

Reduced Coronary Events in Simvastatin-Treated Patients With Coronary Heart Disease and Diabetes or Impaired Fasting Glucose Levels

Subgroup Analyses in the Scandinavian Simvastatin Survival Study

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Background: Patients with diabetes mellitus (DM) have a marked increase in coronary heart disease (CHD) events relative to those without DM. In a previous report from the Scandinavian Simvastatin Survival Study using a clinical case definition of DM (n = 202), simvastatin-treated patients had significantly fewer CHD events compared with placebo-treated control subjects.

Objective: To examine the effect of simvastatin therapy on CHD in patients with DM and impaired fasting glucose levels.

Methods: Using the 1997 American Diabetes Association diagnostic criteria, we assessed the effect of simvastatin therapy post hoc for an average of 5.4 years in Scandinavian Simvastatin Survival Study patients with normal fasting glucose (n = 3237), impaired fasting glucose (n = 678), and DM (n = 483).

Results: Simvastatin-treated patients with DM had significantly reduced numbers of major coronary events (relative risk [RR] = 0.58; P = .001) and revascularizations

(RR = 0.52; P = .005). Total (RR = 0.79; P = .34) and coronary (RR = 0.72; P = .26) mortality were also reduced in DM, but not significantly, due to small sample size. In impaired fasting glucose (IFG) subjects, simvastatin use significantly reduced the number of major coronary events (RR = 0.62; P = .003), revascularizations (RR = 0.57; P = .009), and total (RR = 0.57; P = .02) and coronary (RR = 0.45; P = .007) mortality.

Conclusions: Our results extend previous findings in patients with DM to a larger cohort, confirming the benefit of cholesterol lowering with simvastatin treatment on CHD events. In addition, significant decreases in total mortality, major coronary events, and revascularizations were observed in simvastatin-treated patients with impaired fasting glucose levels. These results strongly support the concept that cholesterol lowering with simvastatin therapy improves the prognosis of patients with elevated fasting glucose levels (≥ 6.0 mmol/L [≥ 110 mg/dL]) or DM and known CHD.

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TYPE 2 diabetes mellitus (DM) is associated with at least a 2-fold increased risk of coronary heart disease (CHD).¹⁻⁵ In addition, the prognosis of clinical CHD is worse in patients with DM than in nondiabetic patients.⁶⁻⁸ Although the role of glycemia in CHD in nondiabetic patients is controversial,^{9,10} recent evidence¹¹ suggests that glycemia may be significantly related to mortality, even in the nondiabetic range, in a combined analysis of 3 longitudinal cohorts (the Whitehall, Paris Prospective, and Helsinki Policeman studies). In the Framingham Offspring Study,¹² CHD risk that was adjusted for obesity, elevated waist-hip ratio, hypertension, low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglyceride levels, and hyperinsulinemia showed continuous increases across the spectrum of nondiabetic glucose tolerance. Metabolic risk factors for type 2 DM

and cardiovascular disease worsened continuously across the spectrum of glucose tolerance categories, beginning in the lowest quintiles of normal fasting glucose (NFG) level.¹²

For editorial comment see page 2627

Excess risk of CHD in patients with DM is not fully understood, but diabetic dyslipidemia is likely to be a major contributor.¹³ Patients with type 2 DM have increased levels of triglyceride, decreased levels of HDL-C, and smaller absolute elevations of low-density lipoprotein cholesterol (LDL-C) levels relative to nondiabetic patients.¹³ However, patients with type 2 DM tend to have total LDL-C values that do not meet the goal by National Cholesterol Education Program Adult Treatment Panel II criteria,¹⁴ and have a greater preponderance of smaller, denser LDL-C that seems more atherogenic.¹³

PATIENTS AND METHODS

TRIAL DESIGN AND PATIENTS

The 4S was a double-masked, randomized, placebo-controlled multicenter clinical trial of long-term simvastatin therapy in patients with CHD carried out at 94 clinical centers in Denmark, Finland, Iceland, Norway, and Sweden. The design, organization, logistics, and main findings on mortality and morbidity have been described in detail previously.^{15,19,20} The study protocol was approved by regional or, if applicable, national ethics committees and by the regulatory agencies in each participating country.

Recruitment and randomization of patients took place from May 19, 1988, to August 16, 1989. Patients were men and women aged 35 to 70 years with previous MI or active, stable angina pectoris who were identified by systematic screening of the medical records of potentially eligible patients.

To qualify for randomization, serum total cholesterol level had to be 5.5 to 8.0 mmol/L (212-309 mg/dL) and serum triglyceride level had to be 2.5 mmol/L or less (≤ 220 mg/dL) measured after 2 months of following a lipid-lowering diet. At randomization, patients who had given informed consent were randomly assigned to take simvastatin, 20 mg/d, or placebo.

Follow-up clinic visits and the methods used in laboratory measurements have been described previously.^{15,19,20} Data on fasting blood glucose levels at baseline and the final study visit are based on whole blood, serum, or plasma glucose determinations carried out in local laboratories as part of routine safety data collection. Fasting glucose information was not available for 46 patients, leaving 4398 patients whose fasting glucose levels were available for analysis. Whole blood values were converted to plasma glucose values by multiplying the whole blood value by 1.15, and serum glucose values were considered equivalent to plasma values.²¹ A total of 678 patients had plasma glucose levels of 6.0 mmol/L or greater (≥ 110 mg/dL) but less than 7.0 mmol/L (< 126 mg/dL), which is diagnostic for IFG by the 1997 ADA criteria.¹⁸ A total of 281 patients had plasma glucose levels of 7.0 mmol/L or greater (≥ 126 mg/dL) (diagnostic for DM by ADA criteria) but did not have a clinical history of DM. Regardless of fasting glucose level,

the 202 previously described¹⁵ patients with a clinical history of DM were classified as having DM. The remaining patients ($n = 3237$) were classified as having NFG. Analysis of National Health and Nutrition Examination Study III data showed that about 4% of the US population have DM by clinical history (DM-Hx), 3% have DM only by elevated glucose values (DM-FG), 7% have IFG, and 86% have NFG using these criteria.¹⁴

Simvastatin dose was titrated to 40 mg/d in patients who did not reach the target serum total cholesterol level of 3.0 to 5.2 mmol/L (116-201 mg/dL) after 6 or 18 weeks using methods that preserved the masked nature of the study, as previously described.^{15,19,20}

Total mortality was the primary end point of 4S. Major coronary events (CHD death, nonfatal MI, and resuscitated ischemic cardiac arrest) constituted the secondary end point. Tertiary end points included (1) any CHD event, which consisted of any secondary end-point event plus any hospital admission for an acute CHD event without a diagnosis of MI (eg, prolonged chest pain or revascularization); (2) any atherosclerotic event, which consisted of any CHD event and fatal or nonfatal cerebrovascular events or other events directly attributed to atherosclerosis; and (3) myocardial revascularization procedures (coronary artery bypass grafting or coronary angioplasty). The procedures for event reporting and diagnostic classification of all study end-point events have been described previously.^{15,19,20}

STATISTICAL METHODS

Analysis of variance or the χ^2 test was used, as appropriate, in statistical testing of differences in the baseline characteristics of normal, impaired fasting glucose, and diabetic subjects who were randomized to receive simvastatin or placebo.

The effect of simvastatin treatment was assessed by calculating relative risk (RR) and 95% confidence intervals for the simvastatin group vs the placebo group with the Cox regression model.²² The assumption of proportionality of hazards in the Cox model was met. Kaplan-Meier survival curves and 6-year survival probability estimates were also calculated for both groups, and the differences between groups were tested using the log-rank test. Two-sided $P < .05$ was regarded as significant.

Several recent studies have focused attention on the benefits of LDL-C lowering in patients with clinical CHD. In the Scandinavian Simvastatin Survival Study (4S),¹⁵ simvastatin treatment reduced major coronary events by 55% ($P = .002$) in 202 patients with DM identified by medical history at baseline. In the Cholesterol and Recurrent Events (CARE) trial,¹⁶ pravastatin sodium treatment reduced the incidence of CHD events (CHD death, nonfatal myocardial infarction [MI], coronary artery bypass graft, and revascularization) by 25% ($P = .05$) in 586 patients with DM. In the Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID) study,¹⁷ pravastatin therapy reduced major CHD (fatal CHD and nonfatal MI) by 19% in 782 patients with DM (95% confidence interval [CI] = -10% to 41%; not significant).

In 1997, the American Diabetes Association (ADA) introduced new criteria for the diagnosis of DM (fasting

glucose level ≥ 7.0 mmol/L [≥ 126 mg/dL]).¹⁸ At the same time, the ADA introduced a new category of impaired fasting glucose (IFG) (fasting glucose level of 6.0-6.9 mmol/L [110-125 mg/dL]), which may be somewhat analogous to the older classification of impaired glucose tolerance. In this article, we examine the effect of simvastatin on CHD in patients with DM and IFG in the 4S using the 1997 ADA criteria. Use of this criteria would be expected to identify a larger number of patients with DM compared with diagnosis by clinical history of DM alone. The larger number of patients should increase the number of end points, thereby increasing the power of analysis.

RESULTS

Table 1 shows the baseline characteristics of patients in the 4S (placebo and simvastatin groups combined)

Table 1. Baseline Characteristics of 4398 Patients by Glucose Status*

Characteristic	NFG (n = 3237)	IFG (n = 678)	DM-FG (n = 281)	DM-Hx (n = 202)	Overall P
Age, y	58.5 ± 7.1	58.7 ± 7.2	58.8 ± 7.0	59.9 ± 6.6	.04
Men, %	80	84	89	78	.001
Qualifying diagnosis, %					
Angina only	22	18	12	20	<.001
MI only	61	66	73	63	<.001
Both angina and MI	17	16	15	17	.70
Hypertension, %	25	26	34	40	<.001
Smokers, %	26	23	29	20	.05
Body mass index, kg/m ²	25.7 ± 3.2	26.3 ± 3.4	26.9 ± 3.8	27.2 ± 3.6	<.001
Systolic BP, mm Hg	138 ± 19.2	139.4 ± 19.5	140.9 ± 20.3	147.1 ± 22.1	<.001
Total cholesterol level, mmol/L†	6.74 ± 0.66	6.75 ± 0.68	6.75 ± 0.69	6.71 ± 0.67	.86
LDL-C level, mmol/L†	4.88 ± 0.66	4.88 ± 0.66	4.80 ± 0.67	4.89 ± 0.67	.44
HDL-C level, mmol/L†	1.20 ± 0.30	1.17 ± 0.29	1.14 ± 0.31	1.13 ± 0.25	<.001
Triglyceride level, mmol/L‡	1.47 ± 0.48	1.55 ± 0.52	1.60 ± 0.53	1.73 ± 0.65	<.001
Apolipoprotein B level, g/L	1.15 ± 0.18	1.17 ± 0.18	1.19 ± 0.19	1.20 ± 0.18	<.001
Fasting glucose level, mmol/L§	5.3 ± 0.5	6.5 ± 0.2	7.6 ± 0.7	9.7 ± 3.4	<.001

*Data are given as mean ± SD unless indicated otherwise. NFG indicates normal fasting glucose; IFG, impaired fasting glucose; DM-FG, diabetes by elevated fasting glucose only; DM-Hx, diabetes by clinical history; MI, myocardial infarction; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

†To convert total cholesterol, LDL-C, and HDL-C from millimoles per liter to milligrams per deciliter, divide millimoles per deciliter by 0.02586.

‡To convert triglycerides from millimoles per liter to milligrams per deciliter, divide millimoles per deciliter by 0.01129.

§To convert fasting glucose from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.05551.

Table 2. Baseline Characteristics of 4398 Patients by Glucose Status and Treatment Assignment*

Characteristics	NFG (n = 3237)		IFG (n = 678)		DM-FG (n = 281)		DM-Hx (n = 202)	
	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo
Age, y	58.6 ± 7.2	58.4 ± 6.9	58.4 ± 7.1	59.1 ± 7.2	59.0 ± 7.1	58.6 ± 6.8	59.9 ± 6.7	59.9 ± 6.5
Sex: Male/Female, %	81/19	80/20	86/14	82/18	88/12	90/10	77/23	79/21
Qualifying diagnosis, %								
Angina only	22	22	18	19	12	13	19	21
MI only	61	61	65	67	75	70	67	60
Both angina and MI	17	17	17	14	13	17	14	20
Hypertension, %	24	25	23	28	35	33	45	34
Smokers, %	25	27	22	25	27	32	16	24
Body mass index, kg/m ²	25.8 ± 3.3	25.7 ± 3.1	26.3 ± 3.2	26.4 ± 3.6	26.8 ± 3.8	27.0 ± 3.7	27.2 ± 3.9	27.3 ± 3.2
Systolic BP, mm Hg	137.5 ± 19.1	138.3 ± 19.4	139.3 ± 19.9	139.6 ± 19.1	140.8 ± 21.2	141.1 ± 19.4	146.9 ± 23.1	147.4 ± 21.1
Total cholesterol level, mmol/L†	6.73 ± 0.66	6.75 ± 0.66	6.76 ± 0.69	6.74 ± 0.67	6.76 ± 0.69	6.75 ± 0.69	6.71 ± 0.70	6.72 ± 0.65
LDL-C level, mmol/L†	4.87 ± 0.66	4.88 ± 0.66	4.89 ± 0.67	4.87 ± 0.65	4.90 ± 0.66	4.88 ± 0.68	4.81 ± 0.69	4.80 ± 0.64
HDL-C level, mmol/L†	1.20 ± 0.30	1.20 ± 0.30	1.17 ± 0.28	1.18 ± 0.29	1.13 ± 0.33	1.14 ± 0.29	1.12 ± 0.26	1.13 ± 0.24
Triglyceride level, mmol/L‡	1.45 ± 0.47	1.48 ± 0.50	1.55 ± 0.48	1.55 ± 0.56	1.60 ± 0.50	1.61 ± 0.55	1.69 ± 0.63	1.78 ± 0.67
Apolipoprotein B level, g/L	1.15 ± 0.18	1.15 ± 0.17	1.17 ± 0.19	1.17 ± 0.17	1.19 ± 0.21	1.18 ± 0.16	1.20 ± 0.18	1.20 ± 0.18
Fasting glucose level, mg/dL§	94.9 ± 9.9	95.4 ± 9.4	116.6 ± 4.1	116.6 ± 4.0	137.1 ± 14.4	135.6 ± 11.9	175.0 ± 61.3	175.8 ± 62.2

*Data are given as mean ± SD unless indicated otherwise. Abbreviations are explained in the first footnote to Table 1.

†To convert total cholesterol, LDL-C, and HDL-C from millimoles per liter to milligrams per deciliter, divide millimoles per deciliter by 0.02586.

‡To convert total triglycerides from millimoles per liter to milligrams per deciliter, divide millimoles per deciliter by 0.01129.

§To convert fasting glucose from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.05551.

by glucose status (NFG, IFG, or DM). Patients with DM are shown separately as DM-FG (n = 281) and DM-Hx (n = 202). Glucose status was significantly related to age, male sex, baseline diagnosis, body mass index (calculated as weight in kilograms divided by the square of the height in meters: weight [kg]/[height (m)]²), systolic blood pressure, triglyceride and HDL-C levels, fasting glucose level, apolipoprotein B level, and smoking status (borderline, P = .05). Low-density lipoprotein and total cholesterol levels did not differ by glucose status.

We also compared the baseline characteristics of patients randomized to receive placebo or simvastatin within each category of glucose status (**Table 2**). As expected, within each category of glucose status (NFG, IFG, or DM), patients randomized to the placebo and simvastatin groups did not differ in cardiovascular risk factors or in characteristics related to CHD, according to demographic variables.

Figure 1 shows the incidence of major coronary events in the placebo group by glucose status at baseline. Rate of major CHD events relative to patients with

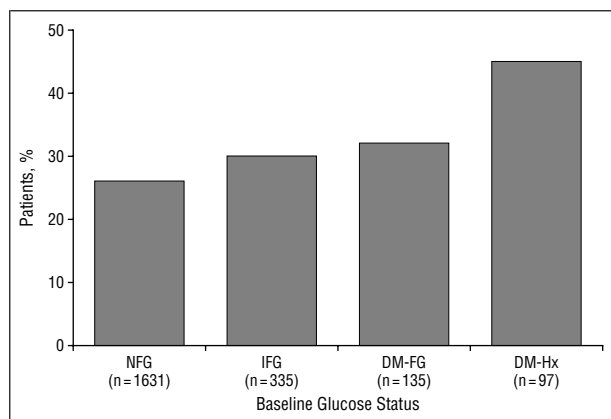


Figure 1. Incidence of major coronary heart disease events by glucose status in the placebo group in the Scandinavian Simvastatin Survival Study. NFG indicates normal fasting glucose; IFG, impaired fasting glucose; DM-FG, diabetes by elevated fasting glucose; and DM-Hx, diabetes by clinical history.

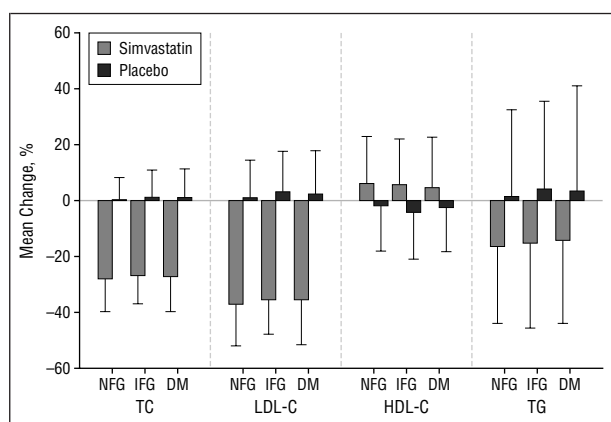


Figure 2. Mean percentage change in lipid and lipoprotein levels by glucose status and treatment assignment (placebo vs simvastatin). NFG indicates normal fasting glucose; IFG, impaired fasting glucose; DM, diabetes mellitus; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglycerides. Error bars indicate SEM.

NFG increased by glucose status, with a progressive rise in events from IFG (RR = 1.15, 95% CI = 0.92-1.42) to DM-FG (RR = 1.19, 95% CI = 0.87-1.63) to DM-Hx (RR = 1.83, 95% CI = 1.34-2.50). When both DM categories (DM-FG and DM-Hx) were combined, patients with DM had a significantly increased risk of CHD events relative to those with NFG (RR = 1.44, 95% CI = 1.14-1.82). To increase statistical power, all patients with DM (DM-FG and DM-Hx) are combined in the remainder of this article, except as noted.

Figure 2 shows the effect of simvastatin therapy on lipoprotein values by glucose status. Simvastatin therapy significantly decreased LDL-C, total cholesterol, and triglyceride levels, and increased HDL-C levels. These effects were similar in each simvastatin-treated group (NFG, IFG, and DM).

Figure 3 shows the 6-year Kaplan-Meier curves for major coronary events by glucose status and treatment group. For all 3 glucose status categories, patients randomized to receive simvastatin had significantly fewer CHD events (59 [23.5%] of 251 patients) than those randomized to receive placebo (428 [26.2%] of 1631 pa-

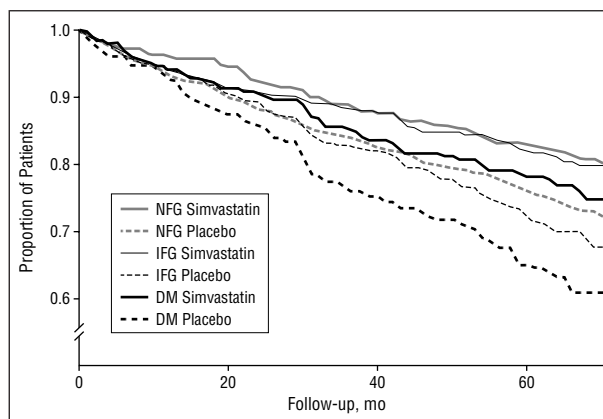


Figure 3. Kaplan-Meier survival curves from the probability of remaining free of a major coronary heart disease event during follow-up in placebo- and simvastatin-treated patients with normal fasting glucose (NFG) levels, impaired fasting glucose (IFG) levels, and diabetes mellitus (DM).

tients). The Kaplan-Meier curve for patients with DM randomized to receive simvastatin was higher than the curve for those with NFG randomized to receive placebo, although these differences were not statistically significant (RR = 0.83; $P = .18$).

Figure 4 shows the incidence of several end points by glucose status and treatment group. Among patients with NFG, the risk reduction in the simvastatin group was statistically significant for (1) major coronary events, odds ratio (OR), -32% (95% CI, -41% to -21%; $P < .001$); (2) total mortality, OR, -28% (95% CI, -43% to -10%; $P = .005$); (3) coronary mortality, OR, -42% (95% CI, -57% to -22%; $P = .001$); and (4) revascularizations, OR, -33% (95% CI, -45% to -19%; $P < .001$). Among patients with IFG, the risk reductions in the simvastatin group were, again, statistically significant for (1) major coronary events, OR, -38% (95% CI, -54% to -15%; $P = .003$); (2) total mortality, OR, -43% (95% CI, -65% to -7%; $P = .02$); (3) coronary mortality, OR, -55% (95% CI, -75% to -19%; $P = .007$); and (4) revascularizations, OR, -43% (95% CI, -63% to -13%; $P = .009$). Among patients with DM overall, the risk reductions were statistically significant for (1) major coronary events, OR, -42% (95% CI, -59% to -20%; $P = .001$), and (2) revascularizations, OR, -48% (95% CI, -58% to -18%; $P = .005$). Simvastatin-treated patients with DM had lower rates of overall mortality (OR, -21%; $P = .34$) and coronary mortality (OR, -28%; $P = .26$), which did not reach statistical significance. Due to small sample size, the risk reduction in patients with DM-FG was statistically significant only for revascularizations, OR, -57% (95% CI, -78% to -19%; $P = .009$). Risk reduction in patients with DM-Hx was statistically significant only for major coronary events, OR, -57% (95% CI, -74% to -29%; $P = .001$).

Figure 5 shows the relation of baseline serum lipid levels to the effect of simvastatin treatment on the risk of major coronary events in patients with DM. This issue was examined by dividing the placebo- and simvastatin-treated groups into 2 strata using the median concentrations for each baseline-level lipid variable in the overall study. Risk reduction by simvastatin treatment did not depend on the baseline levels of LDL-C, HDL-C, or triglycerides ($P = .89, .80, \text{ and } .16$, respectively, test of heterogeneity), although for triglyceride levels, there

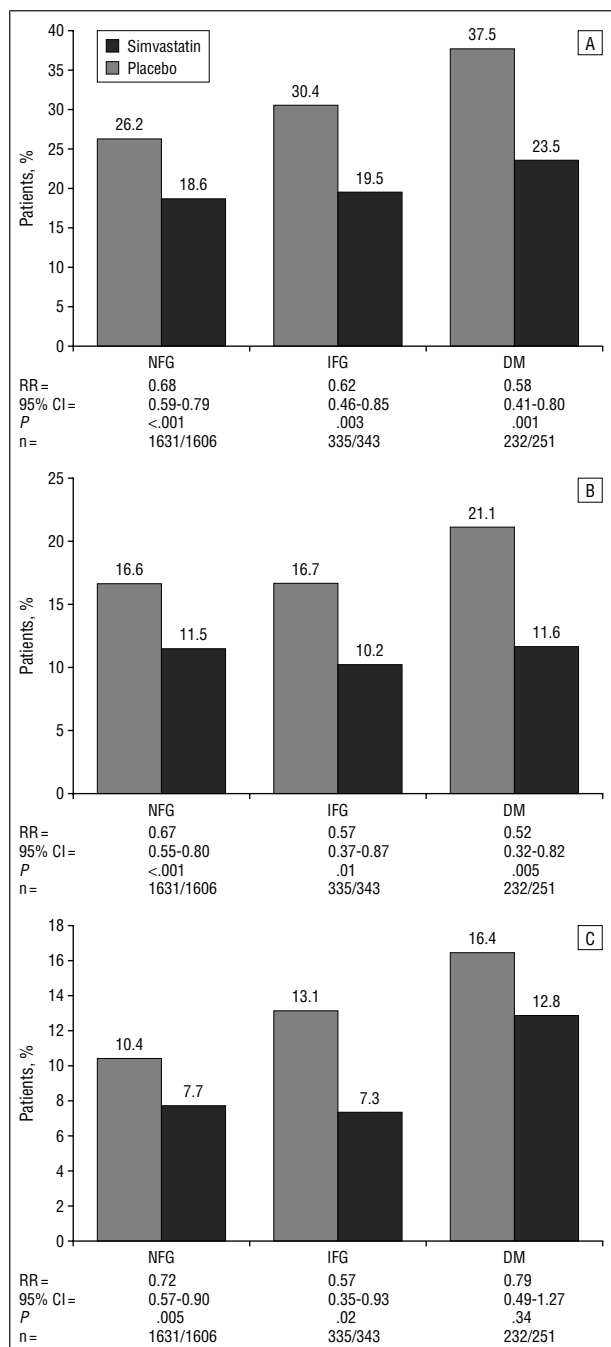


Figure 4. Incidence of end-point events during the Scandinavian Simvastatin Survival Study and relative risk (RR) by glucose status. A, Major coronary heart disease events. B, Revascularizations. C, Total mortality. NFG indicates normal fasting glucose; IFG, impaired fasting glucose; DM, diabetes mellitus; and CI, confidence interval.

was a trend toward a more marked treatment effect among patients with DM in the upper half of the triglyceride distribution.

Table 3 shows the absolute risk and RR of simvastatin therapy for major coronary events by glucose status.

COMMENT

Results of the present study from the 4S confirm earlier findings¹⁵ based on data from patients in the 4S identified by

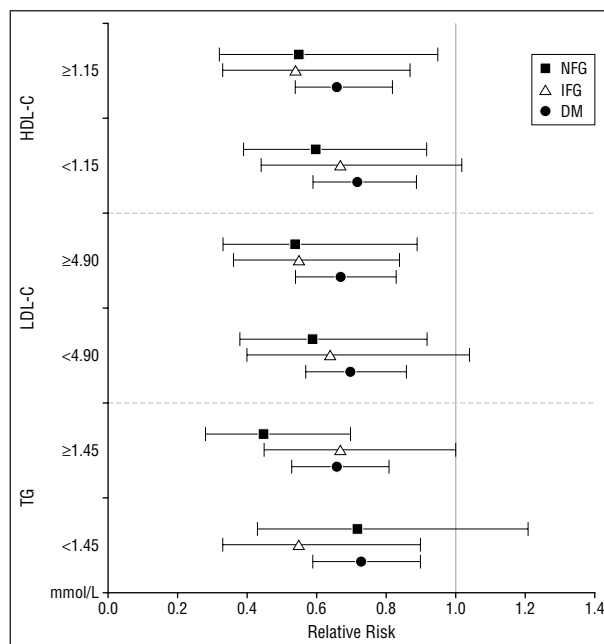


Figure 5. Effects of simvastatin therapy on major coronary events by glucose status, stratified by level of lipid variables. NFG indicates normal fasting glucose; IFG, impaired fasting glucose; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglycerides. Error bars indicate SEM. To convert HDL-C and LDL-C from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.02586. To convert TG from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.01129.

DM-Hx (n = 202). It is based on a larger number of patients (n = 483) by also including those without a clinical history of DM but with fasting glucose levels (DM-FG) above the threshold of fasting plasma glucose defined as diagnostic for DM by the 1997 ADA diagnostic criteria (≥7.0 mmol/L [≥126 mg/dL]). In addition, analysis included patients without DM but with IFG (n = 678).¹⁸ Using the ADA criteria, simvastatin treatment reduced the risk of major coronary events by 42% in patients with DM, and by 38% in those with IFG. Because the present study includes additional patients diagnosed solely by fasting plasma glucose values, the severity of DM in patients identified in this way may have been less than in those identified by DM-Hx, as indicated by the lower mean fasting glucose value in the former group (7.6 [137] vs 9.7 mmol/L [175 mg/dL], respectively). Thus, the current expanded group of patients with DM might be more representative of DM in the general population.

Previously, data were also published from the CARE trial¹⁶ showing a significant 25% reduction in fatal and nonfatal MI and revascularization in patients with DM and previous MI. The reasons for the somewhat smaller decrease in coronary events in the CARE trial than in the 4S is not well understood, but could be due to chance, the lower level of baseline LDL-C in the CARE trial, or the lower degree of LDL lowering with pravastatin than with simvastatin therapy. The larger number of patients in the present study makes chance a less likely explanation for those differences. We compared the efficacy of simvastatin treatment in patients above and below the median value for LDL-C (4.9 mmol/L [187 mg/dL]) (Fig-

Table 3. Absolute and Relative Benefit of Simvastatin Therapy by Glucose Status for Major Coronary Events*

	NFG	IFG	DM
Simvastatin group, No. (%)	299/1606 (18.6)	67/343 (19.5)	59/251 (23.5)
Placebo group, No. (%)	428/1631 (26.2)	102/335 (30.5)	87/232 (37.5)
Relative risk (95% CI)	0.68 (0.59-0.79)	0.624 (0.46-0.85)	0.581 (0.41-0.80)
<i>P</i> relative risk	<.001	.003	.001
Absolute benefit (Kaplan-Meier year 6 estimate)	8.02/100 cases	12.11/100 cases	13.85/100 cases
Number needed to treat	12	8	7

*NFG indicates normal fasting glucose; IFG, impaired fasting glucose; DM, diabetes mellitus; and CI, confidence interval.

ure 5). In these strata, the effectiveness of simvastatin treatment in reducing major coronary events was 40% in the higher LDL-C group and 45% in the lower LDL-C group. Median LDL-C level in the lower group was 4.4 mmol/L (170 mg/dL). Although the overlap of LDL-C levels in the CARE trial and the 4S was limited, at least in the 4S data, the effectiveness of simvastatin treatment in reducing CHD was similar at different LDL-C levels. In the LIPID study,¹⁷ pravastatin treatment reduced CHD by 19% in patients with DM compared with 25% in those without DM. Although the effect of pravastatin therapy on CHD in the diabetic subgroup was not statistically significant, the test of heterogeneity (ie, whether the effect of pravastatin use on CHD was different in patients with and without DM) was not statistically significant. The LIPID study contained more patients with DM (n = 782) than either the 4S (n = 483) or the CARE trial (n = 586). Median LDL-C level in the LIPID study was 3.9 mmol/L (150 mg/dL), which is intermediate between the baseline LDL-C levels in the 4S and CARE trial data. The test for heterogeneity for the effect of pravastatin use on CHD by LDL levels in the LIPID study was also rejected, a result that contrasts with that reported by the CARE trial investigators.¹⁶ All patients in the 4S, CARE trial, and LIPID study had clinical CHD at baseline. In the Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)²³ (a primary prevention trial), in which mean LDL-C was 4.0 mmol/L (150 mg/dL), the percentage reduction in major CHD events with another 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, lovastatin, was -43% (although the number of patients with DM was small [n = 264] and the results for the subgroup were not statistically significant). Thus, the results in patients with DM from AFCAPS/TexCAPS seem to be similar to the 4S in terms of percentage reduction in major coronary events.

In patients with IFG, the RRs of main end points in simvastatin-treated groups were (1) -38% for major coronary events (*P* = .003), (2) -43% for total mortality (*P* = .02), (3) -55% for coronary mortality (*P* = .007), and (4) -43% for revascularizations (*P* = .009). In data from the CARE trial,¹⁶ pravastatin therapy was associated with a decrease in CHD events in the IFG group similar to that seen in those with NFG, although the results were not statistically significant in the IFG group alone. We also showed a modest increase in major coronary events in the IFG group relative to the NFG group (Figure 1), although these results are not statistically significant (*P* = .22). In a recent analysis of 3 prospective studies

(n = 17 285) (the Whitehall, Paris Prospective, and Helsinki Policeman studies), Balkau et al¹¹ showed that the RR (relative to patients without DM in the lowest 80% of the 2-hour glucose distribution) for CHD varied from 1.1 for patients in the 80% to 90% range, 1.2 for those in the 90% to 95% range, 1.0 for those in the 95% to 97.5% range, and 1.3 for those with glucose levels above 97.5% in the maximum. Although the results in the present article are not statistically significant (*P* = .22), they are comparable in magnitude for the effect of glycemia to the study by Balkau et al. Our study was done in patients with a history of previous CHD vs the study by Balkau et al, in which patients were free of CHD at baseline. Also supporting this increased risk for CHD across the spectrum of glucose status are the results of a cross-sectional study¹⁴ using the National Health and Nutrition Examination Study III dataset, which show that IFG had twice and DM had 3 times the prevalence of CHD compared with NFG.

We also analyzed the data in the present study using a number-needed-to-treat (NNT) approach.^{24,25} The NNT was 12 for NFG, 8 for IFG, and 7 for DM, which compare favorably with the NNT for hypertension derived from the Systolic Hypertension in the Elderly (SHEP) study.²⁶ In that study overall, the NNT was 48, and in patients with a history or electrocardiographic evidence of previous MI, the NNT was 15. Thus, considering that statin therapy was at least as effective in patients with as without DM in the CARE trial and the 4S, a strong case can be made for more aggressive lowering of LDL-C levels in patients with DM without a previous MI than is provided by currently accepted national guidelines for cholesterol.²⁷ In their 1999 position paper²⁸ on management of diabetic dyslipidemia, the ADA recommended more aggressive management, for instance, that the LDL-C goal should be ≤ 2.59 mmol/L (≤ 100 mg/dL) for all adults with type 2 DM. This evidence supports the ADA position that all patients with DM should have the same LDL-C goal as those with CHD, and is supported by the high rate of CHD events in patients with DM¹⁻⁵ and the poor prognosis of CHD in patients with DM after MI.⁶⁻⁸

It has recently been shown⁸ that the 1-year case fatality rate for first MI (from the onset of symptoms, thus including prehospitalization mortality) in the Finnish Monitoring International Cardiovascular Disease (FINMONICA) population was 45% in men with DM and 39% in women with DM. These rates were significantly higher than those in nondiabetic men and women (38% and 25%, respectively). Of patients with DM who died, 50% of men and 25% of women died before hospitalization. These in-

dividuals, by definition, could not benefit from secondary prevention strategies, indicating that aggressive management of cardiovascular risk factors in patients with DM (especially men) should precede the onset of clinical coronary artery disease. Recently, the 7-year incidence of MI in nondiabetic patients (aged 45-64 years) with a previous MI at baseline was shown to be similar to that for nondiabetic patients without previous MI (18.8% vs 20.2%, respectively).⁵ If this result can be confirmed in other studies, it might suggest that patients with DM without a previous MI might have an NNT similar to (or even lower than) that for patients with NFG with CHD in the 4S (ie, 12.5). This would support the need for aggressive lipid-lowering therapy, even for patients with DM who do not have clinical evidence of CHD. There is little clinical trial data (except for the AFCAPS/TexCAPS study) currently available to calculate the NNT for lipid lowering in patients with DM without preexisting CHD. Further studies of patients with DM without CHD to evaluate this issue are needed.

One limitation of the present study in patients with DM, and in articles from the CARE trial¹⁶ and the recently published LIPID study,¹⁷ is that these analyses represent results of post hoc subgroup analyses and thus, should be interpreted cautiously. Nevertheless, in each study, the percentage reduction of LDL-C levels in patients with DM was similar to that seen in nondiabetic patients in the same studies, which supports the inference that reduction of LDL cholesterol levels by using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors is likely to benefit patients with DM.

In conclusion, the findings from this study confirm and extend results of a previous analysis showing the benefit of cholesterol lowering with simvastatin therapy in an expanded cohort of patients with DM and overt CHD. They also suggest that patients with CHD and IFG (6.0-6.9 mmol/L [110-125 mg/dL]) benefit from treatment by significant reductions in total and coronary mortality, major coronary events, and revascularizations.

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Correction

Incorrect Key in Figure Legend. In the article by Haffner et al titled "Reduced Coronary Events in Simvastatin-Treated Patients With Coronary Heart Disease and Diabetes or Impaired Fasting Glucose Levels: Subgroup Analysis in the Scandinavian Simvastatin Survival Study" in the December 13/27, 1999, issue of the ARCHIVES (1999;159:2661-2667), 2 of the symbols in the key in Figure 5 were incorrectly labeled. The square should represent DM (diabetes mellitus) and the circle should represent NFG (normal fasting glucose). The figure is reprinted correctly here. The journal regrets the error.

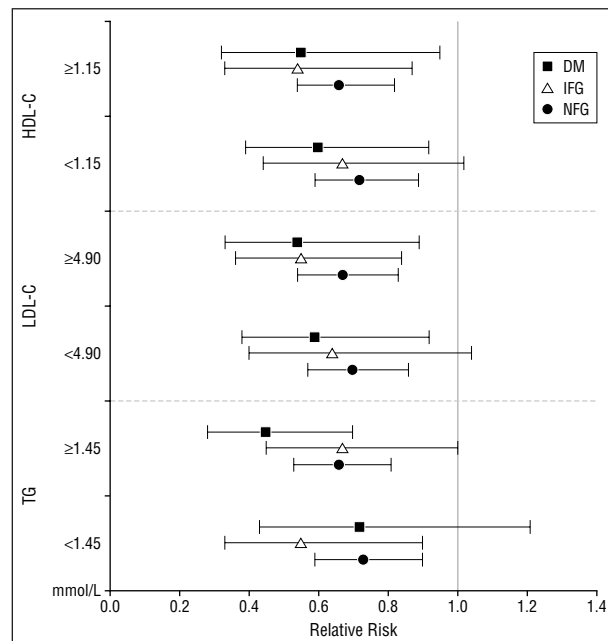


Figure 5. Effects of simvastatin therapy on major coronary events by glucose status, stratified by level of lipid variables. DM indicates diabetes mellitus; IFG, impaired fasting glucose; NFG, normal fasting glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglycerides. Error bars indicate SEM. To convert HDL-C and LDL-C from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.02586. To convert TG from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.01129.