COST EFFECTIVENESS OF SIMVASTATIN TREATMENT TO LOWER CHOLESTEROL LEVELS IN PATIENTS WITH CORONARY HEART DISEASE

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ABSTRACT

Background The Scandinavian Simvastatin Survival Study (4S) showed that lowering cholesterol levels with simvastatin reduces mortality and morbidity in patients with angina pectoris or previous acute myocardial infarction. Before the widespread use of cholesterol-lowering drugs in such patients is recommended, its cost effectiveness should be demonstrated. We estimated the cost effectiveness of simvastatin treatment to lower cholesterol levels in relation to the age, sex, and cholesterol level before treatment of patients with coronary heart disease.

Methods We estimated the cost per year of life gained with simvastatin therapy. To model the increased life expectancy, hazard functions from 4S were used. The costs studied included those of the intervention and the direct and indirect costs associated with morbidity from coronary causes. We prepared separate estimates for men and women at various ages (from 35 to 70 years) and total cholesterol levels before treatment (213 to 309 mg per deciliter).

Results In the analysis limited to direct costs, the cost of each year of life gained ranged from $3,800 for 70-year-old men with 309 mg of cholesterol per deciliter to $27,400 for 35-year-old women with 213 mg of cholesterol per deciliter. When we included indirect costs, the results ranged from a savings in the youngest patients to a cost of $13,300 per year of life gained in 70-year-old women with 213 mg of cholesterol per deciliter.

Conclusions In patients with coronary heart disease, simvastatin therapy is cost effective among both men and women at the ages and cholesterol levels studied. (N Engl J Med 1997;336:332-6.)

SERUM cholesterol is one of the main risk factors for coronary heart disease, and in Western countries the prevalence of elevated cholesterol levels is high.[1] Recently, drugs have been developed that lower these levels effectively.

In the Scandinavian Simvastatin Survival Study (4S), simvastatin (Zocor, Merck) was shown to reduce overall mortality.[2,3] Patients with preexisting coronary heart disease had a reduction in overall mortality of 30 percent, which was exclusively due to a reduction of 42 percent in mortality from coronary causes.[2,3] For all coronary events combined, there was a reduction of 27 percent.[2] Before the widespread use of cholesterol-lowering drugs is recommended, it is important to demonstrate that their use is cost effective. This is especially important because interventions to lower cholesterol levels with drugs involve large populations of patients and potentially high costs.

The use of health care resources and the overall cost effectiveness of treatment to lower cholesterol levels in the 4S trial have previously been described.[4,5] In the present study, we estimated the cost effectiveness of lowering cholesterol levels with simvastatin in relation to the age, sex, and pretreatment cholesterol level of patients with coronary heart disease.

METHODS

We analyzed the cost effectiveness of simvastatin treatment to lower cholesterol levels on the basis of the 4S data.[2] The patients in the present study were men and women 35 to 70 years of age with total cholesterol levels of 213 to 309 mg per deciliter (5.50 to 8.00 mmol per liter) who had a history of angina pectoris or acute myocardial infarction.[2]

Costs were defined as net costs (those of the intervention minus the savings due to the reduction in morbidity from coronary causes), and effects were defined as the number of years of life gained.[6] No adjustment was made for quality of life in order to estimate the number of quality-adjusted years of life gained, because of the lack of valid quality-of-life weights to use for these patients. Our analysis also included costs outside the health care system[6] — namely, the indirect costs (in lost production) attributable to morbidity from coronary causes. Since the inclusion of such indirect costs is controversial, our results are presented both with and without them.[6,7] Health care costs attributable to increases in the number of years of life were not included.[8]

Treatment lasting five years was used in estimating the cost-effectiveness ratios. This period was based on the median follow-up of 5.4 years in the 4S trial.[2] Separate estimates of cost effectiveness were prepared for men and women and for three ages (35, 59, and 70 years) and three pretreatment cholesterol levels (213, 261, and 309 mg per deciliter [5.50, 6.75, and 8.00 mmol per liter]).

Both costs and numbers of years of life gained were discounted by 5 percent to account for the timing of costs and effects.[9] Costs were calculated on the basis of Swedish prices in 1995 and were converted to U.S. dollars at the 1995 exchange rate ($1 = 7.30 kronor).

Estimates of Effects

To calculate the cost effectiveness of simvastatin treatment, we used a modification of a Markov model created to estimate the

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TABLE 1. ESTIMATED LIFE EXPECTANCY OF PATIENTS WITH CORONARY HEART DISEASE BEFORE SIMVASTATIN TREATMENT, ACCORDING TO AGE, SEX, AND PRETREATMENT CHOLESTEROL LEVEL.

TOTAL CHOLESTEROL LEVEL (mg/dl)*	AGE 35		AGE 59		AGE 70	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
	yr of life expected					
213	34.83	44.23	18.77	25.22	12.57	17.50
261	29.73	39.34	15.58	22.29	10.72	15.71
309	24.88	34.14	12.78	19.20	8.97	13.80

*To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

cost effectiveness of efforts to prevent cardiovascular disease.[10] The starting point of the model was a cohort with preexisting coronary heart disease for whom there were data on the study variables (age, sex, and total cholesterol level). The members of the cohort were followed from their current ages to the age of 110 years, which we took to be the longest possible survival. Each year the members of the cohort ran the risk of having a coronary event or dying from a noncoronary cause. Coronary events were classified as either fatal or nonfatal. Persons who had nonfatal events were considered to be in a temporary state of disease for one year after the event (during which they had an increased risk of death); if they survived that year, they were considered to enter a state of chronic disease (during which the risk of death declined but was still greater than that of the normal population). They then either died or continued in that state of chronic disease.

The probabilities of a transition from one of these predefined states to another in the Markov model were based on the hazard functions estimated for the placebo group in the 4S trial. Four hazard functions were used to estimate the probabilities of the following four transitions: the annual risk of a coronary event (among the patients who had not yet had such an event), the annual risk of death from noncoronary causes (among the patients who had not yet had an event), the risk of death during the first year after a coronary event, and the annual risk of death during the second and subsequent years after such an event. A separate hazard function was estimated for the first year after an event because mortality during that year is higher than in subsequent years. Poisson models were used to estimate the hazard functions.[11] Age, sex, and pretreatment total cholesterol level were included as risk factors in the hazard functions so that cost effectiveness in various groups of patients could be estimated. (The risk functions are available from the authors on request.)

Coronary events were defined, as in 4S (in which "any coronary event" was a tertiary end point[2]), to include death from a coronary cause, a definite or probable hospital-verified nonfatal acute myocardial infarction, resuscitation after cardiac arrest, definite silent myocardial infarction, myocardial revascularization, and admission to the hospital for acute coronary heart disease when there was no diagnosis of myocardial infarction. In the model, the proportion of fatal coronary events among all coronary events in 4S was calculated. This proportion was estimated separately for men and for women and in two age groups, persons 35 to 64 years of age and persons 65 years old or older. Among patients 35 to 64 years old, 7.7 percent of events in men and 2.2 percent of events in women were fatal; among patients 65 years old or older, 14.4 and 5.7 percent of events, respectively, were fatal.

Using this model, we estimated the life expectancy of men and women with various ages and cholesterol levels before cholesterol-lowering treatment (i.e., the life expectancy of the people in the placebo group in 4S). Table 1 shows the estimated life expectancy of various groups of patients.

To estimate the increase in life expectancy attributable to treatment with simvastatin, we reduced the annual risk of coronary events during the five years of treatment in the model by 27 percent, the reduction in risk observed in 4S.[2] After five years of treatment, the annual risk was assumed to be equivalent to the risk if there had been no treatment. We estimated the reduction in risk only for the first coronary event and not for subsequent events, because we lacked sufficient data to permit a stable esti-

TABLE 2. COSTS OF HOSPITALIZATIONS IN SWEDISH HOSPITALS FOR VARIOUS DIAGNOSES.*

DIAGNOSIS-RELATED GROUP	CODE†	COST PER HOSPITALIZATION ($)
Specific cerebrovascular disorders except transient ischemic attack	14	3,134
Transient ischemic attack and precerebral occlusions	15	1,592
Heart transplantation	103	80,178
Coronary bypass with cardiac catheterization	106	15,866
Coronary bypass without cardiac catheterization	107	12,094
Percutaneous cardiovascular procedures	112	5,267
Circulatory disorders with acute MI and cardiovascular complication (patient survived)	121	3,800
Circulatory disorders with acute MI, without cardiovascular complication (patient survived)	122	2,902
Circulatory disorders with acute MI (patient died)	123	1,775
Circulatory disorders except acute MI, with cardiac catheterization and complex diagnosis	124	3,008
Circulatory disorders except acute MI, with cardiac catheterization, without complex diagnosis	125	1,501
Heart failure and shock	127	2,472
Cardiac arrest, unexplained	129	1,729
Peripheral vascular disorders with complications or coexisting conditions	130	2,047
Peripheral vascular disorders without complications or coexisting conditions	131	1,325
Atherosclerosis without complications or coexisting conditions	133	1,399
Hypertension	134	1,267
Cardiac congenital and valvular disorders, age >17 years, without complications and coexisting conditions	136	1,738
Cardiac arrhythmias and conduction disorders with complications and coexisting conditions	138	1,694
Cardiac arrhythmias and conduction disorders without complications and coexisting conditions	139	740
Angina pectoris	140	1,345
Syncope and collapse without complications and coexisting conditions	142	985
Chest pain	143	653
Other circulatory system diagnoses with complications and coexisting conditions	144	3,494
Other circulatory system diagnoses without complications and coexisting conditions	145	1,487

*Costs were obtained from the Swedish Institute for Health Services Development.[13] The derivation of the costs shown is explained in more detail in the Methods section. MI denotes myocardial infarction.

†Internationally accepted codes for diagnosis-related groups are shown.[13]

mation of the risk of subsequent events. This assumption is conservative, since the occurrence of an event increases the absolute risk of further events and the cost effectiveness of treatment would thus improve slightly if treatment after the first event was included in the calculation.

Estimates of Costs

In estimating the cost of treatment with simvastatin, we assumed that the only added cost would be that of the drug itself. Simvastatin treatment was assumed not to lead to additional costs for physician visits and laboratory tests, since these are part of the standard treatment after myocardial infarction or angina. The estimated annual cost of the drug was based on the actual consumption of simvastatin by the members of the treatment group in the 4S trial and on the official retail price of the drug in Sweden.[2,12] By this method, the annual cost of the drug was estimated to be $604. To be consistent with the manner in which the effects were estimated, this annual cost was applied to patients only before they had a coronary event.

To estimate the reduction in the cost of coronary events attributable to the simvastatin treatment, annual direct and indirect costs associated with morbidity — those for health care and lost production, respectively — were included in the Markov model. These reductions in annual costs were divided into those occurring during the first year after an event and those during the second and subsequent years (since the costs are substantially higher in the first year). In 4S, data were recorded on all hospitalizations for cardiovascular causes.[4] To estimate the direct costs, we estimated the extra costs incurred through hospitalizations for cardiovascular causes per patient-year during the first year after a coronary event and those during the second and subsequent years. These estimates were based on the data for the patients in the 4S placebo group. To estimate the costs of these hospitalizations, we used the costs of hospitalization for patients in various diagnosis-related groups at four hospitals in Sweden that had patient-based cost-accounting systems[13] (Table 2). (The costs of comparable procedures in the United States have been presented by Mark et al.[14]) The prices we used indicate the cost of treating the patient and are not charges or payments. On this basis, the annual direct costs were estimated to be $7,849 for the first year after an event and $1,041 for subsequent years.

Indirect costs were estimated similarly. The difference between labor production per patient-year before a coronary event and after the event was estimated for the patients in the 4S placebo group who had nonfatal events. The estimates were based on the patients' work status as assessed every six months. We estimated indirect costs among patients 35 to 49 years old and among those 50 to 64 years old, since the proportion of the population that is working becomes smaller with increasing age.

Before the coronary event, the proportion of full-time workers was 0.7500 among patients 35 to 49 years old and 0.4582 among patients 50 to 64 years old. According to our estimates, among 35-to-49-year-olds the proportion of full-time workers decreased by 0.2678 during the first year after an event and by 0.1300 during subsequent years. Among 50-to-64-year-olds, the corresponding figures were 0.1465 and 0.0888. The indirect costs were estimated by applying these estimates to the average annual cost for the labor of a full-time Swedish worker in 1995 ($35,300).[15] Among 35-to-49-year-olds this calculation gave annual indirect costs of $9,453 during the first year after an event and $4,589 during subsequent years. Among 50-to-64-year-olds, the corresponding indirect costs were $5,171 and $3,135.

Sensitivity Analysis

Various analyses of sensitivity were performed that involved 59-year-old men and women with total cholesterol levels of 261 mg per deciliter (the mean age and mean cholesterol level of the study patients at entry). In one analysis, the cost per year of life gained was estimated on the basis of the lower and upper bounds of the 95 percent confidence interval — 0.66 and 0.80, respectively — around the relative risk (0.73) of coronary events in the 4S simvastatin group.[2] Another analysis used the average risk of death from noncoronary causes in Sweden at various ages instead of the risk of death obtained by the hazard function.[15] In one analysis we increased the annual risk of death after a coronary event by 50 percent, and in another analysis we decreased the risk by 50 percent.

In a separate analysis, we included the costs of health care during the years of life gained, using estimates of the cost of health care in Sweden at various ages.[16] The costs associated with morbidity after a nonfatal coronary event were raised and lowered by 50 percent in one analysis. In additional analyses, various costs for the intervention were used. In one estimate the cost of the follow-up was added to that of the intervention, to allow for the possibility that the patients were not already visiting their physicians regularly to have their coronary heart disease treated. An annual cost of $356 ($317 in direct costs and $39 in indirect costs) was used in this analysis.[17] In addition to the cost of follow-up, $808 ($630 in direct costs and $178 in indirect costs), representing the cost of screening, was added in one analysis.[18] A further analysis was based on the price of simvastatin in the United States, which led to an annual cost of $930 for the drug.[4]

Quality of life was included in one sensitivity analysis, since the patients in the study were not in perfect health. We assumed that in this population with preexisting coronary heart disease, 1 year was worth only 0.88 of a year in the life of a person in perfect health[19] but that there was no further reduction in the quality of life. Finally, in one sensitivity analysis, the discount rate applied to costs ranged from 0 to 10 percent. Since the discounting of years of life is controversial,[20] one analysis was also performed in which there was no discounting of effects.

RESULTS

The results of the cost-effectiveness analysis are shown in Table 3 for 59-year-old patients with pretreatment total cholesterol levels of 261 mg per deciliter.[2] For men, the cost per year of life gained was $5,400 when only direct costs were included and $1,600 when indirect costs were also included. For women, these costs were $10,500 and $5,100, respectively.

Table 4 shows the cost for each year of life gained in various groups of patients. When only direct costs were included, the cost per year of life gained was higher for women than for men and, as expected, decreased with increasing cholesterol levels. The cost per year of life gained also decreased with increasing age.

TABLE 3. COST EFFECTIVENESS OF SIMVASTATIN TREATMENT FOR FIVE YEARS IN 59-YEAR-OLD PATIENTS WITH CORONARY HEART DISEASE AND A PRETREATMENT TOTAL CHOLESTEROL LEVEL OF 261 mg PER DECILITER.

VARIABLE	ANALYSIS OF DIRECT COSTS ONLY		ANALYSIS OF DIRECT AND INDIRECT COSTS	
	MEN	WOMEN	MEN	WOMEN
Costs ($)				
Intervention	2,242	2,410	2,242	2,410
Associated morbidity	−718	−725	−1,783	−1,601
Net	1,524	1,685	459	809
Years of life gained	0.28	0.16	0.28	0.16
Cost per year ($)	5,400	10,500	1,600	5,100

Overall, the cost per year of life gained ranged from $3,800 to $27,400 in the various groups of patients when only direct costs were included. When indirect costs associated with morbidity were also included, the treatment led to a savings in the youngest patients (those 35 years old) among both men and women (that is, the reduction in the costs associated with morbidity from coronary causes exceeded the costs of the intervention). In the other groups, the cost per year of life gained ranged from $1,200 to $13,300.

The results of the sensitivity analysis are shown in Table 5. When only direct costs were included, in the various analyses the cost per year of life gained ranged from $3,000 to $12,100 in men and from $4,500 to $21,800 in women. When indirect costs were included, the results in the various analyses ranged from a savings to a cost of $9,300 per year of life gained in men. In women, the cost per year of life gained ranged from $100 to $18,500.

DISCUSSION

We estimated the cost per year of life gained because of cholesterol-lowering treatment with simvastatin in relation to the age, sex, and pretreatment cholesterol level of patients with preexisting coronary heart disease. When only direct costs were studied, the cost ranged from $3,800 to $27,400 in the various groups of patients. When the reduction in the indirect costs associated with morbidity was included, treatment led to a savings among men and women 35 years old, and the cost per year of life gained ranged from $1,200 to $13,300 in the older groups of patients.

The estimated cost-effectiveness ratios were well within the range that was considered cost effective in other studies.[21-24] We thus conclude that, according to the results of 4S, treating patients with coronary heart disease with simvastatin is cost effective in both men and women at the ages and cholesterol levels studied.

This conclusion should not be extrapolated to apply to primary prevention, in which the absolute risks of coronary heart disease are substantially lower. The reason that the cost-effectiveness ratios in this study were so favorable is that we analyzed the cost effectiveness of treating people with coronary heart disease, who are at high risk for coronary events. Even if the reduction in the relative risk were the same in primary prevention, the reduction in the absolute risk would be lower because of the lower absolute risk of coronary heart disease. Further studies are thus needed that are based on reliable data from randomized clinical trials of primary prevention.

The cost effectiveness of lowering cholesterol levels in secondary prevention in the United States has also been studied by Goldman et al.,[24] who estimated the cost per year of life gained with lovastatin (another inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A

TABLE 4. COST PER YEAR OF LIFE GAINED IN PATIENTS WITH CORONARY HEART DISEASE WHO RECEIVED SIMVASTATIN TREATMENT FOR FIVE YEARS.

TOTAL CHOLESTEROL BEFORE TREATMENT (mg/dl)*	AGE 35		AGE 59		AGE 70	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
	dollars					
Analysis of direct costs						
213	11,400	27,400	7,000	16,400	6,200	13,300
261	8,800	18,800	5,500	10,300	4,700	8,500
309	6,700	13,200	4,200	7,100	3,800	6,200
Analysis of direct and indirect costs						
213	Savings	Savings	2,100	8,600	6,200	13,300
261	Savings	Savings	1,600	4,900	4,700	8,500
309	Savings	Savings	1,200	3,200	3,800	6,200

*To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

TABLE 5. SENSITIVITY ANALYSES OF THE COST PER YEAR OF LIFE GAINED WITH SIMVASTATIN TREATMENT FOR FIVE YEARS IN 59-YEAR-OLD PATIENTS WITH CORONARY HEART DISEASE AND A TOTAL CHOLESTEROL LEVEL OF 261 mg PER DECILITER.*

VARIABLE USED IN ANALYSIS†	ANALYSIS OF DIRECT COSTS		ANALYSIS OF DIRECT AND INDIRECT COSTS	
	MEN	WOMEN	MEN	WOMEN
	dollars/yr of life gained			
Reduction in risk				
By 20%	8,200	15,300	4,400	10,000
By 34%	3,800	7,300	100	1,900
Average risk of death from noncoronary causes in Sweden	6,000	12,700	1,800	6,000
Risk of mortality after coronary events				
Increased by 50%	4,500	7,800	1,800	4,000
Decreased by 50%	8,800	20,100	1,600	8,600
With health care costs in gained years included	10,400	16,800	6,600	11,500
Morbidity-associated costs				
Increased by 50%	4,200	8,100	Savings	100
Decreased by 50%	6,700	12,500	4,800	9,900
Intervention costs				
Follow-up	9,700	17,900	6,400	13,600
Follow-up and screening	12,100	21,800	9,300	18,500
Simvastatin at U.S. price	9,800	18,700	6,000	13,200
Adjustment for quality of life with CHD	6,200	11,600	1,900	5,600
Rate of discounting costs and effects				
Costs 10%, effects 10%	7,800	17,700	2,500	8,900
No discounting	3,600	5,100	1,100	2,300
Costs 5%, effects undiscounted	3,000	4,500	1,000	2,200

*CHD denotes coronary heart disease.

†The various sensitivity analyses are described more completely in the Methods section.

reductase) in secondary prevention, using extrapolations from epidemiologic data. Their results are generally in line with those reported here, except in the case of women less than 55 years old with cholesterol levels below 250 mg per deciliter (6.47 mmol per liter), for whom the cost-effectiveness ratios estimated by Goldman et al. were substantially higher than ours. Those authors concluded that secondary prevention with lovastatin was cost effective in all groups of patients studied except women under 55 with cholesterol levels below 250 mg per deciliter.[24]

Although our conclusions generally agree with those of Goldman et al.,[24] we think that our study provides stronger and more reliable evidence of the cost effectiveness of lowering cholesterol levels in patients with coronary heart disease. This is because we used data on the costs and effects of treatment that were obtained directly from a randomized clinical trial in which statistically significant reductions in both coronary events and overall mortality were demonstrated. Furthermore, we estimated the effects of simvastatin in 4S conservatively. In that study, the incidence of cerebrovascular events was reduced by 30 percent.[2] We chose not to include this potential additional effect of simvastatin in our analysis, however, since the comparison of cerebrovascular events between study groups was performed in a post hoc manner.[2] Prospective trials are needed to determine whether a reduction in cerebrovascular events with simvastatin actually occurs.

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