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At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention?

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Background The entire risk factor profile should be taken into account when considering initiating cholesterol lowering drug treatment. Recent treatment guidelines are therefore based on the absolute risk of coronary heart disease. We estimated at what coronary risk it is cost-effective to initiate cholesterol lowering drug treatment in primary prevention for men and women of different ages in Sweden.

Methods The cost-effectiveness was estimated as the incremental cost per quality-adjusted life-year (QALY) gained of cholesterol lowering drug treatment. Treatment was assumed to lower the risk of coronary heart disease by 31%. The analysis was carried out from a societal perspective including both direct and indirect costs of the intervention and morbidity, and the full future costs of decreased mortality. The coronary risk, in a Markov model of coronary heart disease, was raised until the cost per QALY gained corresponded to a specific threshold value per QALY gained. Three different threshold values were used: $40 000, $60 000 and $100 000 per QALY gained.

Results The risk cut-off value for when treatment is cost-effective varied with age and gender. If society is willing to pay $60 000 to gain a QALY it was cost-effective to initiate treatment if the 5-year-risk of coronary heart disease exceeded 2·4% for 35-year-old men, 4·6% for 50-year-old men, and 10·4% for 70-year-old men. The corresponding risk cut-off values for women were 2·0%, 3·5% and 9·1%.

Conclusions The results can serve as a basis for treatment guidelines based on cost-effectiveness.
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Key Words: Cholesterol, cost-effectiveness, coronary heart disease, primary prevention.

Introduction

Coronary heart disease is one of the most common causes of death in Western societies[1]. The risk of coronary heart disease depends on a number of risk factors, of which the cholesterol level is one of the most important[2,3]. Considerable effort has therefore been devoted to developing effective drugs which will lower cholesterol levels, and compelling evidence now exists that the newer generations of drugs (i.e. statins) increase survival in both secondary and primary prevention[4–8].

In addition to demonstrating that medical interventions are effective, it has become important to demonstrate that they are cost-effective, i.e. provide good value for money[9]. This is especially important for interventions, such as cholesterol lowering drugs, that may involve large fractions of the population. In secondary prevention, i.e. in patients with pre-existing coronary heart disease, treatment with cholesterol lowering drugs has been shown to be cost-effective in most patient populations[10]. This is due to the high absolute risk of coronary heart disease in this patient population.

In primary prevention, cholesterol lowering treatment is unlikely to be cost-effective for all patients with elevated cholesterol levels, and so it is crucial to determine in which patient populations treatment should be initiated[11]. In devising treatment recommendations for cholesterol lowering it is not sufficient to focus on the cholesterol level, the entire risk factor profile of the patient needs to be taken into account[12–15]. This is

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because the absolute coronary risk reduction will depend on the absolute risk of the patient, which is a function of all the risk factors. This is recognized in recent treatment guidelines for cholesterol lowering, which base treatment recommendations on the absolute coronary risk[13–15]. From a cost-effectiveness viewpoint it makes sense to devise treatment recommendations based on the absolute coronary risk. However, it is also necessary to incorporate gender and age into the analysis. This is because avoiding a coronary death will lead to a greater gain in life-years for a younger person than for an older person, and for a woman than for a man.

In this study we estimate at what risk of coronary heart disease it is cost-effective to initiate cholesterol lowering drug treatment in Sweden for men and women of different ages.

Methods

The cost-effectiveness was estimated as the incremental cost per quality-adjusted life-year (QALY) gained of cholesterol lowering drug treatment compared to no treatment. QALYs are the currently recommended outcome measure in cost-effectiveness analysis; they are constructed by weighting different health states between 0 (dead) and 1 (full health)[16]. The analysis was carried out from a societal perspective including both direct and indirect costs of the intervention and morbidity, and the full future costs of decreased mortality[17,18].

The estimations were carried out for men and women separately at eight different ages: 35, 40, 45, 50, 55, 60, 65 and 70 years. This corresponds to the ages of the patients in the major clinical trials[4–8], for which evidence exists of a beneficial treatment effect. Treatment was assumed to reduce the annual risk of coronary heart disease by 31% each year of treatment in all patient groups, based on the risk reduction in the West of Scotland coronary prevention study of primary prevention[5]. Treatment was not assumed to affect the risk of stroke. A treatment duration of 5 years was used, consistent with the treatment duration in the major clinical trials[4,5]. It was estimated at what 5-year-risk of coronary heart disease it would be cost-effective to initiate cholesterol lowering drug treatment. For the treatment to be cost-effective the cost per QALY gained had to be at or below a specific cost-effectiveness threshold. The threshold value corresponds to how much society is willing to spend in order to gain a QALY. The estimations were carried out for three different threshold values: $40 000, $60 000 and $100 000 per QALY gained.

The lowest threshold value ($40 000) is a rather conservative estimate of the value of a QALY gained, and treatments with a cost per QALY gained below $40 000 are normally considered highly cost-effective[11,19–21]. The middle threshold value of $60 000 corresponds to the mean value in a recent survey of health economists about what threshold value to use in cost-effectiveness analysis[22]. The highest threshold value ($100 000) was recently used as the value per QALY gained in a study of the value of the increased health of the US population over time[23].

Both costs and QALYs were discounted using a 3% discount rate[16]. All results were estimated in 1999 Swedish Crowns (SEK), and converted to US dollars using the exchange rate of June 1999 ($1 = SEK 8·50).

The cost-effectiveness model

The cost-effectiveness estimations were carried out with a Markov model used in previous analyses[10,24,25]. The starting point of the model is a cohort of men or women at a specific age who are initially free from coronary heart disease. 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 of dying from a non-coronary cause. Coronary events were classified into three classes: myocardial infarction (international disease classification code 410), angina pectoris (international disease classification code 413) and unstable angina pectoris (international disease classification code 411). Persons who had coronary events were considered to be in a temporary state of disease for 1 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.

As a basis for the estimations we entered age- and gender-specific data into the model of the annual incidence in Sweden of coronary heart disease for persons previously free of cardiovascular disease. These data were taken from the National Board of Health and Welfare in Sweden, which registers all hospitalizations due to coronary heart disease in Sweden. We used data about all hospitalisations between 1990 and 1994 due to coronary heart disease among persons older than 35 years and previously free from cardiovascular disease. Coronary heart disease was defined as international disease classification codes 410, 411 and 413, and in the model the coronary events were divided into these different types of events according to the fractions in the data set. Data were also collected about mortality in the first and second years after the coronary event for all individuals in our data set who suffered a coronary event. These data were entered into the model to determine survival after the different types of coronary events. Data about the annual risk of death from non-coronary causes among persons free from cardiovascular disease is also needed. These data were taken from the causes of death statistics in Sweden[1,26].

Based on the incidence and survival data, the model can be used to estimate the average 5-year-risk of a coronary event and the life-expectancy among persons initially free from cardiovascular disease in Sweden.

***Table 1** The average risk of coronary heart disease and the predicted life-expectancy for men and women in Sweden who are initially free from cardiovascular disease*

Age (years)	5-year risk of a CHD event (%)		Life-expectancy (years)	
	Men	Women	Men	Women
35	0·23	0·06	43·18	47·74
40	0·61	0·18	38·45	42·90
45	1·29	0·42	33·83	38·13
50	2·36	0·81	29·32	33·49
55	3·83	1·39	25·02	29·00
60	5·41	2·22	20·94	24·67
65	6·99	3·34	17·20	20·56
70	8·12	4·64	13·84	16·73

CHD=coronary heart disease.

These estimates are shown in Table 1. The estimated life-expectancy among 35-year-old men and women corresponds nearly exactly to the life-expectancy in the general population in Sweden[1]. Among 70-year-olds the estimated life-expectancy is somewhat higher than the life-expectancy in the general population in Sweden. This is logical since the estimated life-expectancy is for a population initially free from cardiovascular disease.

To estimate at what risk level treatment is cost-effective, the coronary risk in the model was raised until the cost per QALY gained of treatment corresponded to the threshold value of a QALY gained used in the estimations. Since an increased risk of coronary heart disease is likely to also increase mortality after a coronary event (due to a higher risk of subsequent coronary events), the annual all-cause mortality after a coronary event was increased by 65% of the increase in the coronary risk. This assumption was based on the estimation that 65% of all-cause mortality in the second year after a coronary event in our Swedish incidence data was due to coronary causes (assuming that the non-coronary mortality is the same among people who suffer coronary events as among the general population). This figure was varied in a sensitivity analysis.

Based on the Swedish incidence data, we also estimated what fraction of men and women of different ages free of cardiovascular disease would be eligible for treatment according to the estimated risk cut-off. To carry out this estimation we assumed that the distribution of the risk of coronary heart disease in the population follows a standard lognormal distribution[27].

Costs

The costs of the intervention were divided into the costs of the drug, the costs of laboratory tests and the costs of physician visits. The annual drug cost was estimated to be $600, based on 40 mg of pravastatin daily and the Swedish official retail prices[28]. Pravastatin with a dose of 40 mg per day was used in the West of Scotland coronary prevention study of primary prevention. An annual cost of laboratory tests of $40 and an annual cost of physician visits of $254 was used, based on a previous estimation of these costs for lipid lowering in primary care in Sweden[25]. The cost of physician visits included both the health care costs and the travelling and time costs for the patients. Thus the total annual intervention cost used was $894.

The morbidity-associated costs after a coronary event were divided into health care costs (direct costs) and lost productivity (indirect costs) due to the coronary event. The costs were divided into the costs in the first year and the annual costs in subsequent years. The costs were based on estimations of the costs after different types of coronary events in Sweden[29]. For myocardial infarction and angina pectoris the direct costs were estimated to be $5882 in the first year and $824 per year in subsequent years. The corresponding costs used for unstable angina pectoris were $10 000 and $824. In the 35–49 years age-group the annual indirect costs were estimated to be $12 941 in the first year after the event and $7647 per year in subsequent years for all coronary events. In the 50–64 years age-group the annual indirect costs were estimated to be $10 588 in the first year and $6471 per year in subsequent years for all coronary events. No indirect costs were assumed after the age of 65 years (the retirement age in Sweden).

It has recently been shown that the difference between total consumption and production in added life-years should be included as a cost in cost-effectiveness analyses from a societal perspective[17]. We therefore included these full future costs. The annual consumption minus production was estimated to be − $9882 in the 35–49 years age-group, − $4353 in the 50–64 years age-group and $18 706 in the 65– years age group, based on a previous analysis for Sweden[30].

Quality of life adjustment

To use QALYs, data about quality of life weights in persons with and without coronary heart disease are needed. For persons free of coronary heart disease we used data from a recent study about the QALY weights in the Swedish general population estimated by the time trade-off method[31]. The following quality weights were used in different age-groups: 0·93 (35–49 years), 0·91 (50–64 years), 0·81 (65–74 years), 0·65 (75–84 years), and 0·60 (85 years). The reduction in the quality weight due to coronary heart disease was assumed to be 0·10, based on some previous studies[32,33]. The treatment as such was not assumed to affect the quality of life.

Sensitivity analysis

Various analyses of sensitivity were performed for a threshold value of a QALY gained of $60 000. In one

***Table 2** The optimal risk cut-off for men and women at different ages for different valuations of a quality-adjusted life-year (QALY) gained. Lipid lowering treatment is cost-effective if the 5-year-risk of coronary heart disease exceeds the per cent risk shown in the table. The percent of the population eligible for treatment according to the risk cut-off is shown in parentheses*

Age (years)	The value of a quality-adjusted life-year gained					
	$40 000		$60 000		$100 000	
	Men	Women	Men	Women	Men	Women
35	3·34 (0·07)	2·95 (<0·01)	2·45 (0·21)	1·99 (<0·01)	1·66 (0·67)	1·24 (0·02)
40	4·06 (0·84)	3·17 (0·04)	3·00 (1·82)	2·28 (0·12)	2·03 (4·46)	1·51 (0·43)
45	5·09 (3·06)	3·93 (0·31)	3·71 (6·01)	2·80 (0·84)	2·47 (12·45)	1·86 (2·36)
50	6·50 (6·53)	5·07 (0·99)	4·61 (12·08)	3·51 (2·47)	3·01 (22·87)	2·27 (6·33)
55	8·27 (10·22)	6·80 (1·84)	5·63 (18·80)	4·53 (4·67)	3·60 (33·08)	2·86 (11·09)
60	11·59 (10·37)	10·08 (2·22)	7·19 (21·63)	6·11 (6·53)	4·45 (37·96)	3·53 (16·74)
65	17·33 (7·95)	15·82 (2·00)	9·13 (22·16)	7·55 (9·42)	5·28 (41·25)	4·23 (23·00)
70	21·36 (7·13)	20·30 (2·42)	10·37 (22·72)	9·10 (12·02)	5·90 (42·84)	4·96 (28·57)

analysis the reduction in risk was varied according to the 95% confidence interval of the relative risk reduction in the West of Scotland coronary prevention study (17%–43%)[5]. In another analysis the relative risk reduction was assumed to be 40% for persons younger than 55 years of age and 27% for persons at or above 55 years of age, based on the subgroup analysis in the West of Scotland coronary prevention study[5]. The relative risk reduction did not differ significantly with age in any of the major clinical trials, but there has been a trend towards a lower relative risk reduction at older ages in several studies[4–8].

In another analysis the increase in the mortality risk after coronary heart disease was varied between 30% and 90% of the increase in the risk of coronary heart disease. The annual intervention cost was varied between $600 and $1200 in one analysis, and in another analysis the annual morbidity-associated costs after a coronary event were raised and lowered by 50%. For comparability with other studies, one analysis was carried out without future costs of decreased mortality. In another analysis both the future costs of decreased mortality and the indirect morbidity costs were excluded, using the cost concept recommended by the Panel on Cost-Effectiveness in Health and Medicine[11]. In one analysis the reduction in quality of life after coronary heart disease was varied between 0 and 0·20. Finally, the rate of discounting costs and QALYs was varied between 0% and 5%, and in one analysis costs were discounted by 3% whereas QALYs were not discounted at all.

Results

The optimal risk cut-off

Table 2 shows at what 5-year-risk of coronary heart disease it is cost-effective to initiate cholesterol lowering drug treatment for men and women at different ages. The optimal risk cut-off is shown for three different threshold values of a QALY gained ($40 000, $60 000 and $100 000). Irrespective of the threshold value, the optimal risk cut-off increased with age and was higher for men than for women. If society is willing to pay $60 000 to gain a QALY, it was cost-effective to initiate treatment if the 5-year-risk of coronary heart disease exceeded 2·4% for 35-year-old men, 4·6% for 50-year-old men and 10·4% for 70-year-old men. The corresponding risk cut-off values for women were 2·0%, 3·5% and 9·1%. When the value of a QALY gained was varied between $40 000 and $100 000 the risk cut-off varied between 3·0% and 6·5% for 50-year-old men and between 2·3% and 5·1% for 50-year-old women.

The fraction of the population eligible for treatment according to the different risk cut-offs is also shown in Table 2. The fraction of the population eligible for treatment increased with age and was higher for men than women. With a value of a QALY gained of $60 000, less than 1% of 35-year-old men and women were eligible for treatment, whereas about 20% of older men and 10% of older women were eligible for treatment.

Sensitivity analysis

In Tables 3 and 4 the result of the sensitivity analysis is shown for a value of a QALY gained of $60 000. In the various sensitivity analyses, the risk cut-off for 50-year-old men varied between 2·9% and 7·8% and the risk cut-off for 50-year-old women varied between 2·2% and 5·9%. The result was most sensitive towards the variations in the risk reduction, the intervention cost, and the rate of discounting costs and QALYs.

Discussion

We have estimated at what risk of coronary heart disease it is cost-effective to initiate cholesterol lowering

Table 3 Sensitivity analysis of the optimal risk cut-off for men for a value of a quality-adjusted life-year (QALY) gained of $60 000

	Age							
	35	40	45	50	55	60	65	70
Baseline estimate (from Table 2)	2·45	3·00	3·71	4·61	5·63	7·19	9·13	10·37
Reduction in risk								
By 17%	4·38	5·17	6·33	7·85	9·36	12·09	15·46	17·13
By 43%	1·81	2·23	2·80	3·46	4·21	5·41	6·99	7·96
By 40% <55 years and 27% ≥55 years	1·95	2·41	2·95	3·71	6·33	8·02	10·33	11·82
Increase in mortality risk after CHD when the CHD risk increases								
30% of the relative increase in CHD risk	3·05	3·59	4·21	4·95	5·96	7·51	9·53	10·75
90% of the relative increase in CHD risk	2·23	2·76	3·46	4·40	5·44	6·99	8·87	10·14
Intervention costs								
Intervention costs $600 per year	1·70	2·11	2·60	3·29	3·91	5·04	6·51	7·33
Intervention costs $1200 per year	3·25	3·89	4·84	5·86	7·18	9·16	11·63	13·47
Annual morbidity-associated costs after CHD								
Increased by 50%	2·34	2·79	3·40	4·22	5·07	6·62	8·67	10·06
Decreased by 50%	2·56	3·21	4·03	5·00	6·18	7·77	9·53	10·68
Cost concept								
Future costs excluded	2·65	2·94	3·37	3·99	4·58	5·57	6·44	7·18
Future costs and indirect morbidity costs excluded	2·90	3·41	3·96	4·63	5·22	5·94	6·44	7·18
Quality of life with CHD								
Same as for persons without CHD	2·59	3·30	4·21	5·36	6·81	8·95	10·98	12·57
0·20 below that for persons without CHD	2·32	2·70	3·21	3·92	4·58	5·94	7·46	8·67
Rate of discounting costs and QALYs								
Costs 5%, QALYs 5%	2·96	3·65	4·47	5·36	6·44	8·13	10·33	11·36
No discounting	1·68	2·05	2·61	3·34	4·21	5·57	7·19	8·67
Costs 3%, QALYs undiscounted	1·61	1·87	2·32	2·90	3·60	4·77	6·03	7·18

CHD=coronary heart disease.

drug treatment in primary prevention in Sweden. Irrespective of the threshold value of a QALY gained, the optimal risk cut-off increased with age and was higher for men than for women. If society is willing to pay $60 000 to gain a QALY, it was cost-effective to initiate treatment if the 5-year-risk of coronary heart disease exceeded 2·4% for 35-year-old men, 4·6% for 50-year-old men, and 10·4% for 70-year-old men. The corresponding risk cut-off values for women were 2·0%, 3·5% and 9·1%. Even though the risk cut-off value increased with age, the fraction of the population eligible for treatment increased with age. With a value of a QALY gained of $60 000, less than 1% of 35-year-old men and women were eligible for treatment, whereas about 20% of older men and 10% of older women were eligible for treatment.

The results can serve as a basis for developing treatment guidelines for cholesterol lowering in primary prevention based on cost-effectiveness. Data from epidemiological studies such as the Framingham study can be used to determine the absolute risk of coronary heart disease of individual patients as done in current treatment guidelines based on absolute risk[12–15,34]. By comparing the absolute risk of a patient with the risk cut-off value for that age and gender it can be determined if cholesterol lowering drug treatment is cost-effective. Such an approach would be easy to use in clinical practice and provides a convenient way to incorporate risk factors other than the cholesterol level into the treatment decision.

Some current guidelines for cholesterol lowering treatment base treatment recommendations on the absolute risk of coronary heart disease[13–15]. In the Sheffield table for primary prevention, lipid lowering treatment was recommended if the 1-year-risk of coronary heart disease exceeded 3%[13,14], and in the recommendations by the European Society of Cardiology treatment was recommended if the 10-year-risk of coronary heart disease exceeded 20%[15]. A problem with these recommendations, from a cost-effectiveness viewpoint, is that the risk cut-off for treatment is independent of age and gender. As shown by our results, the optimal risk cut-off value varied greatly, especially with age. The risk cut-off values in the above guidelines are reasonably similar to our estimates at older ages, but are well above our estimates at younger ages. Thus from a cost-effectiveness viewpoint, the guidelines seem overly conservative as a basis for treatment decisions in younger and middle-aged men and women.

***Table 4** Sensitivity analysis of the optimal risk cut-off for women for a value of a quality-adjusted life-year (QALY) gained of $60 000*

	Age							
	35	40	45	50	55	60	65	70
Baseline estimate (from Table 2)	1·99	2·28	2·80	3·51	4·53	6·11	7·55	9·10
Reduction in risk								
By 17%	4·07	4·08	4·82	5·93	7·59	10·28	13·13	15·89
By 43%	1·39	1·70	2·10	2·72	3·45	4·61	5·63	6·89
By 40% <55 years and 27% ≥55 years	1·51	1·81	2·27	2·88	5·07	6·74	8·50	10·41
Increase in mortality risk after CHD when the CHD risk increases								
30% of the relative increase in CHD risk	2·35	2·78	3·37	4·18	5·20	6·74	8·50	9·89
90% of the relative increase in CHD risk	1·90	2·11	2·60	3·29	4·26	5·68	7·23	8·66
Intervention costs								
Intervention costs $600 per year	1·30	1·60	1·98	2·56	3·17	4·18	5·30	6·45
Intervention costs $1200 per year	2·80	3·00	3·65	4·53	5·87	7·80	9·76	11·70
Annual morbidity-associated costs after CHD								
Increased by 50%	1·93	2·18	2·64	3·31	4·26	5·68	7·33	8·80
Decreased by 50%	2·05	2·39	2·96	3·71	4·80	6·47	7·77	9·41
Cost concept								
Future costs excluded	2·26	2·34	2·64	3·04	3·62	4·39	5·04	5·91
Future costs and indirect morbidity costs excluded	2·41	2·53	2·88	3·35	3·99	4·61	5·04	5·91
Quality of life with CHD								
Same as for persons without CHD	2·05	2·39	3·00	3·90	5·07	6·96	8·82	10·41
0·20 below that for persons without CHD	1·93	2·18	2·60	3·20	3·99	5·04	6·59	7·78
Rate of discounting costs and QALYs								
Costs 5%, QALYs 5%	2·47	2·74	3·33	4·14	5·20	6·96	8·82	10·41
No discounting	1·33	1·60	2·02	2·64	3·45	4·61	5·95	7·34
Costs 3%, QALYs undiscounted	1·27	1·46	1·78	2·25	2·79	3·75	4·65	5·68

CHD=coronary heart disease.

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