Effect of Simvastatin Treatment on Cardiovascular Resource Utilization in Impaired Fasting Glucose and Diabetes

Findings from the Scandinavian Simvastatin Survival Study

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OBJECTIVE — The Scandinavian Simvastatin Survival Study showed that simvastatin treatment reduced cardiovascular events in hypercholesterolemic subjects with coronary heart disease. The clinical benefits of therapy were similar in all three subgroups: normal fasting glucose (NFG, n = 3,237), impaired fasting glucose (IFG, n = 678), and diabetes (n = 483). This analysis compared the costs of simvastatin treatment with the costs of cardiovascular disease–related hospitalizations in the three subgroups.

RESEARCH DESIGN AND METHODS — The cost of simvastatin treatment was defined as the average retail price and the cost of drug safety monitoring and adverse experiences. The costs of cardiovascular disease–related hospitalizations were determined by actual rates of hospitalization and 1995 MEDSTAT diagnosis-related group costs.

RESULTS — Within trial, simvastatin treatment cost ~$6,000 per patient. Simvastatin treatment reduced cardiovascular disease–related hospitalizations by 23% in NFG (P = 0.001), 30% in IFG (P = 0.015), and 40% in diabetic subjects (P = 0.007) within trial (median follow-up of 5.4 years). Average length of stay was reduced by 2.4 days in diabetic subjects (P = 0.021). Total cardiovascular disease–related hospital days were reduced by 28% ($P < 0.001$) in NFG, 38% (P = 0.005) in IFG, and 55% ($P < 0.001$) in diabetic subjects. For NFG subjects, simvastatin reduced the average cost of cardiovascular disease–related hospitalizations by $3,585, which offset 60% of the cost of simvastatin therapy. For IFG subjects, average cardiovascular disease–related hospitalization costs were reduced by $4,478, which offset 74% of the drug cost. For diabetic subjects, there was a net cost savings of $1,801 per subject within trial.

CONCLUSIONS — Simvastatin significantly reduced cardiovascular disease–related hospitalizations and total hospital days for all three groups and significantly reduced length of stay for the diabetic group in addition to providing significant clinical benefits. The benefits were greatest in the diabetic group, with estimated cost savings within trial from simvastatin treatment.

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Several large prospective randomized controlled clinical trials have established the clinical and economic benefits from improvements in lipid values in patients with coronary heart disease (CHD) (1–3) and patients without documented CHD (4,5). In the Scandinavian Simvastatin Survival Study (4S), simvastatin, a hydroxymethylglutaryl-CoA reductase inhibitor, reduced total mortality in patients with CHD by 30% and CHD mortality by 42% (1).

Patients with impaired fasting glucose (IFG), impaired glucose tolerance, or diabetes have an increased risk of cardiovascular events and death compared with individuals with normal glucose levels (6–14). In the Framingham Offspring Study, CHD risk adjusted for obesity, increased waist-to-hip ratio, hypertension, low levels of HDL cholesterol, elevated triglyceride levels, and hyperinsulinemia showed continuous increases across the spectrum of nondiabetic glucose tolerance (15). Metabolic risk factors for type 2 diabetes and cardiovascular disease (CVD) worsened continuously across the spectrum of glucose-tolerance categories, beginning in the lowest quintiles of normal fasting glucose (NFG) level. A recent meta-analysis of 20 studies and almost 100,000 subjects by Coutinho et al. (16) concluded that there is a progressive relationship between glucose levels and cardiovascular risk. The increased risk begins within the normal nondiabetic blood glucose range and increases with progressive elevation of glucose levels (16). Supporting this increased risk for CHD across the entire spectrum of glucose levels is a cross-sectional study using the National Health and Nutrition Examination Survey (NHANES)

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Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease; CVD, cardiovascular disease; DRG, diagnosis-related group; 4S, Scandinavian Simvastatin Survival Study; IFG, impaired fasting glucose; MI, myocardial infarction; NFG, normal fasting glucose; NHANES, National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of subjects by glucose status*

	NFG	IFG	Diabetes	Overall significance (*P*)
n	3,237	678	483	
Age (years)	58.5 ± 7.1	58.7 ± 7.2	59.3 ± 6.8	0.073
Male sex (%)	80	84	84	0.001
Qualifying diagnosis (%)				
Angina only	22	18	16	<0.001
MI only	61	66	69	<0.001
Both angina and MI	17	16	16	0.571
Hypertension (%)	25	26	36	<0.001
Smoking status				
Smoker (%)	26	23	25	0.306
Total cholesterol (mmol/l)	6.74 ± 0.66	6.75 ± 0.68	6.74 ± 0.68	0.891
LDL cholesterol (mmol/l)	4.88 ± 0.66	4.88 ± 0.66	4.85 ± 0.67	0.719
HDL cholesterol (mmol/l)	1.20 ± 0.30	1.17 ± 0.29	1.13 ± 0.29	<0.001
Triglycerides (mmol/l)	1.47 ± 0.48	1.55 ± 0.52	1.66 ± 0.58	<0.001

Data are *n*, means ± SD, %, or *P*.

III data set showing that IFG had twice and diabetes three times the prevalence of CHD compared with NFG (17).

CHD is associated with two to four times greater mortality in people with diabetes than those without diabetes and is responsible for the majority (65–80%) of deaths among diabetic patients in the U.S. (18). Many of these deaths are caused by acute rupture of a coronary artery atherosclerotic plaque with subsequent myocardial ischemia leading to an acute fatal myocardial infarction (MI). Many of these patients also die suddenly without warning symptoms. Premature mortality following MI is significantly higher among diabetic patients, as is the rate of post-MI congestive heart failure (7). Recent evidence from a combined analysis of three longitudinal cohorts suggests that glycemia may be significantly related to mortality even in the nondiabetic range (Whitehall Study, Paris Prospective Study, and the Helsinki Policemen Study) (14).

It has been shown that control of blood glucose to near-normal levels will substantially reduce the development of microvascular complications in types 1 and 2 diabetic patients (19–21). However, the ability of blood glucose control to reduce macrovascular events (e.g., accelerated atherosclerosis, CHD, large-artery peripheral vascular disease, and cerebrovascular disease) is less compelling (21). Elevated blood cholesterol levels, hypertension, and cigarette smoking, three well-known risk factors for CHD in the general population, have also been shown to be risk factors for death in patients with diabetes (9). The U.K. Prospective Diabetes Study showed the favorable impact of blood pressure control on the macrovascular complications of diabetes (22). Because elevated cholesterol and triglycerides are associated with increased mortality in diabetes, it is logical to assume that improvement of the lipid profile should favorably affect the macrovascular complications of diabetes (23).

To assess whether treatment of elevated cholesterol levels decreased the risk of cardiac events and mortality, a post-hoc subgroup analysis from the 4S examined lipid lowering in 202 diabetic subjects with CHD (24). Patients treated with simvastatin had LDL cholesterol levels 36% lower than placebo-treated subjects and had a reduction in relative risk of total mortality of 43% (95% CI 0.3–1.08), as well as a reduction of

Table 2—*Proportion of patients hospitalized per 100 patients and number of hospitalizations per 100 patients by glucose status*

	NFG				IFG				Diabetes			
	Patients hospitalized		Hospitalizations		Patients hospitalized		Hospitalizations		Patients hospitalized		Hospitalizations	
	Placebo	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin
CHD												
MI	19.5	13.4	25.9	18.0	21.5	12.5	28.4	15.7	30.6	15.1	45.3	18.7
Angina	11.0	9.2	17.5	13.6	11.6	12.2	19.1	16.9	12.1	10.4	20.3	13.5
Left ventricular heart failure	0.8	0.7	1.4	1.1	0.3	1.2	0.9	1.2	3.4	0.4	6.9	0.4
Revascularization procedures												
CABG	15.0	9.4	15.2	9.6	13.7	9.0	13.7	9.0	17.7	10.8	18.1	10.8
PTCA	1.9	2.7	2.6	3.5	4.2	1.5	5.7	1.5	3.0	0.8	3.0	0.8
Total CHD	48.2	35.4	62.6	45.8	51.3	36.4	67.8	44.3	66.8	37.5	93.6	44.2
Cerebrovascular												
Stroke	3.3	2.3	3.5	2.4	1.8	1.7	2.1	1.7	6.0	4.8	6.9	6.0
Transient ischemic attack	1.3	0.7	1.5	0.7	0.3	0.9	0.3	0.9	1.7	1.6	1.7	1.6
Total	4.6	3.0	5.0	3.1	2.1	2.6	2.4	2.6	7.7	6.4	8.6	7.6
Other cardiovascular	10.3	9.7	13.9	14.2	9.0	8.2	12.9	11.1	9.9	8.0	15.1	18.7
Total CVD	63.1	48.1	81.5	63.1	62.4	47.2	83.1	58.0	84.4	51.9	117.3	70.5

CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty.

55% (95% CI 0.27–0.74) in relative risk for major CVD-related events as compared with placebo-treated subjects. This finding suggested that LDL cholesterol lowering with simvastatin might benefit diabetic patients with CHD by reducing the risk of coronary and other atherosclerotic events. Whether these results apply to diabetic patients without documented CHD is unknown. These results in diabetic subjects with CHD were subsequently confirmed by subgroup analysis of two other end-point trials. In the Cholesterol and Recurrent Events Trial, CHD events (defined as CHD death, nonfatal MI, coronary artery bypass graft, and revascularization) were reduced by 25% ($P = 0.05$) in 586 diabetic subjects (25). In the Long-Term Intervention with Pravastatin in Ischemic Disease study, major CHD (defined as fatal CHD and nonfatal MI) was reduced by 19% in 782 diabetic subjects (P = NS) (3). More recently, Haffner et al. (26) performed an expanded analysis of 4S using the 1997 American Diabetes Association (ADA) diagnostic criteria and showed that undiagnosed diabetic subjects with fasting glucose levels ≥126 mg/dl (7.0 mmol/l) and those with IFG also benefited from simvastatin treatment.

The clinical benefit achieved in the 4S patient population was associated with a significant reduction in resource utilization with a 37% reduction in revascularizations percutaneous transluminal coronary angioplasty/coronary artery bypass graft surgery, a 26% reduction in frequency of hospitalizations, and a 34% reduction in total length of hospitalizations. The economic impact of this reduction of direct costs over the study period was estimated to be $3,872 per patient. These reductions in hospitalizations and coronary revascularization procedures related to ischemic heart disease offset the majority (88%) of the cost of simvastatin therapy in the overall cohort of 4,444 subjects (27–28).

Using resource utilization data prospectively collected from 4S, we have evaluated the effect of simvastatin on CVD-related hospitalizations in three subgroups of study participants classified retrospectively by fasting glucose levels using the new ADA diagnostic criteria (29). An analysis of NHANES III data showed that ~4% of the U.S. population has diabetes by clinical history, 3% has diabetes only by elevated glucose values, 7% has IFG, and 86% of the population has NFG using these criteria (17). A cost consequences analysis was also performed to describe the economic impli-

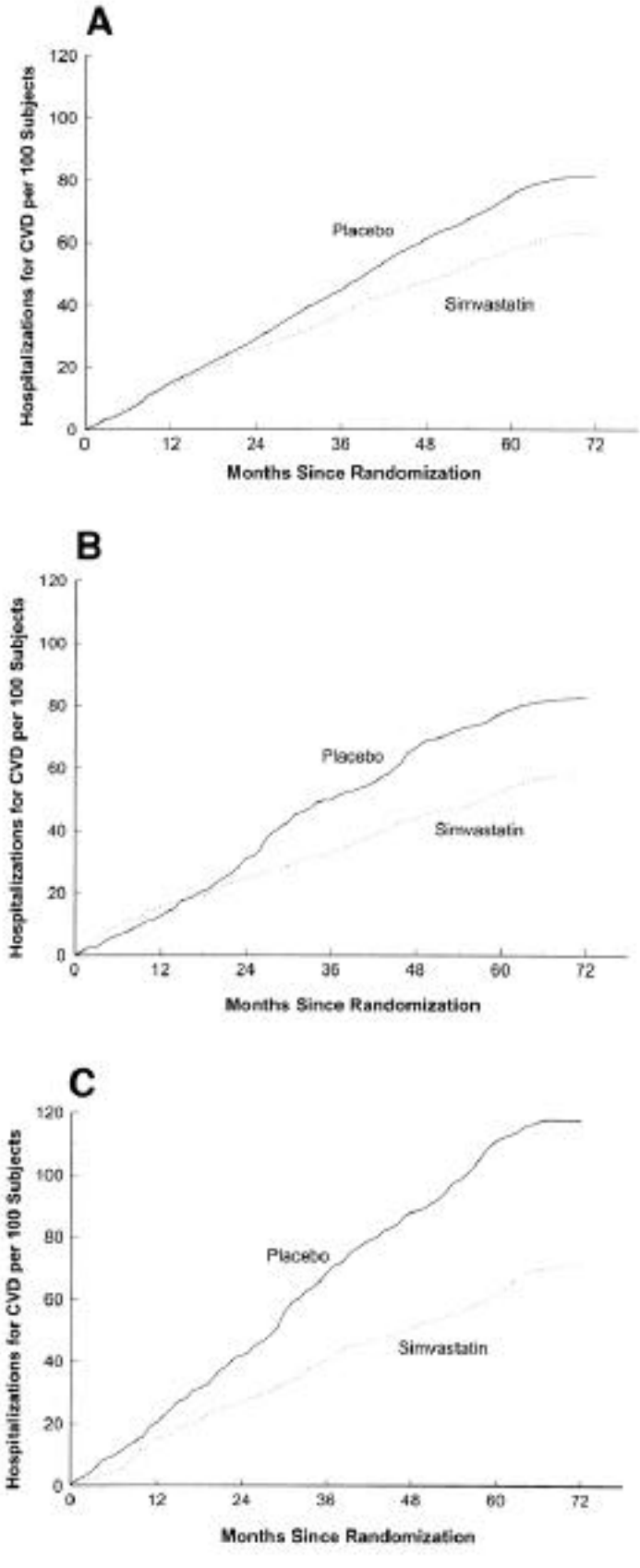

Figure 1—*Cumulative number of CVD-related hospitalizations per 100 subjects during the 4S trial in each glucose status subgroup.* A, *NFG;* B, *IFG;* C, *diabetes.*

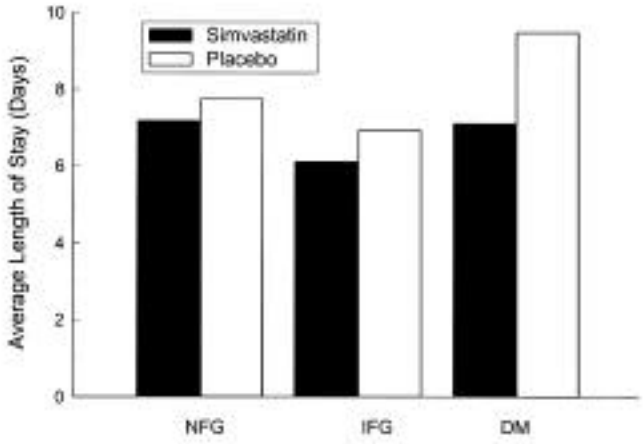

Figure 2—*Average length of stay per CVD-related hospitalization in 4S by glucose status subgroup. DM, diabetes.*

cations of these reductions in CVD-related resource utilization resulting from the use of long-term simvastatin therapy. Since cardiovascular event rates and resource utilization have been shown to be higher in subjects with IFG and diabetes, presumably due to increasing severity of hyperglycemia as well as greater prevalence of cardiovascular risk factors including dyslipidemia, we hypothesized that there would be greater offset of the costs of simvastatin therapy in subjects with IFG and diabetes.

RESEARCH DESIGN AND METHODS

Trial design and patients

The 4S was a double-blind randomized prospective placebo-controlled multicenter clinical trial of simvastatin therapy in patients with CHD carried out at 94 clinical centers throughout Scandinavia. The study design, methods, and the main clinical and economic findings have been previously described in detail (1,26,30).

Briefly, men and women 35–70 years of age with previous MI or active stable angina pectoris, identified by systematic screening of the patient records of potentially eligible patients, were evaluated for participation. For a subject to qualify for randomization, his or her serum total cholesterol had to be 5.5–8.0 mmol/l (212–309 mg/dl) and serum triglycerides ≤2.5 mmol/l (220 mg/dl) measured after a 2-month period on a low-fat diet. Patients who had provided informed consent were then randomly assigned to take 20 mg simvastatin daily or a placebo. The simvastatin and placebo dosages were titrated to 40 mg daily in patients who did not reach the target serum total cholesterol level of 3.0–5.2 mmol/l (116–201 mg/dl) after 6 or 18 weeks, using methods that preserved the study blind.

The data shown here on fasting blood glucose at baseline and at the final study visit have also been previously described (26). Regardless of fasting glucose, the 202 subjects with a clinical history of diabetes were classified as having diabetes. Fasting glucose information was available for 4,348 patients (97.8% of 4S subjects). There were 678 subjects with IFG (fasting glucose 6.0 mmol/l or 110 mg/dl to 7.0 mmol/l or 126 mg/dl). There were 281 subjects with plasma glucose levels diagnostic for diabetes (≥7.0 mmol/l or 126 mg/dl) but without a clinical history of diabetes. The remaining patients (n = 3,237) were classified as having NFG.

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 points. Tertiary end points included *1*) any CHD event that consisted of any secondary end-point event plus any hospital admission for an acute CHD event without a diagnosis of MI (e.g., prolonged chest pain or revascularization); *2*) any atherosclerotic event that consisted of any CHD event and, in addition, fatal or nonfatal cerebrovascular events or other events directly attributed to atherosclerosis; and *3*) myocardial revascularization procedures (either coronary artery bypass grafting or coronary angioplasty). The procedures for event reporting and diagnostic classification of all study end-point events have been previously described (1,26,30).

Analysis and statistical methods

The data elements in this resource utilization analysis including CVD–related hospital admissions, type of admission, use of revascularization procedures, admission date, and discharge date were collected prospectively on case report forms. As previously described, each CVD-related hospitalization was assigned a DRG code based on the definition of clinical events as determined by the independent end-point classification committee and the complications and comorbidities that occurred during the hospitalization. Hospitalizations were also grouped into seven mutually exclusive categories (acute MI, angina pectoris, left ventricular failure, stroke, transient ischemic cerebrovascular attack, revascularization procedures, and other cardiovascular events including arrhythmias) to facilitate DRG coding.

For each glucose subgroup of 4S patients, the cumulative number of CVD-related hospitalizations per 100 patients was determined among patients in the two treatment groups (simvastatin and placebo). The proportion of patients hospitalized and the average number of CVD-related hospitalizations (total and by category) were also tabulated. Moreover, 95% CIs and P values for the change and percentage change from placebo in the total number of CVD-related hospitalizations for patients receiving simvastatin were calculated using the bootstrap method (31). The length of stay for each CVD-related hospitalization was calculated from admission and discharge dates. The mean and median length of stay per CVD-related hospitalization was obtained and treatment differences within and across subgroups were assessed using analysis of variance. The cumulative number of hospital bed days per 100 patients was also obtained with treatment differences (and percentage change) compared using the bootstrap method (31).

Economic analyses were performed from the perspective of a private single-payer of direct medical costs. Each CVD-related hospitalization was assigned a cost based on the cost per DRG code obtained from the 1995 MEDSTAT health-care cost and utilization statistics for the U.S. (32). CVD-related hospitalization costs were then adjusted to 1998 U.S. dollars using the medical consumer price index. These adjusted costs were used to estimate the average per-patient cost for CVD-related hospitalizations for patients randomized to simvastatin and placebo within each subgroup. For patients

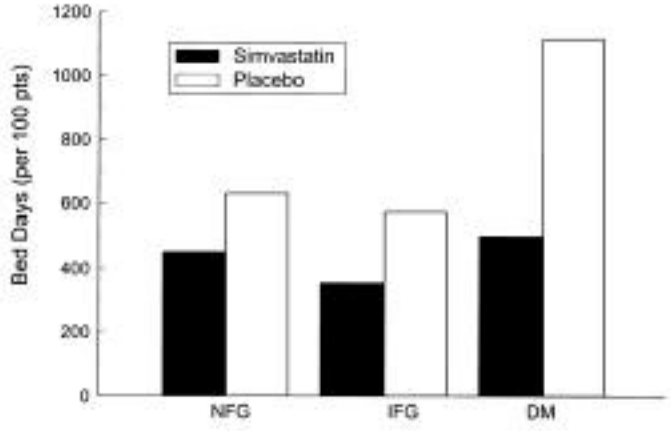

Figure 3—*Average number of bed days for CVD-related hospitalizations per 100 subjects in 4S by glucose status subgroup. DM, diabetes.*

randomized to simvastatin, the cost of therapy was estimated based on the average number of days each dose was prescribed during the study period and the 1998 average retail price. To estimate the cost of drug monitoring in clinical practice, we assumed that during the first year, one additional lipid profile would be obtained (assigned cost of $35 at randomization). In addition, liver test monitoring was assumed to occur at baseline, month 6, year 1, and annually thereafter at a cost of $16 per test. Costs associated with an abnormal liver test for the simvastatin treatment group were accounted for by an additional liver function test. A single hospitalization for myopathy was conservatively estimated as the 1995 MEDSTAT cost of a hospitalization for rhabdomyolysis (33). The average total cumulative cost for patients randomized to simvastatin was estimated by adding the average cost for CVD-related hospitalizations and the average cost of simvastatin treatment minus the cost for CVD-related hospitalizations for patients randomized to placebo. A 3% annual discount rate was applied to the costs of both simvastatin treatment and CVD-related hospitalizations.

RESULTS — The results of the main study have been reported previously (1,24,26). The median duration of follow-up for both treatment groups was 5.4 years. The baseline characteristics of the three groups of subjects by glucose status are shown in Table 1. There were differences between the groups with respect to sex, qualifying diagnosis, hypertension, and lipid levels.

The overall safety profile of simvastatin over 5 years of treatment was excellent, as previously reported for the full cohort (33). There was only one serious adverse experience that was clearly related to simvastatin therapy in the NFG subgroup: an episode of myopathy presenting with leg pain and markedly elevated creatinine phosphokinase values, but without renal complications (33). Among the three subgroups distinguished by glucose status at baseline, the incidence of transaminase elevations per 100 subjects reported by investigators as adverse experiences considered possibly, probably, or definitely drug related in the simvastatin group (placebo in parentheses for reference) were 11.2 (7.3) (NFG subgroup), 16.3 (9.6) (IFG subgroup), and 11.2 (12.9) percent (diabetes subgroup).

The proportion of subjects hospitalized and number of hospitalizations per 100 subjects by glucose status is shown in Table 2. Hospitalization rates among subjects with NFG and IFG were similar. However, a greater proportion of diabetic subjects was hospitalized for CVD-related events and there were significantly more CVD-related hospitalizations per 100 diabetic subjects during the study ($P < 0.02$ and $P < 0.03$, respectively). Strikingly, simvastatin-treated diabetic subjects had only a fraction of the hospitalizations for MI of placebo-treated patients; hospitalizations were reduced by 59% ($P < 0.001$). There was also a reduction of 55% for hospitalizations for any CHD-related diagnosis ($P < 0.0001$). Hospitalizations for MI or any CHD-related diagnosis in the diabetic subjects were reduced with simvastatin treatment to about the frequency observed in the placebo-treated NFG subgroup. Figure 1 shows the cumulative number of CVD-related hospitalizations per 100 subjects during the 4S trial in the NFG, IFG, and diabetic subgroups. The cumulative number of hospitalizations per 100 subjects was reduced with treatment by 23% in the NFG subgroup ($P = 0.001$), by 30% in the IFG subgroup ($P = 0.015$), and by 40% in the diabetic subgroup ($P = 0.007$). The length of stay per CVD-related hospitalization was significantly reduced by 2.4 days mean ($P = 0.021$) and 3 days median in the simvastatin-treated patients in the diabetic subgroup, but not in the other two subgroups (mean length of stay shown in Fig. 2). Figure 3 shows that total cardiovascular disease–related hospitalization days were significantly reduced in all three subgroups (28% [$P < 0.001$] in NFG, 38% [$P = 0.005$] in IFG, and 55% [$P < 0.001$] in diabetes subjects).

The discounted drug-acquisition cost of simvastatin therapy within trial per subject as calculated by the average retail price was $5,777 in NFG, $5,788 in IFG, and $5,640 in the diabetic subgroups (Table 3). Safety monitoring and health-care costs for the transaminase elevations and the one serious adverse experience clearly attributable to simvastatin were estimated to add

Table 3—*Discounted simvastatin and hospitalization costs by glucose status*

	NFG		IFG		Diabetes	
	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo
n	1,606	1,631	343	335	251	232
Simvastatin cost ($)						
Prescription	5,776.89	—	5,788.42	—	5,639.89	—
Monitoring	239.67	—	240.67	—	235.94	—
Adverse events	6.60	—	2.49	—	1.68	—
Subtotal	6,023.16	—	6,031.58	—	5,877.50	—
Hospital costs ($)	9,192.93	12,778.29	8,259.72	12,737.72	9,926.70	17,605.03
Total ($)	15,216.08	12,778.29	14,291.30	12,737.72	15,804.20	17,605.03

Simvastatin cost is based on U.S. average retail price; discount rate is 3%.

Table 4—*Discounted net hospital cost, % simvastatin cost offset, and net cost (with 95% CI), by glucose status*

	NFG	IFG	Diabetes
Net hospital cost ($)	−3,585 (−5,074 to −2,089)	−4,478 (−7,638 to −1,649)	−7,678 (−11,834 to −3,824)
% Simvastatin cost offset	59.5 (34.9 to 84.4)	74.2 (27.6 to 125.2)	130.6 (65.1 to 204.7)
Net cost ($)	2,438 (937 to 3912)	1,554 (−1,526 to 4,317)	−1,801 (−6,023 to 2,065)

Simvastatin cost is based on U.S. average retail price; discount rate is 3%.

only $246 in NFG, $243 in IFG, and $238 in diabetic subgroups per subject to simvastatin treatment costs over the duration of the study.

For NFG subjects, simvastatin reduced the average cost of CVD-related hospitalizations by $3,585, which offset 60% of the cost of simvastatin therapy (Table 4). For IFG subjects, average CVD-related hospitalization costs were reduced by $4,478, which offset 74% of the drug cost. For diabetic subjects, there was a net cost savings of $1,801 per subject within trial (Fig. 4). The average cumulative discounted cost per patient in the diabetes subgroup during the course of the trial is shown in Fig. 5 with the total costs in the simvastatin group (simvastatin treatment plus CVD-related hospitalizations) crossing over and becoming less than the costs of the placebo-treated group (CVD-related hospitalizations) for the latter half of the trial.

CONCLUSIONS — In addition to the documented clinical benefits demonstrated by 4S, simvastatin treatment significantly reduced CVD-related resource utilization as measured by CVD-related hospitalizations in all three glucose status subgroups: NFG (23%, $P = 0.001$), IFG (30%, $P = 0.015$), and diabetes (40%, $P = 0.007$). Treatment with simvastatin significantly reduced length of stay for the diabetic group. By reducing CVD-related hospitalization, simvastatin treatment offset much of the cost of the medication with increasing offsets in the NFG (60%) and IFG (74%) subgroups. A net cost savings of $1,801 per subject within trial was observed in the diabetic subgroup.

We have previously shown that the CVD-related event rate in diabetic subjects was higher than in either the NFG or IFG subgroup. This higher rate of CVD-related events, and the reduction in frequency of those events to placebo-treated NFG levels in the simvastatin-treated diabetic subgroup, seems to explain the bulk, if not all, of the increasing economic benefit of simvastatin treatment. The cost of drug treatment is essentially the drug-acquisition cost due to the favorable long-term tolerability profile observed within trial. There was only one serious adverse experience that was unambiguously drug-related in 4S, and this added little to the total cost of simvastatin therapy.

Although hospitalizations and total hospital days have been shown to decrease with treatment, previous studies have not demonstrated a difference in length of hospitalization between the simvastatin- and placebo-treated groups. In this analysis, only in the diabetic subgroup did we observe a statistically significant difference in length of stay between the two treatment groups. One possible explanation for this difference is the marked reduction in MI and left ventricular heart failure in the simvastatin-treated diabetic subgroup with a redistribution of hospitalizations to less serious conditions.

Previously, the cost-effectiveness of simvastatin treatment in the overall 4S population has been shown as well as in the subgroup of subjects with diabetes by clinical history (27,28,34,35). Other studies have demonstrated the cost-effectiveness of the treatment of diabetes and its complications including hypertension, nephropathy, and retinopathy (36–41). Studies to directly compare the cost-effectiveness of these different therapies have not been performed.

A limitation of the current study is that these analyses represent post-hoc subgroup analyses using the 1997 ADA diagnostic criteria. These analyses were not the primary objective of the original study and therefore must be interpreted with caution. This analysis of resource utilization was limited to a within-trial comparison of direct CVD-related resource utilization. The analysis included only medical costs from subjects with CVD-related hospitalizations and therefore was not reflective of all associated costs, but it is not expected that the latter would differ between treatment groups. Hospital costs derived from 1995 U.S. MEDSTAT data were applied to Scandinavian hospitalizations. There were differences between U.S. and Scandinavian health-care systems at the time of the study. Treatment of CVD is constantly evolving and has changed since the study was completed. The U.S. average retail price was

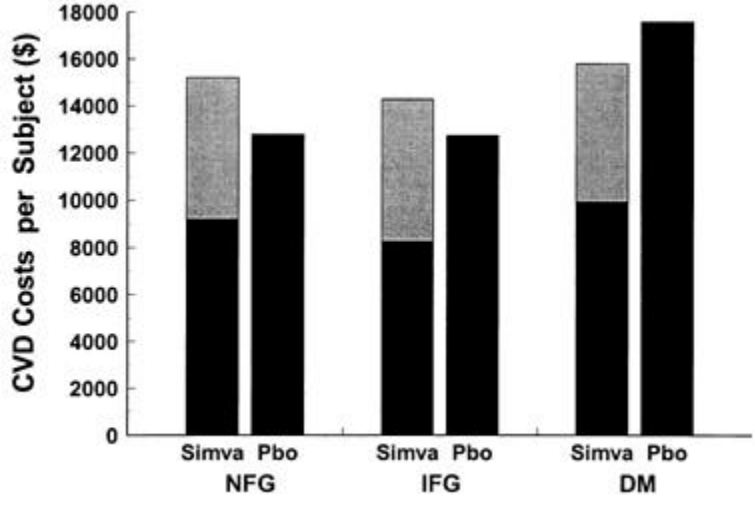

Figure 4—*Discounted CVD-related hospitalization and drug costs per subject in 4S by glucose status subgroup. The dark bars are CVD-related hospitalization costs and the lighter bars are drug treatment costs. DM, diabetes; Pbo, placebo; Simva, simvastatin.*

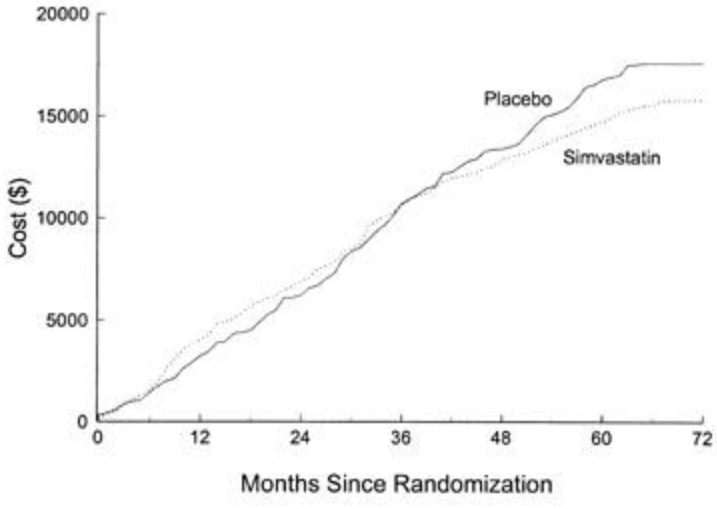

Figure 5—*Average cumulative discounted cost per subject during the trial in the diabetes subgroup.*

used for simvastatin, but drug-acquisition prices are highly variable, with managed care organizations often obtaining discounts. The perspective of patients who have medication benefits as a component of their health insurance was also not considered. The costs associated with drug treatment monitoring were estimated from prescribing information and adverse experiences reported during the trial reasonably attributed to simvastatin based on its well-defined safety profile. Costs of drug safety monitoring as calculated in the study may have been higher compared with usual clinical practice. There was also no inclusion of indirect costs, including lost wages and productivity.

Compliance in the use of simvastatin was carefully monitored in 4S and better than in a typical clinical practice setting. This may have both increased the benefit as well as cost and it is difficult to assess the impact of such compliance on these outcomes. Subjects were provided annual physical examinations and some subjects received additional medical care in connection with the clinical trial. Thus, the intensity of care may have been greater than that typically provided in the community. Also, we did not evaluate changes in quality of life and functional status of subjects in this analysis. The benefits derived from increasing life span as a result of avoiding fatal CVD-related events were not considered.

In conclusion, in addition to providing significant clinical benefits, simvastatin treatment reduced CVD-related hospitalizations and total hospital days for all subjects. Average length of stay was significantly reduced only for diabetic subjects. For NFG subjects, simvastatin offset 60% of the cost of therapy. For IFG subjects, simvastatin offset 74% of the drug cost. For diabetic subjects, there was a net savings of $1,801 in direct medical costs per subject within trial.

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