

Cost-effectiveness of cholesterol lowering

Results from the Scandinavian Simvastatin Survival Study (4S)

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An analysis of the cost-effectiveness of simvastatin was conducted, based on the Scandinavian Simvastatin Survival Study (4S). The total cost of hospitalization in the placebo group was 52.8 million Swedish kronor (SEK) (£5.15 million), compared with SEK 36.0 million (£3.51 million) in the simvastatin group. This amounts to a 32% reduction, or a saving of SEK 16.8 million (£1.6 million) or SEK 7560 (£738) per patient.

The net cost per patient for the duration of the study (5.4 years) was SEK 13 540 (£1324). Simvastatin treatment saved an estimated 0.377 undiscounted life years (0.240 life years discounted at 5% per annum). The cost of simvastatin therapy per discounted life-year saved was therefore SEK

56 400 (£5502). Sensitivity analysis, examining the effect of different life expectancies, costs of initiation and monitoring of simvastatin therapy, and discount rates, showed the results to be stable.

Conclusion The cost per life-year saved of simvastatin in the treatment of post-myocardial infarction and angina patients, as determined from 4S data, is well within the range normally considered cost-effective.
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Key Words: Cost-effectiveness, cholesterol lowering, simvastatin (4S).

Introduction

The Scandinavian Simvastatin Survival Study (4S) reported a 30% reduction in relative risk of mortality from any cause ($P=0.0003$) in patients with angina pectoris or prior myocardial infarction^[1]. This was due to a 42% reduction in death from coronary disease; non-cardiovascular mortality was unaffected. In addition, simvastatin treatment was associated with a 26% reduction in the rate of hospitalization for acute cardiovascular disease ($P<0.0001$), a 32% reduction in coronary revascularization procedures ($P<0.00001$), and a 34% reduction in the number of days spent in hospital with the above conditions (9951 days vs 15 089, $P<0.0001$)^[2].

These data establish the clinical benefit of lowering low density lipoprotein (LDL) cholesterol in post-

myocardial infarction and angina patients. However, the assistance of health economic analysis must be used when applying these results broadly to medical practice to ensure the wise allocation of finite health care resources. Previous cost-effectiveness studies of drug therapy to lower cholesterol^[3–8] have been modelled on epidemiological data, which require assumptions about how risk factor reduction translates into reductions in clinical events and resource utilization.

We report on the cost-effectiveness of treating coronary heart disease patients with simvastatin 20–40 mg once daily, using survival and cost data gathered prospectively during the Scandinavian Simvastatin Survival Study.

Methods

The design and principal results of 4S have been reported in detail elsewhere^[1,2,9]. For the present analysis, data were gathered prospectively on hospital admissions for acute cardiovascular events and revascularization procedures, and the utilization of simvastatin. These

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data were combined with cost data from Sweden^[10,11] to calculate the cost-effectiveness of simvastatin according to the following formula.

$$\text{Cost per life-year saved} = \frac{(\text{Cost of simvastatin treatment}) - (\text{Costs of hospitalization and procedures avoided due to simvastatin treatment})}{(\text{Life-years saved})}$$

In the base case analysis, both costs and benefits were discounted at 5% per annum.

Simvastatin had little impact on the use of other cardiovascular medications^[2], which therefore were not included in the present analysis.

Cost of simvastatin

The incremental cost of simvastatin was considered to be that of the drug itself; use of simvastatin was assumed not to incur costs due to physician visits and laboratory tests, as such activities are part of the standard treatment of post-myocardial infarction and angina patients.

Hospitalization and procedure costs

The costs of acute cardiovascular hospitalizations were estimated by applying costs per case in Sweden based on diagnosis related groups^[11]. An inflation factor of 6.5% was used to convert 1993 to 1995 prices. The methodology for assignment of diagnosis related group codes to hospitalizations has been discussed previously^[2]. Costs for such codes with and without cardiac catheterization were applied to each hospitalization based on Swedish proportions^[11].

Data about hospitalizations for cardiovascular events were aggregated from all the countries contributing patients to the study because rates of hospitalization and the effect of simvastatin therapy were similar in all the participating countries (Fig. 1).

Life-years saved

Total life-years saved were estimated by combining life-years saved during 4S with the mortality difference at 5.5 years. The boundary of 5.5 years was selected in order to avoid unstable results due to marked reduction in patient numbers during later years of follow-up. Total life-years saved were calculated from the area between the Kaplan–Meier survival curves over 5.5 years, discounted at 5% per annum. The additional benefit of being alive after 5.5 years of treatment was estimated using an average life expectancy of 10 years, based on actuarial data^[12] and disregarding future treatment effects. Additional life expectancy was discounted by assuming a constant 5% death rate over a period of 20 years.

Sensitivity analysis

The following sensitivity analyses were conducted: (1) A 20% variation in estimated life expectancy at the end of the trial; (2) Use of a Weibull failure time model as an alternative method for calculation of life-years saved^[13]. The Weibull method projects life expectancy on the basis of in-trial observations, whereas the Kaplan–Meier method relies on external epidemiological data. Life expectancy among placebo patients alive at 5.5 years was projected to be 21.96 years by the Weibull method, compared with the assumed 10 years in the Kaplan–Meier model; (3) Extra costs of initiating and monitoring simvastatin treatment, where laboratory tests and regular physician office visits are not part of standard care. A cost of SEK 382 (£37.27) was used for the panel of laboratory tests (serum [S] lipoprotein profile, S-ALT, S-ASAT, S-CPK, S-creatinine, S-TSH, blood [B] Hg, fasting B-glucose), and SEK 788 (£76.89) for physician visits^[14], using 1991 data inflated to 1995 by a factor of 15.9%. These were both assumed to be required four times a year in the first year and once a year thereafter; (4) The effects of varying the discount rate for costs and benefits.

International comparison analysis

Cost-effectiveness ratios for eight other European countries plus Australia and New Zealand were derived by combining national diagnosis related group-based hospitalization costs and medication costs (sources available from the author) with the simvastatin and hospital utilization data gathered during 4S. Value added tax (VAT) was not included in these calculations because it represents transfer payments rather than a true societal cost.

Currency conversions were made at exchange rates quoted in the *Financial Times* 15 December 1995.

Results

Cost of simvastatin

Simvastatin 10, 20 or 40 mg · day⁻¹ was taken for 0.1%, 61.6% and 31.6%, respectively, of the total follow-up time of the trial. Patients randomized to simvastatin took no drug for 6.7% of total follow-up time. The 1995 costs for simvastatin 10, 20 and 40 mg · day⁻¹ were SEK 7.46, 12.20 and 14.91, respectively^[10]. Combining drug utilization with costs, the average undiscounted daily cost of simvastatin was SEK 12.23 (£1.19), and the discounted cost during the study was SEK 21 100 (£2059) per patient.

Hospitalization and procedure costs

The total cost of hospitalizations for acute cardiovascular events and procedures in the placebo group was SEK

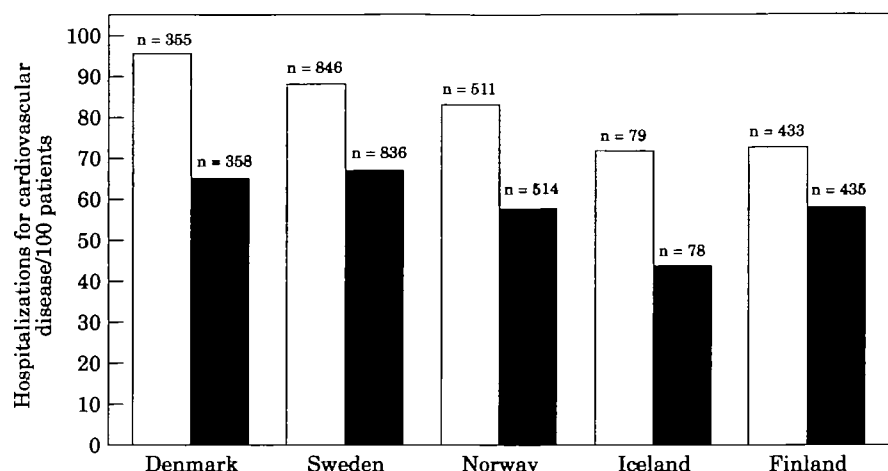


Figure 1 In-trial hospitalization rates for cardiovascular events in countries participating in 4S. □ = placebo; ■ = simvastatin. n = number of patients in each country.

52.8 million (£5.15 million), compared with SEK 36.0 million (£3.51 million) in the simvastatin group, a 32% reduction of SEK 16.8 million (£1.6 million) or SEK 7560 (£738) per patient (Table 1).

Cost per life-year saved

Gain in life expectancy per patient during the trial was 0.065 years undiscounted (0.054 years discounted). The total discounted gain in life expectancy from 5.5 years of simvastatin treatment was 0.240 life-years (0.377 life-years undiscounted) and the cost per discounted life-years saved was SEK 56 400 (£5502).

Sensitivity analysis

The results of the sensitivity analyses are summarized in Table 2 and indicate that the basic findings were stable across a range of alternative scenarios.

International comparison analyses

Cost-effectiveness ratios derived by applying international costs to 4S data were similar across the countries examined, ranging from £4137 per life-years saved in France to £8824 in New Zealand (Table 3).

Discussion

The cost-effectiveness ratios of simvastatin in 4S was SEK 56 400 (£5502) per life-year saved. This figure is based on direct costs only and is probably an overestimate of the total cost to save a life-year as the reduction in morbidity with simvastatin may be expected to yield savings in indirect costs. In addition, there may be savings in direct costs other than those due to

hospitalizations, such as ambulatory care, including cardiac catheterization, nursing home stays and home health care. Improved quality of life due to reduced occurrence of angina and heart failure was also not taken into consideration.

The cost-effectiveness ratios for simvastatin is sensitive to the method used to calculate the gains in life-expectancy (Table 2). A change in life expectancy to 8 or 12 years in the Kaplan–Meier estimate changed the discounted life-years saved from 0.24 years in the standard model to 0.211 years and 0.265 years, respectively, and the cost per life-year saved to SEK 64 100 (£6254) and SEK 51 000 (£4985). The Weibull estimate yielded a discounted life-year saved of 0.36 and a cost per life-year saved of SEK 37 600 (£3668). This implies a life expectancy at the end of the trial that is more than the average for Swedes aged 64 (16.2 years for men and 20.0 years for women)^[12]. The Kaplan–Meier method was preferred in this study because it makes a clear distinction between life-years gained during and after the trial, and because it is a conservative estimate based on life expectancy for people with coronary heart disease^[23].

Cost-effectiveness comparisons

There is no absolute standard for an acceptable cost-effectiveness ratio and comparisons between studies are hampered by differences in methodology, absolute and relative prices and the choice of the comparator. Some interpretation of the results is possible, nevertheless.

The cost-effectiveness of treating moderately elevated blood pressure was estimated for Sweden using the same methodology as the present study^[15]. The cost-effectiveness ratio estimated for simvastatin in 4S is well within the range considered cost-effective in that study. A U.S. survey has reported a median cost-effectiveness ratio of approximately \$19 000 (£12 338)

Table 1 Number of hospitalizations and cost per hospitalization in different diagnosis related groups

Diagnosis related group code	Number of events		Cost per event (SEK)
	Placebo (n=2223)	Simvastatin (n=2221)	
Specific cerebrovascular disorders except transient ischaemic attack ^[14]	80	61	22 876
Transient ischaemic attack and pre-cerebral occlusions ^[15]	30	19	11 619
Heart transplantation ^[103]	1	0	585 303
Coronary bypass with cardiac catheterization* ^[106]	3	2	115 819
Coronary bypass without cardiac catheterization* ^[107]	340	213	88 283
Percutaneous cardiovascular procedures ^[112]	67	63	38 449
Circulatory disorders with acute MI and cardiovascular complication, discharged alive ^[121]	223	148	27 743
Circulatory disorders with acute MI, without cardiovascular complication, discharged alive ^[122]	328	203	21 183
Circulatory disorders with acute MI, died ^[123]	79	43	12 961
Circulatory disorders except acute MI, with cardiac catheterization and complex diagnosis* ^[124]	26	19	21 955
Circulatory disorders except acute MI, with cardiac catheterization, without complex diagnosis* ^[125]	149	118	10 959
Heart failure and shock ^[127]	45	23	18 046
Cardiac arrest, unexplained* ^[129]	0	1	12 620
Peripheral vascular disorders with complications or co-morbidity ^[130]	16	18	14 942
Peripheral vascular disorders without complications or co-morbidity ^[131]	-2	1	9670
Atherosclerosis without complications or co-morbidity* ^[133]	10	7	10 213
Hypertension ^[134]	1	0	9521
Cardiac congenital and valvular disorders, age more than 17 yrs, without complications and co-morbidity* ^[136]	1	0	12 684
Cardiac arrhythmias and conduction disorders with complications and co-morbidity ^[138]	83	136	12 365
Cardiac arrhythmias and conduction disorders without complications and co-morbidity ^[139]	10	14	5405
Angina pectoris* ^[140]	307	240	9822
Syncope and collapse without complications and co-morbidity ^[142]	3	1	7189
Chest pain* ^[143]	10	12	4770
Other circulatory system diagnoses with complications and co-morbidity ^[144]	20	20	25 507
Other circulatory system diagnoses without complications and co-morbidity ^[145]	71	41	10 852
Total events	1905	1403	
Undiscounted hospitalization cost	SEK 58.7 million (£5.73 million)	SEK 39.7 million (£3.87 million)	—
Discounted hospitalization cost	SEK 52.8 million (£5.15 million)	SEK 38.0 million (£3.51 million)	—
Discounted hospitalization cost per patient	SEK 23 760 (£2318)	SEK 16 200 (£1580)	Net reduction per patient SEK 7560 (£738)

For diagnosis related groups which depend upon use of cardiac catheterization (identified with an asterisk) the allocation of hospitalization frequency is based on the relative frequency of diagnosis related groups with and without cardiac catheterization in Sweden for hospitalizations of the same type.

for 310 life-saving medical interventions^[16]. Cost-effectiveness ratios for percutaneous transluminal coronary angioplasty ranged from \$5300–\$7400 (£3441–£4805) per life-year saved for patients with severe angina to \$24 000–\$110 000 (£15 584–£71 429) per life-year saved for mild angina^[16–18]. Ratios for coronary artery bypass grafting varied from \$2300–\$5600 (£1494–£3636) per life-year saved in patients with left main disease, to \$12 000 (£7792) per life-year saved in patients with

three-vessel disease and \$28 000–\$75 000 (£18 182–£48 701) for two-vessel disease^[16–19]. Ratios for beta-blockers post-myocardial infarction have been calculated at \$360–\$17 000 (£234–£11 039)^[16,20,21], although another study has shown beta-blockers to be cost saving in selected patients^[22]. At SEK 56 400 (£5502) the cost-effectiveness ratio of simvastatin in 4S is thus comparable with percutaneous transluminal coronary angioplasty for moderate to severe angina,

Table 2 Sensitivity analysis

	Cost per life-years saved (£)
Standard analysis	SEK 56 400 (£5502)
Life expectancy at end of trial.	
8 years	SEK 64 100 (£6254)
12 years	SEK 51 100 (£4985)
Weibull estimates of life-years saved	SEK 37 600 (£3668)
Cost of initiating and monitoring simvastatin:	
Laboratory tests only	SEK 69 400 (£6771)
Laboratory tests and office visits	SEK 96 100 (£9376)
Discount rate:	
Costs 10%, benefits 10%	SEK 76 040 (£7419)
Costs 0%, benefits 0%	SEK 39 500 (£3854)
Costs 5%, benefits 0%	SEK 36 000 (£3512)

Table 3 International comparisons of cost-effectiveness. National currencies converted to pounds sterling (GBP) at exchange rates quoted in the Financial Times 15 December 1995

Country	Cost per life-years saved	
	National currency	(GBP)
Sweden	56 400 SEK	(5502)
Norway	62 333 NOK	(6361)
Belgium	235 507 BFr	(5165)
France	31 646 FFr	(4137)
Germany	17 220 DM	(7827)
Italy	14 463 000 Lit	(5869)
Portugal	1 933 417 Esc	(8312)
Spain	1 160 679 Pta	(6148)
U.K.	6983 GBP	
Australia	12 417 \$AUS	(5970)
New Zealand	20 825 \$NZ	(8824)

coronary artery bypass grafting for left main or three-vessel disease, or beta-blockers post-myocardial infarction, and is lower than coronary artery bypass grafting for two-vessel disease or tissue type plasminogen activator as an alternative to streptokinase in acute myocardial infarction^[16-21,23].

International comparisons

Estimates based on the 4S utilization data and local national costs revealed that the cost-effectiveness ratio of simvastatin was consistent in various countries (Table 3) despite international differences in costs of hospitalization and drug prices. These analyses must be interpreted with caution, however, because they are based on Scandinavian hospital admission data and procedure rates. Hospitalizations for acute events tend to be dictated by clinical parameters, but procedures can be highly variable according to local practices. The population rates for percutaneous transluminal coronary

angioplasty in countries participating in 4S are similar to the European average; rates of coronary artery bypass grafting in those countries are, however, slightly higher than in Europe as a whole^[24]. While the data from 4S may be representative of other countries with similar health care systems, these limitations must be borne in mind.

We conclude that the cost per life-year saved of simvastatin in the treatment of post-myocardial infarction and angina patients, as determined from 4S data, is well within the range ordinarily considered cost-effective in the health care systems of the countries evaluated in this study.

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