Cholesterol Lowering With Simvastatin Improves Prognosis of Diabetic Patients With Coronary Heart Disease

A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S)

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OBJECTIVE — To assess in diabetic patients with coronary heart disease (CHD) the effect of cholesterol lowering with simvastatin on mortality and the risk of CHD and other atherosclerotic events.

RESEARCH DESIGN AND METHODS — A post hoc subgroup analysis was carried out on data from 202 diabetic patients and 4,242 nondiabetic patients with previous myocardial infarction or angina pectoris, serum total cholesterol 5.5–8.0 mmol/l, and serum triglycerides ≤2.5 mmol/l who were participating in the Scandinavian Simvastatin Survival Study (4S). Participants in the 4S were randomly assigned to double-blind treatment with simvastatin, 20 mg daily, with blinded dosage titration up to 40 mg daily, according to cholesterol response during the first 6–18 weeks, or placebo. Endpoints were *1*) total mortality, 2) major CHD events (CHD death or nonfatal myocardial infarction), *3*) other acute atherosclerotic events, *4*) myocardial revascularization procedures.

RESULTS — Over the 5.4-year median follow-up period, simvastatin treatment produced mean changes in serum lipids in diabetic patients similar to those observed in nondiabetic patients. The relative risks (RRs) of main endpoints in simvastatin-treated diabetic patients were as follows: total mortality 0.57 (95% CI, 0.30–1.08; $P = 0.087$), major CHD events 0.45 (95% CI, 0.27–0.74; $P = 0.002$), and any atherosclerotic event 0.63 (95% CI, 0.43–0.92; $P = 0.018$). The corresponding RRs in nondiabetic patients were the following: 0.71 (95% CI, 0.58–0.87; $P = 0.001$), 0.68 (95% CI, 0.60–0.77; $P < 0.0001$), and 0.74 (95% CI, 0.68–0.82; $P < 0.0001$).

CONCLUSIONS — The results strongly suggest that cholesterol lowering with simvastatin improves the prognosis of diabetic patients with CHD. The absolute clinical benefit achieved by cholesterol lowering may be greater in diabetic than in nondiabetic patients with CHD because diabetic patients have a higher absolute risk of recurrent CHD events and other atherosclerotic events.

The risk of coronary heart disease (CHD) death and serious nonfatal CHD events is markedly increased in diabetic patients relative to nondiabetic subjects (1–4). Furthermore, clinically manifest CHD has a worse prognosis in diabetic patients than in nondiabetic subjects (5–9). The excessive CHD risk in diabetic patients is in part explained by adverse effects of diabetes on serum lipids and other general cardiovascular risk factors, but a large part of the excessive risk is evidently caused by enhancing effects of the diabetic state itself on atherogenesis and/or thrombogenesis (10).

Adverse effects of diabetes on serum lipids are more pronounced in NIDDM than in IDDM (11). Serum lipid abnormalities in NIDDM are characterized by decreased HDL cholesterol and elevated total and VLDL triglyceride levels, whereas total cholesterol and LDL cholesterol levels in patients with this type of diabetes do not differ from those in nondiabetic subjects. Serum total cholesterol has been shown to be as powerful a predictor of CHD mortality and morbidity in middle-aged diabetic patients, most of whom have NIDDM, as it is in nondiabetic subjects of the same age; however, at every level of total cholesterol, diabetic patients have two to three times higher CHD risk than do nondiabetic subjects (3,12,13).

Trial experience on the effect of cholesterol lowering on the risk of CHD in diabetic patients is almost completely lacking. A subgroup analysis on diabetic patients included in the Helsinki Heart Study, a 5-year CHD primary prevention trial using gemfibrozil as a lipid-lowering drug, has been published (14). This subgroup analysis, based on 135 diabetic patients randomized to double-blind treatment with gemfibrozil or placebo, gave evidence suggestive of a treatment benefit. The 5-year incidence of major CHD events (CHD death or nonfatal myocardial infarction) in diabetic patients was 3.4% in the gemfibrozil group and 10.5% in the placebo group ($P = 0.19$).

The results of the Scandinavian Simvastatin Survival Study (4S) have recently been reported (15,16). The 4S was designed to study the effect of cholesterol lowering with simvastatin, an inhibitor of 3-hydroxy-3-hydroxymethyl coenzyme A (HMG-CoA) reductase, on mortality and morbidity in patients with CHD. A total of 4,444 patients with previous myocardial infarction or angina pectoris and with serum cholesterol levels of 5.5–8.0 mmol/l

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CHD, coronary heart disease; HMG, 3-hydroxy-3-hydroxymethyl; RR, relative risk; 4S, Scandinavian Simvastatin Survival Study.

and serum triglyceride levels of ≤2.5 mmol/l were randomly allocated to receive simvastatin or placebo. Over the 5.4-year median follow-up period, simvastatin produced mean changes in serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides of −25, −35, 8, and −10%, respectively. Simvastatin treatment reduced CHD mortality by 42% ($P < 0.00001$), thus reducing all-cause mortality by 30% ($P = 0.0003$). The incidence of major CHD events (CHD death or nonfatal myocardial infarction) was reduced by 34% ($P < 0.00001$). We now report on a subgroup analysis of the data on diabetic patients included in the 4S to evaluate the effect of cholesterol lowering with simvastatin on mortality and the risk of CHD events and other atherosclerotic events in diabetic patients with CHD.

RESEARCH DESIGN AND METHODS

Trial design and patients

The 4S was a double-blind, randomized, placebo-controlled multicenter clinical trial of long-term simvastatin therapy in patients with CHD carried out in 94 clinical centers in Denmark, Finland, Iceland, Norway, and Sweden. The design, organization, and practical aspects of the trial and the main findings on mortality and morbidity have been described in detail previously (15,17). The study protocol was approved by regional or, if applicable, national ethics committees and by the regulatory agencies in each of the participating countries.

Recruitment and randomization of the patients took place in 1988–1989. Patients were men and women aged 35–70 years with previous myocardial infarction or angina pectoris who were identified by systematic screening of the patient records of potentially eligible patients. Cardiovascular exclusion criteria were myocardial infarction during the preceding 6 months, antiarrhythmic therapy, congestive heart failure requiring treatment with digitalis or diuretics or vasodilators, persistent atrial fibrillation, hemodynamically important valvular heart disease, unstable angina pectoris, planned coronary artery surgery or angioplasty, and previous stroke. Impaired hepatic function or any other serious disease or condition potentially leading to problems in participation also led to exclusion.

To qualify for randomization, serum total cholesterol had to be 5.5–8.0 mmol/l and serum triglycerides ≤2.5 mmol/l after a 2-month period before which the patients had received advice about a lipid-lowering diet. At randomization, patients who had given their informed consent were randomly assigned to take 20 mg simvastatin daily or placebo.

Of the 4,444 randomized patients, 4,242 were nondiabetic (2,126 randomized to placebo and 2,116 to simvastatin) and 202 were diabetic (97 randomized to placebo and 105 to simvastatin). The diagnosis of diabetes was based on information from patient records before the baseline examination. Of the 202 diabetic patients (158 men and 44 women), 24 (12%) were treated with insulin, 78 (39%) with oral hypoglycemic drugs (61 with a sulfonylurea only, 4 with metformin only, and 13 with both a sulfonylurea and metformin), and 100 (50%) with diet only.

Follow-up visits and laboratory measurements. Follow-up clinic visits and methods used in laboratory measurements have been previously described (15,17). The data shown in this report on fasting blood glucose at baseline and at the final study visit are based on whole-blood or plasma glucose determinations carried out in the local labo-

Table 1—*Baseline characteristics of nondiabetic and diabetic patients*

	Nondiabetic	Diabetic	P value
n	4,242	202	
Age (years)	56.6 ± 7.1	59.9 ± 6.6	0.008
Men	3,459 (82)	158 (72)	NS
Qualifying diagnosis			
Angina only	874 (21)	40 (20)	NS
Infarction only	2,656 (63)	128 (63)	
Both angina and infarction	712 (17)	34 (17)	
Years since diagnosis of CHD			
<1	1,148 (27)	43 (21)	0.006
1–5	1,807 (43)	82 (41)	
>5	1,287 (30)	77 (38)	
Chest pain on exertion			
No pain	1,714 (40)	61 (30)	<0.001
Pain on heavy exertion	1,648 (39)	73 (36)	
Pain on light exertion	880 (21)	68 (34)	
Secondary diagnoses			
Hypertension	1,082 (26)	80 (40)	<0.001
Claudication	230 (5)	24 (12)	<0.001
Previous CABG or angioplasty	326 (8)	13 (6)	NS
Concomitant therapy			
Aspirin	1,563 (37)	77 (38)	NS
β-blockers	2,402 (57)	123 (61)	NS
Calcium-channel blockers	1,294 (31)	86 (34)	<0.001
Smoking status			
Never smoked	1,045 (25)	74 (37)	<0.001
Ex-smoker	2,099 (49)	88 (44)	
Smoker	1,098 (26)	40 (20)	
BMI (kg/m²)	25.9 ± 3.3	27.2 ± 3.6	<0.001
sBP (mmHg)	138.4 ± 19.4	147.1 ± 22.1	<0.001
dBP (mmHg)	83.3 ± 9.5	85.1 ± 9.4	0.012
Heart rate (beats/min)	63.8 ± 10.0	68.1 ± 10.7	<0.001
Total cholesterol (mmol/l)	6.75 ± 0.66	6.71 ± 0.67	NS
LDL cholesterol (mmol/l)	4.88 ± 0.66	4.80 ± 0.67	NS
HDL cholesterol (mmol/l)	1.19 ± 0.30	1.13 ± 0.25	0.006
Triglycerides (mmol/l)	1.49 ± 0.50	1.73 ± 0.65	<0.001
Serum creatinine ≥130 mmol/l	67 (2)	5 (2)	NS
Proteinuria	284 (7)	34 (17)	<0.00001

Data are means ± SD or *n* (%). No data were missing on categorical variables. Missing data on continuous variables for 0–2% of nondiabetic patients and for 0–0.5% of diabetic patients. sBP, systolic blood pressure; dBP, diastolic blood pressure. CABG, coronary artery bypass grafting.

Table 2—*Baseline characteristics of diabetic patients randomized to placebo or simvastatin*

	Placebo	Simvastatin
n	97	105
Age (years)	59.9 ± 6.5	59.9 ± 6.7
BMI (kg/m²)	27.3 ± 3.2	27.2 ± 3.9
sBP (mmHg)	147.4 ± 21.1	146.9 ± 23.1
dBP (mmHg)	85.5 ± 9.3	84.6 ± 9.6
Heart rate (beats/min)	68.7 ± 10.8	67.6 ± 10.5
Blood glucose (mmol/l)	8.60 ± 2.99	8.56 ± 2.95
Total cholesterol (mmol/l)	6.72 ± 0.65	6.71 ± 0.70
LDL cholesterol (mmol/l)	4.80 ± 0.64	4.81 ± 0.69
HDL cholesterol (mmol/l)	1.13 ± 0.24	1.12 ± 0.26
Triglycerides (mmol/l)	1.78 ± 0.67	1.69 ± 0.63

Data are means ± SD. Data on BMI was missing for one patient in the simvastatin group and on LDL and HDL cholesterol for one patient in the placebo group. None of the differences between the placebo group and simvastatin group were statistically significant. sBP, systolic blood pressure; dBP, diastolic blood pressure.

ratories as part of the safety data collection. Since these data are shown only for the comparison of blood glucose levels in diabetic patients randomized to placebo or simvastatin, plasma glucose values were not converted to blood glucose values or vice versa. Baseline blood glucose values were missing for three diabetic patients (one in the placebo group and two in the simvastatin group). Blood glucose values available nearest to baseline were used to replace these missing values. Diabetic patients were under the care of their own physicians for the treatment of diabetes.

Dosage titration and compliance. The simvastatin dose was titrated to 40 mg daily in patients who did not reach the target serum total cholesterol level of 3.0–5.2 mmol/l after 6 or 18 weeks by using methods that preserved the study blind, as previously described (15,17).

At each clinic visit, the returned tablets were counted and related to the number of days since the last visit. Compliance was assessed by calculating the proportion of dosages consumed by days since the previous visit.

Endpoints. Total mortality was the primary endpoint of the 4S. Major CHD events (CHD death or nonfatal myocardial infarction) formed the secondary endpoint. Tertiary endpoints included: *1*) any CHD event, i.e., the secondary endpoint event or hospital admission for acute CHD event without a diagnosis of myocardial infarction (mainly prolonged chest pain); 2) any atherosclerotic event, i.e., death from or hospital admission for such an event (CHD event or a myocardial revascularization procedure, either coronary artery bypass grafting or coronary angioplasty, or cerebrovascular or peripheral vascular disease event); and *3*) myocardial revascularization procedures. The procedures for event reporting and diagnostic classification of all study endpoint events have been previously described (15,17).

Statistical methods

Student's *t* test or χ^2 test was used, as appropriate, in statistical testing of differences in the baseline characteristics of nondiabetic and diabetic participants or diabetic patients randomized to simvastatin or placebo.

The effect of simvastatin treatment was assessed by calculating relative risk (RR) and 95% CIs for the simvastatin group versus the placebo group with the Cox regression model (18). Kaplan-Meier survival curves and 6-year survival probability estimates were also calculated for the simvastatin group and the placebo group, and the differences between treatment groups were tested by log-rank test. Two-sided *P* values <0.05 were regarded as significant.

RESULTS — Table 1 shows the baseline characteristics of the nondiabetic and diabetic participants in the 4S. Diabetic patients were somewhat older, and a larger proportion of them had their CHD diagnosed >5 years before randomization. Greater proportions of diabetic patients reported chest pain on exertion, hypertension, or claudication and a greater proportion received calcium-channel blockers compared with nondiabetic patients. A greater proportion of diabetic patients had never smoked. Diabetic patients were more obese and had higher systolic and diastolic blood pressure and heart rate. Total and LDL cholesterol levels were similar in nondiabetic and diabetic patients, but diabetic patients had lower HDL cholesterol and higher triglycerides. Proteinuria was more frequent in diabetic than in nondiabetic patients.

As shown in Table 2, diabetic patients randomized to placebo and simvastatin were well matched at baseline. This also applied to other relevant characteristics related to their CHD or other cardiovascular conditions or risk status (data not shown).

Among patients randomized to simvastatin, the daily dosage of the drug was increased to 40 mg in 37% of nondiabetic patients and in 33% of diabetic patients. Median follow-up time in nondiabetic patients was 5.4 years (range for those surviving, 5.0–6.2 years) and in diabetic patients 5.3 years (range for those surviving, 5.0–6.0 years).

Among nondiabetic patients, 13% in the placebo group and 10% in the simvastatin group stopped taking their tablets (NS). Corresponding figures among diabetic patients were 19 and 12% (NS). In these four groups, adverse clinical events were the reason for discontinuation in 5, 5, 11, and 6%, respectively, and patient reluctance accounted for most of the remainder.

Over the whole course of the trial, in the simvastatin-treated nondiabetic patients, the mean changes from baseline in total, LDL, and HDL cholesterol and triglycerides were −24, −34, 8, and −9%, respectively; in simvastatin-treated diabetic patients, they were almost identical: −27, −36, 7, and −11%, respectively.

Fasting blood glucose measurements both at baseline and at the final visit of the trial were available for 69 diabetic patients receiving placebo and 86 diabetic patients receiving simvastatin. The mean ± SD blood glucose at baseline was 8.51 ± 2.88 mmol/l in placebo-treated patients and 8.61 ± 3.03 mmol/l in simvastatin-treated patients (NS). At the final visit, the mean values for blood glucose were 9.16 ± 3.26 and 8.89 ± 2.96 mmol/l, respectively (NS).

Mortality and occurrence of CHD events and other atherosclerotic vascular disease events

Mortality and the occurrence of different forms of nonfatal atherosclerotic events during follow-up in nondiabetic and diabetic patients randomized to placebo or

Table 3—*Mortality and occurrence of nonfatal atherosclerotic events during follow-up in nondiabetic and diabetic patients randomized to placebo or simvastatin*

	Nondiabetic		Diabetic	
	Placebo	Simvastatin	Placebo	Simvastatin
n	2,126	2,116	97	105
Death				
Death from CHD	172 (8.1)	99 (4.7)	17 (17.5)	12 (11.4)
Death from other cardiovascular cause	15 (0.7)	24 (1.1)	3 (3.1)	0
Death from noncardiovascular cause	45 (2.1)	44 (2.1)	4 (4.1)	3 (2.9)
Death from any cause	232 (10.9)	167 (7.9)	24 (24.7)	15 (14.3)
Nonfatal events				
Definite MI	246 (11.6)	157 (7.4)	24 (24.7)	7 (6.7)
Probable MI	191 (9.0)	135 (6.4)	11 (11.3)	4 (3.8)
Intervention-associated MI	22 (1.0)	10 (0.5)	3 (3.1)	2 (1.9)
Silent MI	97 (4.6)	85 (4.0)	12 (12.4)	5 (4.8)
Resuscitated cardiac arrest	0	1 (0.1)	0	0
Nonfatal major CHD event	466 (21.9)	339 (16.0)	35 (36.1)	14 (13.3)
Non-MI CHD event	310 (14.6)	280 (13.2)	21 (21.6)	15 (14.3)
CABG or angioplasty	363 (17.1)	237 (11.2)	20 (20.6)	15 (14.3)
Cerebrovascular disease event	85 (4.0)	56 (2.6)	10 (10.3)	5 (4.8)
Other atherosclerotic event	12 (0.6)	12 (0.6)	0	1 (1.0)

Data are number of patients (%). A patient with two or more events of different types will appear more than once in a column but only once in a row. MI, myocardial infarction. CABG, coronary artery bypass grafting.

simvastatin are shown in Table 3. The numbers of patients with the 4S secondary endpoint (CHD death or nonfatal myocardial infarction) were as follows: in nondiabetic patients, 578 (27.2%) in the placebo group and 407 (19.2%) in the simvastatin group; in diabetic patients, 44 (45.4%) in the placebo group and 24 (22.9%) in the simvastatin group.

Figure 1 summarizes the reduction in risk of different endpoints in nondiabetic and diabetic patients expressed in terms of RR and 95% CIs in the simvastatin group relative to the placebo group. In nondiabetic patients, the risk reduction in the simvastatin group was statistically significant for the endpoints shown in the figure, with the exception of cerebrovascular disease events (RR from 0.57 to 0.77; P = 0.097 for cerebrovascular disease events, P = 0.001 for total mortality, $P < 0.0001$ for other endpoints). In diabetic patients, the reduction in the risk of total mortality (RR = 0.57; P = 0.087) or CHD mortality (RR = 0.64; P = 0.242) did not reach statistical significance because of small sample size. However, the risk of a major CHD event was significantly reduced (RR = 0.45; P = 0.002) in diabetic patients, and the same applied for the risk of any CHD event (RR = 0.61; P = 0.015) and any atherosclerotic event (RR = 0.63; P = 0.018). The reduction in the risk of having to undergo coronary artery bypass grafting or coronary angioplasty (RR = 0.68; P = 0.265) and in the risk of cerebrovascular disease events (RR = 0.38; P = 0.071) in diabetic patients failed to reach statistical significance, although the latter was near to it

The Kaplan-Meier 6-year (70-month) probability of survival (Fig. 2) was 88.4% in nondiabetic patients in the placebo group vs. 91.6% in the simvastatin group. In diabetic patients, it was 68.8% in the placebo group vs. 84.0% in the simvastatin group. The probability of escaping a major CHD event (Fig. 3) was 71.3% in nondiabetic patients in the placebo group vs. 79.8% in the simvastatin group. In diabetic patients, it was 50.7% in the placebo group vs. 75.1% in the simvastatin group.

The relationship of baseline serum lipid levels to the effect of simvastatin treatment on the risk of major CHD events in diabetic patients was examined by dividing the placebo-treated and simvastatin-treated groups into two strata using the median values for the baseline level of each lipid variable in the whole diabetic group as cut-off points (Table 4). The risk reduction by simvastatin treatment was not dependent on the baseline level of total, LDL, or HDL cholesterol or triglycerides ($P > 0.3$ for each pairwise comparison), although there was a trend to a more marked treatment effect among those diabetic patients who were in either the lower half of the HDL cholesterol distribution or the upper half of the triglyceride distribution.

CONCLUSIONS — This post hoc subgroup analysis of the data on diabetic patients included in the 4S provides the first trial-based evidence that cholesterol lowering reduces the risk of major CHD events and other atherosclerotic events in

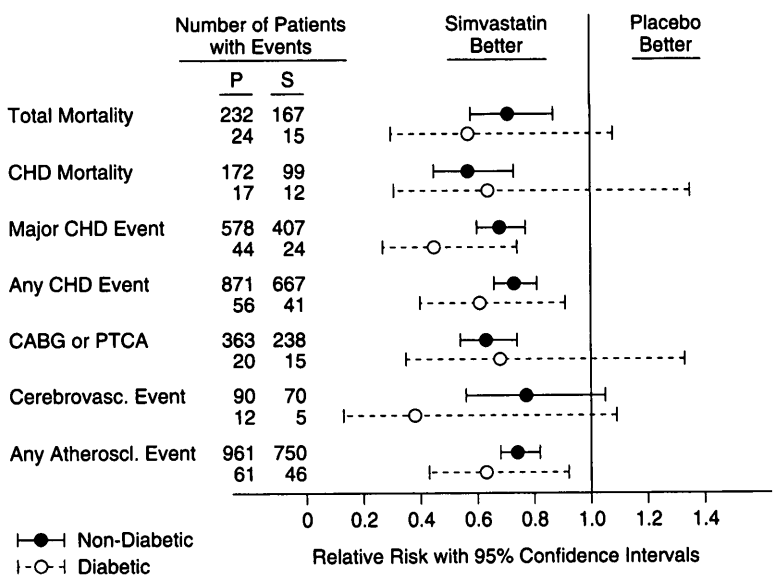

Figure 1—*Reduction in the risk of different endpoints expressed as RR (simvastatin [S] group vs. placebo [P] group) with 95% CIs in nondiabetic and diabetic patients.*

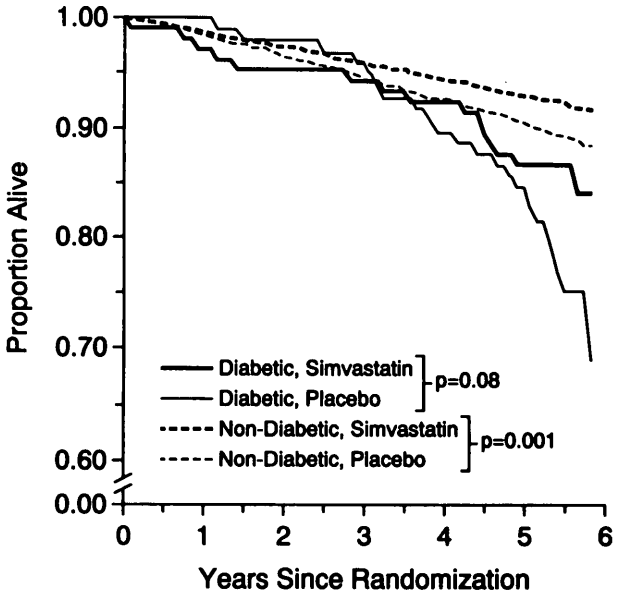

Figure 2—*Kaplan-Meier curves for total mortality during follow-up in nondiabetic and diabetic patients treated with placebo or simvastatin in the 4S.*

diabetic patients with CHD. The reductions in risk in diabetic patients, 55% (95% CI, 24–73%) for major CHD events and 37% (95% CI, 8–57%) for any atherosclerotic event, were of a magnitude equal to the reductions observed in nondiabetic patients, 32% (95% CI, 23–40%) and 26% (95% CI, 18–32%), respectively. The reduction in total mortality was 43% in diabetic patients (95% CI, −8 to 70%) and 29% in nondiabetic patients (95% CI, 13–42%), suggesting that the effect of cholesterol lowering on the risk of death is similar in diabetic and nondiabetic patients.

Although it was not possible on the basis of the information available to accurately classify the 202 diabetic patients participating in the 4S according to type of diabetes, almost all of them presumably had NIDDM, 50% of them being treated with diet only, 39% with oral hypoglycemic drugs, and only 12% with insulin. These diabetic patients, however, were not fully representative of patients of the same age with NIDDM and clinically manifest CHD in the general population. Only 4.5% of the 4S participants had diabetes, a figure that is much smaller than the expected prevalence of diabetes in unselected patients with CHD. In a recent study carried out in nine European countries, the prevalence of diabetes was 18% in unselected CHD patients in the same age range as the 4S participants (EuroASPIRE Study Group, unpublished observations). The high proportion of diet-treated patients among the 4S diabetic participants suggests that patients with more severe forms of diabetes were underrepresented in the 4S. The general 4S exclusion criterion of "reduced life expectancy due to other serious diseases" may have contributed to the exclusion of diabetic subjects with serious complications. Thus, patients with advanced diabetic nephropathy were evidently excluded, because despite increased prevalence of proteinuria in the 4S diabetic patients, elevated serum creatinine was equally rare in the diabetic and nondiabetic 4S patients. Moreover, since diabetic patients tend to develop more severe clinical manifestations of CHD, the rather strict cardiovascular exclusion criteria, particularly exclusion of patients with congestive heart failure or recent unstable phases of CHD, may have led investigators to exclude many diabetic patients. Exclusion of patients with serum triglycerides >2.5 mmol/l must have led to the exclusion of a relatively large number of diabetic patients; this may also have led to a decrease in the CHD risk of the 4S diabetic patients because elevated serum triglyceride level has been shown to be an important predictor of CHD risk in diabetes (19,20). Despite all these exclusions, the incidence of major CHD events observed during the whole 4S trial period was 1.7-fold higher in placebo-treated diabetic patients than in placebo-treated nondiabetic patients.

With the caveat that the prognosis of diabetic CHD patients participating in the 4S was probably somewhat better than that of unselected diabetic CHD patients of the same age in the general population, we have estimated on the basis of our study the potential benefit of simvastatin treatment for 6 years in nondiabetic and diabetic patients with CHD who have serum total cholesterol 5.5–8.0 mmol/l and serum triglycerides ≤2.5 mmol/l. The results of these calculations based on Kaplan-Meier probability esti-

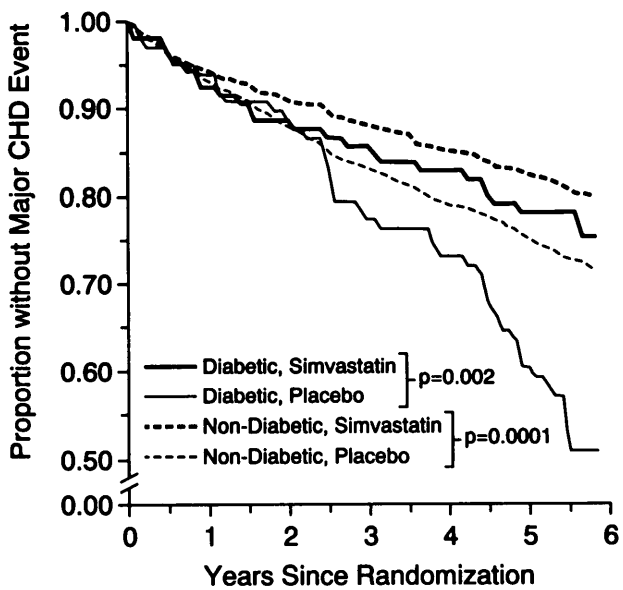

Figure 3—*Kaplan-Meier survival curves for the probability of remaining free of a major CHD event during follow-up in nondiabetic and diabetic patients treated with placebo or simvastatin in the 4S.*

Table 4—*Effect of simvastatin treatment on the risk of major coronary heart disease events in diabetic patients by baseline serum lipid levels*

Lipid variable	Placebo/simvastatin	Subjects with events		RR (95% CI) (simvastatin vs. placebo)	*P* value
		Placebo	Simvastatin		
Total cholesterol (mmol/l)					
<6.25	46/52	18 (39)	11 (21)	0.50 (0.23–1.05)	0.07
≥6.25	51/53	26 (51)	13 (25)	0.44 (0.22–0.85)	0.02
LDL cholesterol (mmol/l)					
<4.85	47/50	22 (47)	12 (24)	0.46 (0.23–0.93)	0.03
≥4.85	49/55	22 (45)	12 (22)	0.45 (0.22–0.91)	0.03
HDL cholesterol (mmol/l)					
<1.10	43/50	21 (49)	10 (20)	0.34 (0.16–0.72)	0.005
≥1.10	53/55	23 (43)	14 (26)	0.56 (0.29–1.08)	0.08
Triglycerides (mmol/l)					
<1.70	45/54	19 (42)	12 (22)	0.50 (0.24–1.02)	0.06
≥1.70	52/51	25 (48)	12 (24)	0.42 (0.21–0.84)	0.01

Data are *n* or *n* (%) unless otherwise indicated. The groups were divided into two strata by the median for each lipid variable in the whole diabetic group. Treatment–by–lipid level interactions were not significant.

mates of escaping an event are as follows: Simvastatin treatment of 100 CHD patients for 6 years would prevent an expected major CHD event in 9 out of 29 nondiabetic patients, compared with 24 out of 46 diabetic patients expected to have an event. For any atherosclerotic event, simvastatin treatment of 100 CHD patients for 6 years would prevent such an event in 9 out of 46 nondiabetic patients, compared with 18 out of 63 diabetic patients expected to have an event.

Because of the exclusion of patients with serum triglycerides >2.5 mmol/l, the serum triglyceride distribution of the 4S diabetic subjects was truncated. There is a close inverse correlation between concentrations of triglycerides and HDL cholesterol; therefore, HDL cholesterol in the 4S diabetics might have been slightly lower without that exclusion criterion. Yet the mean serum triglycerides were significantly higher and HDL cholesterol was significantly lower in the 4S diabetic subjects than in the 4S nondiabetic subjects. An interesting observation was that the treatment effect did not appear to depend on baseline serum total or LDL cholesterol levels (Table 4). In this respect, the results in the 4S diabetic subjects were similar to those observed in the whole 4S group (21) or in the West of Scotland Coronary Prevention Study, a primary prevention trial using pravastatin (22). There was, however, a statistically nonsignificant trend to a more marked treatment effect among those 4S diabetic subjects who were in either the lower half of the HDL cholesterol distribution or the upper half of the triglyceride distribution, i.e., in patients with serum lipid abnormalities more characteristic of NIDDM (11).

The main limitation of our study is that it is a post hoc subgroup analysis based on a relatively small number of selected diabetic patients participating in a large trial of secondary prevention of CHD. Further information on the effect of cholesterol lowering on the prognosis of diabetic patients with CHD will be forthcoming from other recently completed and ongoing secondary prevention trials that include diabetic patients.

It may be argued that the distinction between primary prevention in high-risk individuals and secondary prevention in patients with clinically established CHD is even more arbitrary in diabetic patients than in nondiabetic subjects. Because the impact of diabetes on CHD risk is superimposed on the impact of serum lipids and other cardiovascular risk factors, diabetic patients form a group at particularly high risk. A study on the prognosis of unselected diabetic and nondiabetic subjects who had their first myocardial infarction before the age of 65 years (based on the FINMONICA myocardial infarction register) showed that 49% of diabetic men and 45% of diabetic women died within 1 year (23). In nondiabetic subjects, the corresponding figures were 36 and 23%. More than half of the deaths, in both diabetic and nondiabetic subjects, occurred before they could be hospitalized for their first infarction. These gloomy figures emphasize the importance of both primary and secondary prevention and raise the question to what extent should lessons learned from secondary prevention trials of cholesterol lowering be applied to primary prevention in asymptomatic high-risk individuals such as diabetic patients.

In conclusion, the results of this subgroup analysis of the 4S data strongly suggest that cholesterol lowering with simvastatin improves prognosis in diabetic patients with CHD. The absolute clinical benefit achieved by cholesterol lowering in terms of events prevented may be greater in diabetic than in nondiabetic patients with CHD because diabetic patients have a higher absolute risk of recurrent CHD events and other atherosclerotic events.

Note added in proof

After the submission of this article for publication, the results of the Cholesterol and Recurrent Events (CARE) trial were published (Sacks et al., *N Engl J Med* 335:1001–1009, 1996). In that trial, which lasted for 5 years, 4,159 patients with myocardial infarction aged <75 years who had plasma total cholesterol levels <6.2 mmol/l were randomized to either 40 mg of pravastatin or placebo. The number of participants with diabetes diagnosed before baseline was 586 (14%). The primary endpoint (CHD death or nonfatal myocardial infarction) was reduced by 24% ($P = 0.003$) by pravastatin treatment. In a subgroup analysis using a more broadly defined CHD event endpoint (CHD death, confirmed nonfatal myocardial infarction, coronary artery bypass grafting, or coronary angioplasty), pravastatin treatment resulted in a 23% reduction of CHD events in nondiabetic patients ($P < 0.001$) and a 25% reduction in diabetic patients ($P = 0.05$).

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The participating investigators and centers have been listed in the main reports of the Scandinavian Simvastatin Survival Study (15,17).

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