal myocardial infarction) by 34% ($P<.00001$). The relative reduction in the risk of MCEs was independent of the baseline levels of total, LDL, and HDL cholesterol.[3] One or more MCEs were observed in 622 (28%) of the 2223 patients in the placebo group and 431(19%) of the 2221 patients in the simvastatin group ($P<.00001$). The large number of patients with clinical end points in 4S and the substantial changes in serum lipoprotein levels in the simvastatin group offered the opportunity to study the relationship between outcome and baseline lipoprotein levels and changes from baseline in the simvastatin group. Our objective was to determine which baseline lipoproteins predict coronary events and which lipoprotein changes produced by therapy could best account for the observed clinical benefits.

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Methods

Study Design and Patients

4S was a double-blind, randomized, placebo-controlled, multicenter clinical trial of long-term simvastatin therapy in patients with CHD. The design of the trial and the main findings on mortality, morbidity, and long-term safety have been described previously.[1-4] In brief, the patients were men and women 35 to 70 years old (mean, 58.7 years) with a history of acute myocardial infarction or angina pectoris. For them to qualify for randomization, their serum total cholesterol had to be between 5.5 and 8.0 mmol/L (213 and 310 mg/dL) and serum triglyceride levels ≤2.5 mmol/L (220 mg/dL), after dietary advice 2 months previously.

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Selected Abbreviations and Acronyms

apo = apolipoprotein
CHD = coronary heart disease
MCE = major coronary event
4S = Scandinavian Simvastatin Survival Study

Patients were randomized to placebo or simvastatin 20 mg/d, with titration to 40 mg simvastatin at 12 or 24 weeks in patients who did not reach the study target of a serum total cholesterol level of 3.0 to 5.2 mmol/L (116 to 201 mg/dL) after 6 or 18 weeks. Clinic visits with lipid determination took place at 6 and 18 weeks and at 6 months, and thereafter every 6 months. All patients were accounted for at the end of the study. Median follow-up time was 5.4 years (range, 4.9 to 6.3 years).

Measurement of Lipoprotein Components

Blood samples were collected after 12 to 14 hours of fasting and left to coagulate for 1 to 2 hours at room temperature. Serum was separated by centrifugation and divided into three aliquots. One tube was shipped unfrozen to the central laboratory the same day to be analyzed for total cholesterol, and the two other tubes were frozen immediately at −20°C. The frozen serum was shipped batchwise in insulated containers with dry ice to the central laboratory to be analyzed within 3 months.

Cholesterol and triglycerides were measured enzymatically by the method of Boehringer Mannheim. HDL cholesterol was measured after precipitation of apo B–containing lipoproteins by heparin-MnCl. Although the accuracy and precision of the analyses were monitored continuously by daily analyses of HDL cholesterol in control sera, a small temporary drift during 1992 in the HDL cholesterol assay of unknown cause was discovered at the completion of the study. LDL cholesterol was calculated according to the Friedewald formula.[5] Serum apo A-I and apo B were measured by immunoturbidimetry by test kits with antisera and standards from Orion. The lipoprotein measurements were stored in a secure computer at the central laboratory and were not disclosed outside the laboratory during the trial.

The baseline values of lipids and apolipoproteins are means of two measurements from serum collected ≈2 months after dietary advice, the first at the beginning of the single-blind placebo period and the second 2 weeks later on the day of randomization, except for apo A-I and apo B, which were measured only at randomization.

End Points

End-point definition has been described previously.[1] In brief, all end-point events were classified by an independent end-point classification committee. The primary study end point was death from any cause. The secondary end point was MCEs, defined as fatal or nonfatal definite or probable acute myocardial infarction, including silent myocardial infarction; sudden cardiac death; or resuscitated cardiac arrest. Although there were 438 deaths (the primary end point), the secondary end point, MCEs, is more appropriate for correlation analyses because it is not diluted by noncoronary events and because >1000 patients had one or more MCEs, providing greater statistical power. Only the first end-point event was included in the analysis.

Statistical Methods

Because the 1-year measurements were the first to be performed after completion of the dose titration procedure, only baseline and year 1 values were used in the principal analyses, avoiding the problem of "using the future to predict the future."[6] Patients with MCEs in the first year of the study were excluded from the analyses relating year 1 or percent change at year 1 values to subsequent MCEs.

Age, sex, smoking at baseline, a history of hypertension, myocardial infarction, and diabetes were included as covariates in all the statistical models. Baseline lipid and apolipoprotein values were included in the statistical models that assessed the relationship between percent change in lipoprotein components at year 1 (which is essentially independent of baseline) and MCEs but not in the models that assessed the relationship between year 1 absolute lipoprotein value (which is strongly correlated with the baseline value) and MCEs. Logistic regression was used to estimate the proportion of patients with MCEs as a function of baseline and year 1 lipoprotein components. The Cox proportional hazards model was used to assess the relationship between lipoprotein values (baseline, year 1, and percent change from baseline) and MCEs. This model was compared with other potential models and previous studies in a sensitivity analysis.

The relative importance of lipids in a pair was assessed by selecting a primary and a secondary lipid from all combinations of total, LDL, and HDL cholesterols and triglycerides. Linear regression with the primary lipid value as the independent variable and the secondary lipid value as the dependent variable provided the residual of the secondary lipid, which was then included with the primary lipoprotein in a Cox proportional hazards model. The significance of the residual in this model indicated whether or not it added predictive information.

All analyses were based on the intention-to-treat principle, and a two-sided value of $P<.05$ was considered statistically significant.

Results

The frequency distribution of serum lipoprotein components in the simvastatin group at baseline and at 1 year is shown in Fig 1. There were no important differences in baseline values between the two treatment groups. There were negative correlations at baseline between HDL cholesterol and triglycerides ($r=-.40$) and between LDL cholesterol and HDL cholesterol ($r=-.22$).

Following dietary advice provided at the recruitment visit, patients fulfilling the entry criteria on average reduced their serum total cholesterol level by 2.1% and increased their triglyceride level by 2.9% between the recruitment and randomization visits (≈2 months apart). Fig 2 shows the mean concentrations of serum lipoprotein components in the placebo and simvastatin groups during the trial. At 6 weeks, at which point all patients randomized to simvastatin were taking 20 mg/d, there was a 28% reduction in serum total cholesterol, a 38% reduction in LDL cholesterol, an 8% increase in HDL cholesterol, and a 15% decrease in triglycerides. The corresponding changes in the placebo group were −1%, −1%, 0%, and 3%. Over the median 5.4-year follow-up period, the mean reductions in the placebo and simvastatin groups were serum total cholesterol, +1%, −25%; LDL cholesterol, +1%, −34%; HDL cholesterol, +1%, + 8%; triglycerides, +7%, −9%; apo A-I, −3%, −3%; apo B, −3%, −27%; and total/HDL cholesterol ratio, 0%, −39%, respectively. Three quarters of the simvastatin-treated patients had mean LDL cholesterol levels reduced 30% or more, and a quarter of the patients achieved reductions of >45%. Because the analyses are based on the intention-to-treat principle, patients who discontinued study therapy but continued to provide blood samples are included. This contributes to the slight increases in serum total and LDL cholesterol and in triglyceride levels in the simvastatin group over the course of the study.

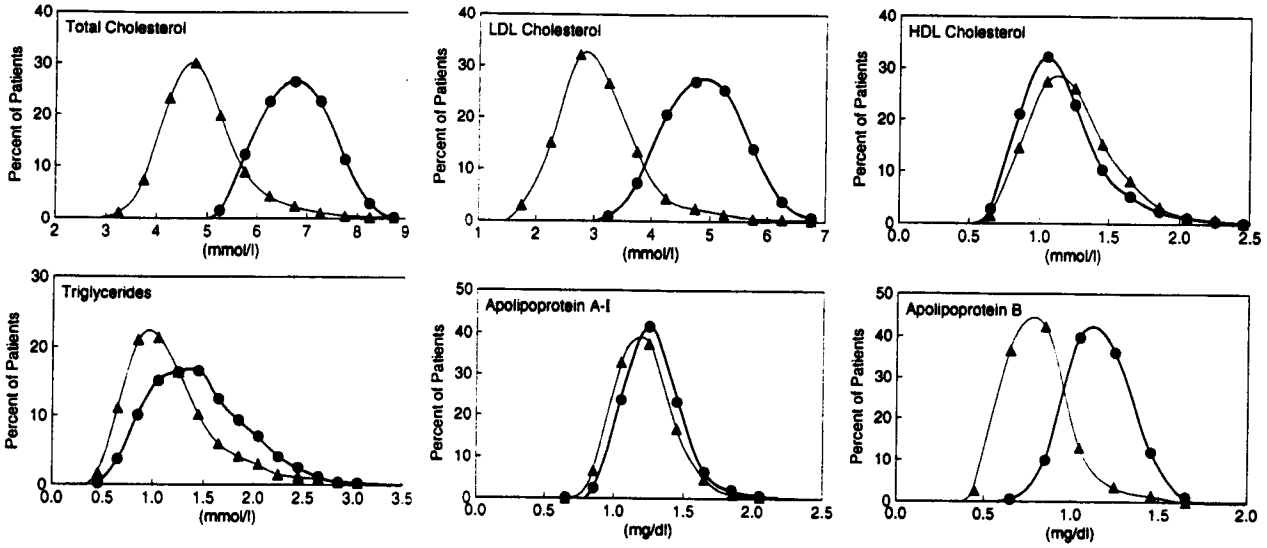

Figure 1. Frequency distribution of baseline (●) and 1-year (▲) lipoprotein component levels in the simvastatin group. To convert mmol/L to mg/dL, multiply by 38.7 for cholesterol and 88 for triglycerides.

The study target of a total cholesterol level ≤5.2 mmol/L (201 mg/dL) at 6 and 18 weeks on 20 mg simvastatin therapy was reached in 1398 patients (63%) in the simvastatin group. In the remainder, who tended to be less responsive to 20 mg and have higher baseline LDL and total cholesterol levels (Table 1), the dosage of simvastatin was increased to 40 mg/d. At 1 year, 77% of patients had total cholesterol ≤5.2 mmol/L.

A total of 622 patients (28%) in the placebo group had one or more MCEs, compared with 431 (19%) in the simvastatin group ($P<.0001$). This end point included coronary death (189 versus 111 in the placebo and simvastatin groups, respectively), definite or probable nonfatal acute myocardial infarction (418 versus 279), silent myocardial infarction (109 versus 90), resuscitated cardiac arrest (0 versus 1), and myocardial infarction associated with invasive procedures (mainly CABG) (25 versus 12). During the first year of therapy the difference in MCEs was small (151 patients in the placebo group and 131 in the simvastatin group). However, from year 2 through year 6 of therapy, the risk of MCEs and coronary deaths in the simvastatin group were reduced by 40% and 47% relative to the placebo group, respectively.

The relationships between baseline lipoprotein components and MCEs in the two treatment groups are shown in Table 2. In the placebo group, all lipids and ratios except apo A-I were significantly related to MCE risk, especially non-HDL cholesterol ($P=.002$), triglycerides ($P=.007$), and total cholesterol/HDL cholesterol ratio($P=.008$). In the simvastatin group, the only significant relationships were with HDL cholesterol ($P=.026$), apo B ($P=.039$), and the total cholesterol/HDL cholesterol ratio ($P=.009$). The association of baseline triglycerides with MCEs in the placebo group but not the simvastatin group is illustrated in the logistic regression plot shown in Fig 3.

The relationships between 1-year levels of lipoprotein components in the simvastatin group and the subsequent incidence of MCEs are shown in Table 3. Significant correlations were observed for all lipoproteins except for triglycerides, HDL cholesterol, and apo A-I. For example, a 1-mmol/L (38.7-mg/dL) reduction of serum total cholesterol is associated with a 22.5% reduction in MCE risk ($P=.0001$). Fig 4 shows the relationship between the 1-year levels of LDL cholesterol in the placebo and simvastatin groups and the subsequent incidence of MCEs.

The relationship between the percent change in serum lipids from baseline to 1 year in the simvastatin group and the reduction in risk of MCEs is shown in Table 4. For each additional percentage point reduction in total cholesterol, the

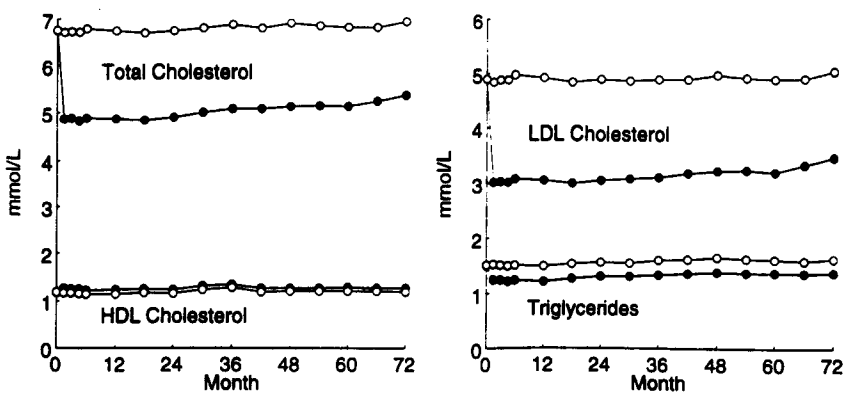

Figure 2. Mean levels of lipids in the placebo (○) and simvastatin (●) groups over the course of study. To convert mmol/L to mg/dL, multiply by 38.7 for cholesterol and 88 for triglycerides.

TABLE 1. Mean Lipid Changes in Patients Taking 20 mg Simvastatin Throughout and in Patients Titrated to 40 mg After 12 Weeks or 6 Months of Therapy

	Baseline, mmol/L	6 Weeks or Pretitration, mmol/L	Mean Change From Baseline, %	12 Months, mmol/L	Mean Change from Baseline, %
Patients taking 20 mg simvastatin throughout (n=1312)					
TC	6.5	4.5	−30.7	4.7	−28.4
LDL-C	4.7	2.7	−41.4	2.9	−37.9
HDL-C	1.14	1.22	7.7	1.20	5.7
TG	1.5	1.2	−18.2	1.3	−17.0
Patients titrated to 40 mg simvastatin (n=722)					
TC	7.1	5.7	−18.6	5.1	−27.0
LDL-C	5.1	3.7	−26.4	3.3	−35.8
HDL-C	1.25	1.35	8.9	1.29	5.2
TG	1.5	1.4	−6.5	1.2	−14.8

TC indicates total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; and TG, triglycerides. n=number of patients with data at all time points in the table.

MCE risk was reduced by 1.9% (P=.00005). Changes in LDL and HDL cholesterol both contributed to the reduction in risk, but LDL cholesterol changes appear more important, as is evident in the larger absolute regression coefficient and lower P value. Fig 5 shows the modeled curvilinear relationship between reduction in LDL cholesterol and reduction in risk. According to the model, the incremental benefit became progressively less as the LDL cholesterol reduction increased. Reduction in triglycerides did not contribute to risk reduction.

Table 5 presents the results of the pairwise analysis of the predictive value of lipids and apolipoproteins measured after 1 year for the risk of MCEs in the simvastatin group. All lipids and apolipoproteins with the exception of triglycerides and HDL cholesterol had statistically significant correlations to risk when analyzed as a primary variable in pairs with other lipids and apolipoproteins. Of the primary single lipids in the model, LDL cholesterol had the regression coefficients with the highest statistical significance. The contribution of the secondary lipid to the prediction of risk was variable. For example, with total cholesterol as the primary lipid, HDL cholesterol provided additional predictive information (P=.022). Conversely, with LDL cholesterol as the primary lipoprotein component, none of the other lipids or apolipoproteins provided significant additional predictive information, indicating that the LDL level at 1 year carries most of the prognostic information. With LDL cholesterol level as a primary variable, percent change in LDL cholesterol did not provide significant residual information, but neither did LDL cholesterol level when paired as a secondary variable with percent change of LDL cholesterol. Therefore, it was not possible to determine which of these highly correlated measures of efficacy is more important.

Several modifications of the Cox regression analysis were performed to explore the robustness of the results. Table 6 contains results of the most commonly used alternative analyses together with results from the Lipid Research Clinics Study[7] and Helsinki Heart Study[8] for comparison. The estimates of the relationship between reduction in LDL and reduction in MCEs was quite similar for all methods and highly statistically significant. The HDL cholesterol–MCE relationship was marginally significant for most analyses. The 4S time-dependent analyses indicated a significant relationship between triglycerides and MCEs that was not seen in the analyses based on year 1 data or in the other two studies.

TABLE 2. Relationship of Serum Lipoprotein Components at Baseline and Risk Reduction of MCEs According to Cox Proportional Hazards Regression Models*

Variable	Difference†	Risk Difference, %	Placebo, 95% CI	P	Risk Difference, %	Simvastatin, 95% CI	P
TC	−1 mmol/L	−14.0	−23.6 to −3.2	.013	−4.7	−17.5 to 10.1	.512
TG	−1 mmol/L	−17.6	−28.5 to −5.1	.007	0.5	−17.8 to 22.8	.965
HDL-C	0.1 mmol/L	−3.1	−6.0 to −0.2	.036	−4.0	−7.4 to −0.5	.026
LDL-C	−1 mmol/L	−12.8	−22.6 to −1.8	.024	−11.0	−23.0 to 2.8	.113
Non–HDL-C	−1 mmol/L	−16.4	−25.3 to −6.5	.002	−10.4	−21.8 to 2.6	.111
TC/HDL-C	−1	−7.1	−12.0 to −1.9	.008	−8.3	−14.2 to −2.1	.009
Apo A-I	0.1 g/L	−1.8	−5.5 to 2.2	.374	−3.6	−8.1 to 1.2	.139
Apo B	−0.1 g/L	−5.3	−9.3 to −1.1	.014	−5.1	−9.6 to −0.3	.039

Abbreviations as in Table 1. Apo indicates apolipoprotein.

*In each model, the covariates included are sex, age, qualifying by myocardial infarction, smoking, hypertension, and diabetes.

†Arbitrary units that do not represent the same fraction of the average level of each lipoprotein component. To convert mmol/L to mg/dL, multiply by 38.7 for cholesterol and 88 for triglycerides.

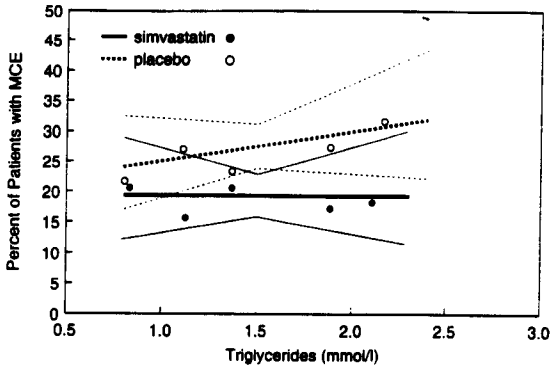

Figure 3. Relationship between baseline triglyceride levels and MCEs with 95% CIs in the placebo and simvastatin groups, adjusted for sex, age, history of myocardial infarction, smoking, hypertension, and diabetes. Points represent the mean value for each quintile. To convert mmol/L to mg/dL, multiply by 88.

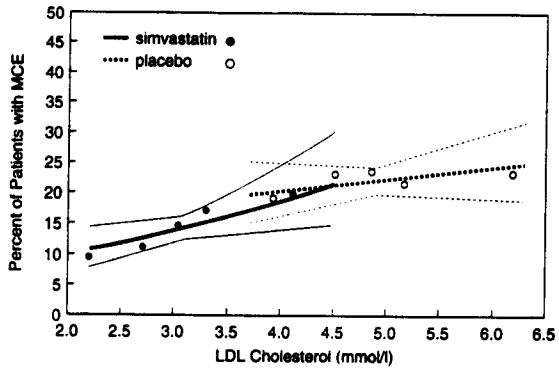

Figure 4. Relationship between LDL cholesterol levels at year 1 and subsequent risk of MCEs in the placebo and simvastatin groups, with 95% CIs. Points represent the mean value for each quintile. To convert mmol/L to mg/dL, multiply by 38.7.

However, this effect was only about one third that of LDL cholesterol in the time-dependent analyses.

Discussion

At baseline, 95% of patients had LDL cholesterol levels of 3.0 to 6.0 mmol/L (116 to 232 mg/dL), a range spanning so-called normal as well as very high levels. In the placebo group, all baseline lipoprotein components were clearly related to the risk of subsequent MCEs, except for apo A-I (Table 2). In the simvastatin group, the relationships between baseline lipoproteins and MCEs were relatively weak, as we have previously noted using a quartile analysis.[3] This can be attributed to the drug effect, which varies from patient to patient, producing a redistribution of baseline lipid values within a few weeks.

There is abundant evidence that serum and LDL cholesterol are major risk factors for CHD,[9-13] and current guidelines emphasize reduction of LDL cholesterol.[9,10,14] Epidemiological studies have often associated high triglyceride levels and CHD incidence, but the relationship tends to weaken or disappear with multivariate analysis.[15,16] This is largely a consequence of the strong inverse relationship between the levels of triglycerides and HDL cholesterol and between HDL cholesterol level and CHD incidence.[13] As a result, there is a range of opinion on the role of elevated plasma triglycerides in the pathogenesis of CHD: in North America it has generally not been considered a major independent risk factor,[15] whereas in parts of Europe it is given more weight.[17] Isolated hypertriglyceridemia may not increase CHD risk, but there is evidence that it amplifies the risk in patients with high LDL cholesterol and low HDL cholesterol,[17] who tend to have high levels of small, dense LDL cholesterol.[18] The HDL cholesterol level is determined partly by complex exchanges of triglycerides and cholesterol esters between chylomicrons and VLDLs and HDL,[19] which could contribute to its strong inverse relationship with CHD.

As shown in Tables 4 and 5, in the simvastatin group the reductions in total, LDL, and non-HDL cholesterol and apo B were all strongly related to risk reduction. Not only LDL but also the denser fraction of VLDL (IDL) is atherogenic,[15] consistent with the strong relationship between non-HDL cholesterol (essentially LDL cholesterol plus VLDL cholesterol) and risk in our study. The modeled relationships are not linear (Figs 5A and 5B). The model estimates a 45%

TABLE 3. Relationship of Serum Lipoprotein Components in the Simvastatin Group Measured After 1 Year of Therapy and the Subsequent Risk of MCEs According to the Cox Proportional Hazards Regression Model*

Variable	Difference†	Risk Difference, %	95% CI	P
TC	−1 mmol/L	−22.5	−31.9 to −11.9	.0001
TG	−1 mmol/L	−3.1	−22.8 to 21.7	.788
HDL-C	0.1 mmol/L	−3.7	−7.5 to 0.3	.07
LDL-C	−1 mmol/L	−27.8	−36.8 to −17.6	<.00001
Non–HDL-C	−1 mmol/L	−24.9	−33.7 to −14.9	.00001
TC/HDL-C	−1	−17.6	−24.3 to −10.3	.00001
Apo A-I	0.1 g/L	−2.3	−8.0 to 3.7	.445
Apo B	−0.1 g/L	−8.8	−14.1 to −3.2	.0025

Abbreviations as in Table 1.

*In each model, the covariates included are sex, age, qualifying by myocardial infarction, smoking, hypertension, and diabetes.

†Arbitrary units that do not represent the same fraction of the average level of each lipoprotein component. To convert mmol/L to mg/dL, multiply by 38.7 for cholesterol and 88 for triglycerides.

TABLE 4. Relationship of 1% Decrease in Serum Lipoprotein Components (Increase for HDL Cholesterol and for Apo A-I) From Baseline to 1 Year in the Simvastatin Group and Incidence of MCEs According to a Cox Proportional Hazards Regression Model*

Variable	Regression Coefficient	SEM	Risk Reduction (%) for Each Additional 1% Lipid Reduction	95% CI	P
TC	0.0200	0.0047	1.9	(1.0 to 2.8)	.00005
TG	0.00187	0.0021	0.2	(−0.2 to 0.6)	.37
HDL-C	−0.00773	0.0037	−0.8	(0.1 to 1.5)	.039
LDL-C	0.0169	0.0035	1.7	(1.0 to 2.4)	<.00001
Non–HDL-C	0.0166	0.0037	1.7	(0.9 to 2.4)	.00001
TC/HDL-C	0.0133	0.0029	1.3	(0.8 to 1.9)	<.00001
Apo A-I	−0.00352	0.0051	−0.4	(−0.6 to 1.3)	.487
Apo B	0.0109	0.0038	1.1	(0.3 to 1.8)	.004

Abbreviations as in Table 1.

*In each model, the covariates included are baseline value of the lipoprotein/apolipoprotein ratio, sex, age, qualifying with myocardial infarction, smoking, hypertension, and diabetes.

The risk reduction for a lipid reduction of x% is given by the formula $(e^{rx}-1)\times 100\%$, where r is the regression coefficient.

reduction in MCEs for a 35% reduction in LDL, which is close to the 40% reduction in MCEs observed in years 2 through 6 of the study. There was a weaker relationship between HDL cholesterol increase and risk reduction and no significant relationship for triglycerides and apo A-I. There was a small effect of triglycerides in the time-dependent analyses, which may be attributable to the reduced variability of serum triglycerides when averaged over time, compared with the single measurement at year 1 in the principal analysis. Also, triglyceride-rich lipoproteins could affect short-term risk (for example, through an effect on thrombogenesis) rather than the long-term atherosclerotic process per se. However, triglyceride reduction is at most a minor contributor to MCE reduction in the 4S population. Whether larger and more consistent effects occur in patients with serum triglycerides higher than the 2.5 mmol/L (220 mg/dL) 4S cutoff remains to be demonstrated.

Analogous analyses in the Lipid Research Clinics Primary Prevention Trial (LRC-CPPT)[7] and the Helsinki Heart Study[8] produced relationships generally similar to those observed in 4S, except for the greater effect of changes in HDL cholesterol in the Helsinki Heart Study. In both trials, the number of end points were relatively few and the observed changes in LDL cholesterol were modest. In the Helsinki Heart Study,[8] there was a large reduction (35%) in serum triglycerides, but as in 4S, it did not predict CHD events.

We have previously reported that the relative risk reduction produced by simvastatin is independent of the baseline LDL cholesterol level.[3] There is also no evidence in 4S for any percent reduction or on-treatment threshold level below which further lipid lowering is futile. In the Post Coronary Artery Bypass Graft Trial, reducing mean LDL cholesterol levels to <100 mg/dL (2.6 mmol/L) retarded the progression of atherosclerosis in grafts more than less aggressive lipid lowering. Current US guidelines recommend a reduction of LDL cholesterol in CHD patients to <100 mg/dL (2.6 mmol/L).[10,14] This level was reached (at 1 year) by 23% of the patients in 4S (a low percentage reflecting the study goal of total cholesterol <5.2 mmol/L [201 mg/dL], the submaximal average dose of 27 mg/d, and the high baseline LDL cholesterol). Our results are consistent with the continuous relationship between serum cholesterol and CHD mortality[11] and the rarity of coronary disease

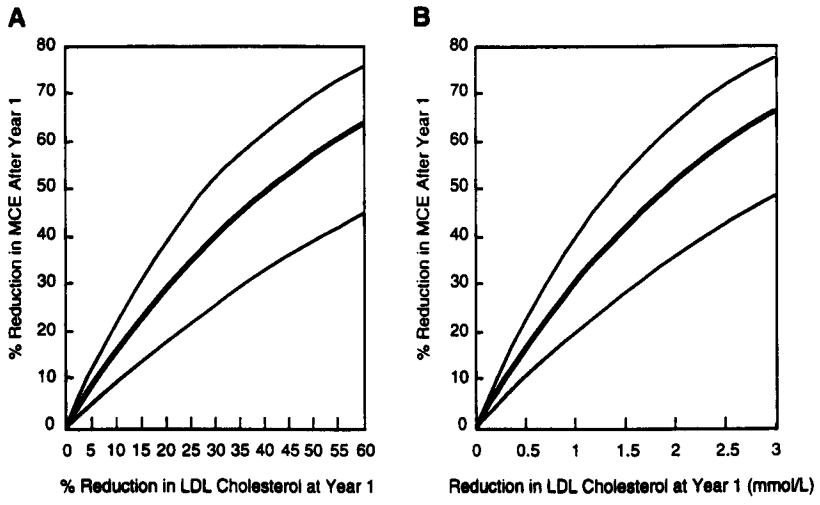

Figure 5. Modeled relationship between MCE risk reduction after year 1 and (A) LDL cholesterol percent reduction at year 1 and (B) absolute change in LDL cholesterol at year 1. The lighter curves define the 95% CI. To convert mmol/L to mg/dL, multiply by 38.7.

TABLE 5. Residual Risk Information of Secondary Lipids to MCEs in the Simvastatin Group: Cox Proportional Hazards Model Using 1-Year Values

Primary Lipid*	Secondary Lipid†	Partial Correlation Coefficient	Significance of Partial Correlation Coefficient, *P*
TC	HDL-C	−0.035	.022
	LDL-C	0.044	.004
	TG	−0.013	.390
	TC/HDL-C	0.041	.007
HDL-C	TC	0.064	.00003
	LDL-C	0.070	<.00001
	TG	−0.005	.744
	TC/HDL-C	0.066	.00001
LDL-C	TC	−0.022	.154
	HDL-C	−0.018	.232
	TG	−0.006	.681
	TC/HDL-C	0.022	.141
	LDL-C % change	0.014	.359
LDL-C % change	LDL-C	0.027	.081

Abbreviations as in Table 1. The partial correlation coefficient represents the residual information provided by the secondary lipid.

*The primary lipid correlations include all information for that lipid plus all information shared between the primary and secondary lipids.

†The secondary lipid provides a measure of the residual information, independent of the primary lipid.

in populations with very low serum cholesterol levels, even when other risk factors are prevalent.[20,21] In contrast, the authors of the Cholesterol and Recurrent Events (CARE) study concluded that there was no effect of pravastatin therapy in patients with baseline LDL cholesterol <125 mg/dL (3.2 mmol/L).[22] However, the 95% CI in this subgroup included a risk reduction of up to 23%. The risk of misinterpretation of results in small subgroups that appear to be different from those of the study as a whole is well known.[23]

Because 4S was designed to test the hypothesis that lowering serum cholesterol reduces mortality and not to provide answers to the questions addressed in this report, the rigorous methods used for the original analysis could not be applied. Although our data are drawn from a randomized, placebo-controlled trial, the conclusions in this paper derive from within-group analyses, as opposed to comparison of randomized groups. Although we attempted to correct for factors associated with risk (age, sex, smoking history, hypertension, and diabetes), our analyses could have been influenced by other unknown factors (as is typically the case in observational studies). In addition, even though there were 1053 patients with MCEs (774 with the first MCE in years 2 through 6), these may still have been insufficient to detect all meaningful correlations.

The analyses presented in this report were not predefined; rather, they were selected from a large number of exploratory analyses of the relationship between lipoprotein levels and risk. We tried to identify methods that were simple, conservative, and least likely to be confounded, but ultimately our choices were a matter of judgment. As shown in Table 6, there are several alternative methods that could have been used, but none improved the robustness of the results. In some alternative analyses, even minor modification of the methods used introduced marked changes in coefficients and significance levels. On the other hand, LDL cholesterol percent change and year 1 value in the simvastatin group correlated consistently with MCE risk reduction by several different analytic methods.

Despite the limitations discussed above, our conclusions are generally consistent with epidemiological data,[11,21,24] other intervention studies,[7,8] and meta-analyses.[25–27] However, randomized trials are needed to confirm them. For example, our main conclusion that greater reduction in LDL cholesterol should further reduce coronary risk will be tested in a new trial in the United Kingdom. This study (SEARCH) will randomize post-MI patients to simvastatin 20 or 80 mg/d, the

TABLE 6. Sensitivity Analysis: Relationship Using Various Statistical Techniques Between a 1% Change in Lipoproteins in the Simvastatin Group in 4S, the Cholestyramine Group in LRC-CPPT,[7] and the Gemfibrozil Group in the Helsinki Heart Study,[8] and the Reduction in the Risk of MCEs

	Baseline Lipid in Model?	LDL Cholesterol		HDL Cholesterol		Triglycerides	
		% Risk Reduction (95% CI)	*P*	% Risk Reduction (95% CI)	*P*	% Risk Reduction (95% CI)	*P*
Statistical model							
Year 1 percent change	No	−1.6 (−2.2 to −0.9)	<.00001	−0.6 (−1.3 to 0.1)	.100	−0.2 (−0.6 to 0.2)	.355
	Yes*	−1.7 (−2.4 to −1.0)	<.00001	−0.8 (−1.5 to −0.1)	.039	−0.2 (−0.6 to 0.2)	.373
Time-dependent Cox	No	−1.9 (−2.7 to −1.2)	<.00001	−0.5 (−1.3 to 0.2)	.174	−0.6 (−1.0 to −0.2)	.006
proportional hazard†	Yes	−2.3 (−3.0 to −1.5)	<.00001	−0.9 (−1.7 to −0.1)	.025	−0.7 (−1.2 to −0.3)	.002
Time-dependent Cox	No	−1.5 (−2.2 to −0.8)	.00002	−0.4 (−1.1 to 0.3)	.223	−0.6 (−0.9 to −0.2)	.002
with values in previous 2 years only†	Yes	−1.7 (−2.4 to −1.0)	<.00001	−0.8 (−1.5 to −0.1)	.040	−0.6 (−1.0 to −0.3)	.001
Other studies							
LRC-CPPT	Yes	−1.9 (−3.0 to −0.8)	.00075	−1.1 (−2.4 to 0.1)	.070	−0.1 (−0.6 to 0.3)	.529
Helsinki Heart Study	Yes	−2.3 (−4.4 to −0.1)	.040	−3.1 (−5.4 to −0.8)	.008	−0.5 (−1.4 to 0.4)	.275

*The model used for this article.

†Includes events that occurred in the first year.

larger dose producing an average reduction in LDL cholesterol of 47%.[28]

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References

1. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344: 1383–1389.
2. Pedersen TR, Berg K, Cook TJ, Faergeman O, Haghfelt T, Kjekshus J, Miettinen T, Musliner TA, Olsson AG, Pyörälä K, Thorgeirsson G, Tobert JA, Wedel H, Wilhelmsen L. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1996;156:2085–2092.
3. Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1995;345:1274–1275.
4. Kjekshus J, Pedersen TR, for the Scandinavian Simvastatin Survival Study Group. Reducing the risk of coronary events: evidence from 4S. *Am J Cardiol*. 1995;76:64C–68C.
5. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
6. Wolfe RA, Strawderman RL. Logical and statistical fallacies in the use of Cox regression models. *Am J Kidney Dis*. 1996;27:124–129.
7. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results, II: the relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984; 251:365–374.
8. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Mäenpää H, Mälkönen M, Mänttäri M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjöblom T, Nikkilä EA. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA*. 1988;260:641–651.
9. Pyörälä K, De Backer G, Graham I, Poole-Wilson P, Wood D, on behalf of the Task Force. Prevention of coronary heart disease in clinical practice: recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Eur Heart J*. 1994;15:1300–1331.
10. Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA*. 1993;269:3015–3023.
11. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256: 2823–2828.
12. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Nedeljkovic S, Nissinen A, Toshima H. Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty-five-year follow-up of the Seven Countries Study. *JAMA*. 1995;274: 131–136.
13. Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease: the Framingham Study. *Ann Epidemiol*. 1992;2:23–28.
14. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, Ockene IS, Pearson TA, Reed J, Smith SC Jr, Washington R. When to start cholesterol-lowering therapy in patients with coronary heart disease: a statement for healthcare professionals from the American Heart Association Task Force on Risk Reduction. *Circulation*. 1997;95:1683–1685.
15. The National Institutes of Health Consensus Development Conference on Triglyceride, HDL, and Coronary Heart Disease. *Triglyceride, High Density Lipoprotein, and Coronary Heart Disease. NIH Consensus Statement (Feb. 26–28, 1992)*. 1992:10.
16. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.
17. Assmann G, Schulte H. The importance of triglycerides: results from the Prospective Cardiovascular Munster (PROCAM) Study. *Eur J Epidemiol*. 1992;1:99–103.
18. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. *Circulation*. 1997;95:69–75.
19. Patsch JR, Miesenbock G, Hopferwieser T, Muhlberger V, Knapp E, Dunn JK, Gotto AM Jr, Patsch W. Relation of triglyceride metabolism and coronary artery disease: studies in the postprandial state. *Arterioscler Thromb*. 1992;12:1336–1345.
20. Szatrowski TP, Peterson AV Jr, Shimizu Y, Prentice RL, Mason MW, Fukunaga Y, Kato H. Serum cholesterol, other risk factors, and cardiovascular disease in a Japanese cohort. *J Chronic Dis*. 1984;37:569–584.
21. Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ*. 1991;303:276–282.
22. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C-C, Davis BR, Braunwald E, for the Cholesterol, and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009.
23. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;2:349–360.
24. Burchfiel CM, Laws A, Benfante R, Goldberg RJ, Hwang L, Chiu D, Rodriguez B, Curb JD, Sharp DS. Combined effects of HDL cholesterol, triglyceride, and total cholesterol concentrations on 18-year risk of atherosclerotic disease. *Circulation*. 1995;92:1430–1436.
25. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ*. 1994;308:367–372.
26. Gordon DJ. Cholesterol lowering and total mortality. In: Rifkind BM, ed. *Lowering Cholesterol in High Risk Individuals and Populations*. New York, NY: Marcel Dekker; 1995:33–47.
27. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation*. 1998;97:946–952.
28. Davidson MH, Stein EA, Dujovne CA, Hunninghake DB, Weiss SR, Knopp RH, Illingworth DR, Mitchel YB, Melino MR, Zupkis RV, Dobrinska MR, Amin RD, Tobert JA. The efficacy and six-week tolerability of simvastatin 80 and 160 mg/day. *Am J Cardiol*. 1997;79:38–42.