UNIVERSITY
OF YORK

CENTRE FOR HEALTH ECONOMICS
HEALTH ECONOMICS CONSORTIUM

Economic Evaluation of Drug Therapy for Hypercholesterolaemia in the United Kingdom

by

Michael Drummond, Alistair McGuire
and Astrid Fletcher

DISCUSSION PAPER 104

University of York

Centre for Health Economics

ECONOMIC EVALUATION OF DRUG THERAPY FOR HYPERCHOLESTEROLAEMIA IN THE UNITED KINGDOM

by

Michael F. Drummond

Alistair L. McGuire

and

Astrid E. Fletcher

January 1993

The Authors

Mike Drummond is Professor of Economics at the Centre for Health Economics, University of York. Alistair McGuire is a Senior Research Fellow at the Centre for Sociolegal Studies, Wolfson College, Oxford. Astrid Fletcher is a Senior Lecturer in Epidemiology at Hammersmith Hospital.

Acknowledgements

We are grateful to Henry Glick, Joe Heyse, Bryan Luce, Gerry Oster, Eugene Smith, Gilbert Thompson and an anonymous referee for constructive comments on earlier drafts of the paper, and to members of the Delphi panel for their assistance. Joe Heyse also performed additional statistical analysis to facilitate the transformation of life-years to quality-adjusted life-years. However, any remaining errors and the views expressed, are our responsibility. We are also grateful to Merck, Sharp and Dohme for providing funds for the study through a research grant to the University of Birmingham (where Michael Drummond was based at the time of the study).

The study is being published to enhance debate about this important area of therapeutic care. The conclusions expressed in this paper are those of the authors, and not necessarily those of the funders.

Further Copies

Further copies of this document are available (at price £4.00 to cover the cost of publication, postage and packing) from:

The Publications Secretary,
Centre for Health Economics,
University of York,
Heslington,
YORK, YO1 5DD.

Please make cheques payable to the University of York. Details of other Papers can be obtained from the same address, or telephone York (0904) 433648 or 433666.

ABSTRACT

The last decade has shown a concerted effort in the UK to find ways of reducing coronary heart disease (CHD), culminating in the recent government target of a 30% reduction in the rates in people under the age of 65 years to be achieved between 1988 and 2000 by modification of the main risk factors: diet, smoking and physical fitness. It is generally accepted that the best prospect for achieving this is a combination of a population based approach, aimed at changing behaviour across the whole population, and intensified advice and treatment to those at highest risk.

Several reports have discussed the relative importance of elevated cholesterol (hypercholesterolaemia) as a risk factor for CHD and the pros and cons of more concerted efforts to identify individuals with high cholesterol levels, either by mass screening or by opportunistic testing by GPs. For individuals who are found to have hypercholesterolaemia, it is generally agreed that diet should be first line therapy. However, when dietary measures fail to reduce cholesterol to target levels, do the benefits of drug therapy justify the costs?

This paper assesses the cost-effectiveness of drug therapy for primary prevention of hypercholesterolaemia in patients for whom dietary measures have failed. The estimates of effectiveness, in life years gained, are based on a risk assessment model, using epidemiological data and the results from clinical trials of cholesterol-lowering drugs.

The cost per life year gained for men from treatment with one of the newer drugs (simvastatin 20mg daily) ranged from £11,900 to £56,650, depending on age and pre-treatment cholesterol level. Cost-effectiveness ratios for women were substantially higher. Primary prevention by drug therapy is most cost-effective at pre-treatment levels of 8mmol/L and above, and when other risk factors are taken into account. In this case the cost-effectiveness ratios are comparable with those for a number of current health care interventions in the UK.

These estimates of cost-effectiveness are the best that can be obtained using currently available epidemiology data. Whether or not drugs lower overall mortality is still currently being debated. Further clinical trials are underway with adequate statistical power to assess whether the previously reported increase in non-CHD deaths in intervention studies is a chance finding or not.

INTRODUCTION

Deaths from coronary heart disease (CHD) in the United Kingdom are among the highest in the world owing to our relatively poor performance in reducing this cause of mortality.[1] CHD rates have declined by around 10% since the mid 1970s. Larger decreases are found in younger age groups, with reductions of nearly a third in men under the age of 50 years. The smallest benefits have been in the over 60s. In contrast, some other countries, most noticeably the USA and Australia, have experienced a 50% decline in CHD mortality since the early 1970s, with similar reductions across all age groups.

It is generally accepted that risk factor modification, either through medical care or lifestyle changes, has contributed to the observed decline in CHD in the USA and Australia, although the magnitude of the contribution remains contentious. It has been estimated that, in the USA, reduced cholesterol levels accounted for 30% of the observed decline in mortality between 1968 and 1976 and a lower prevalence of smoking (in men) for 24%.[2] The UK population has disturbingly high levels of common CHD risk factors such as elevated cholesterol. 35% of the population aged 25–64 years have levels of 6.5 mmol/L or above, and 11% have levels over 7.8 mmol/L.[3]

The last decade has shown a concerted effort in the UK to find ways of reducing CHD, culminating in the recent government target of a 30% reduction in the rates in subjects under the age of 65 years to be achieved between 1988 and 2000 by modification of the main risk factors: diet, smoking and physical fitness.[4] It is generally accepted that

the best prospect for achieving this is a combination of a population based approach, aimed at changing behaviour across the whole population, and intensified advice and treatment to those at highest risk.[5] It has been pointed out, however, that a more important target would be a 50% reduction since this has been achieved by other countries.[6]

Mass screening has been advocated as the most reliable method of identifying subjects with high cholesterol levels.[7,8] One of the arguments against mass screening is that not all subjects at the highest risk of CHD are in the top of cholesterol distribution and therefore other risk factors must also be considered. For example, using data from the large American multiple risk factor intervention trial it has been suggested that there is minimal advantage at certain ages in lowering cholesterol in subjects with no other risk factors, for example, young non-smokers with a low blood pressure.[9] Antagonists of mass screening therefore argue that the guidelines for drug therapy based on cut-off points are not practical because they do not identify high risk individuals, but those with high lipid levels. Protagonists maintain that without mass screening subjects with familial hyperlipidaemia, a very high risk group, will be missed.

The Kings Fund Consensus Conference Report considered that the mass measurement of blood cholesterol levels in the population was not justified, but that cholesterol testing should be done in any individual with one or more major risk factors for CHD.[10] Subsequent to the consensus statement, the Department of Health Standing Medical Advisory Committee recommended opportunistic screening of high risk individuals.[11] The Committee estimated the overall cost-effectiveness of a basic testing and treatment programme among adults 40-69 years to be approximately £3100 per life-year

gained (£3000 per quality-adjusted life-year (QALY) gained) (1988-89 prices).

Although a programme of opportunistic testing may be justified, there is still considerable debate about the treatment alternatives. The current treatment guidelines[7,8] are that subjects with cholesterol levels between 5.2 and 6.5 mmol/L should receive general dietary counselling and advice on other risk factors; those with levels above 6.5 mmol/L should receive clinical care. This would consist of dietary advice and consideration for drug treatment in the presence of other risk factors if dietary measures have failed to reduce cholesterol to target levels. Levels of above 7.8 mmol/L would probably require drug treatment but in conjunction with diet and only after diet alone had failed to achieve target levels.

However, based on an overview of trials including dietary modification, Ramsey and colleagues have suggested that dietary measures may have minimal effects on cholesterol reduction, around 2% and suggested that the current guidelines on management of high cholesterol should be modified.[12]

Therefore, a substantial number of those patients identified by opportunistic testing may be considered for drug therapy if dietary measures fail. However, evidence on the effectiveness of drug therapy is mixed. Experimental evidence from trials shows that a 10% fall in serum cholesterol is associated with a reduction of 15-20% in CHD over a 2 year period, while the prospective epidemiological data give an estimate of a 30% reduction in CHD for a 10% fall in cholesterol accruing over several decades.[13]

But meta-analyses of the randomised trials in primary prevention[14] and secondary prevention[14-16] have shown an increase in non-cardiovascular mortality in the intervention group. An increase in non-cardiovascular mortality was also found in two dietary trials but not in a trial combining antismoking and dietary advice. The increases in non-cardiovascular mortality include cancer deaths (no specific site), accidents, suicides and violence. Whether this is due to competing risk, a chance finding, an adverse cholesterol-lowering effect, or an adverse drug effect[16] remains under debate.[17]

Although there are doubts about the impact of treatment on overall mortality, the number of patients on therapy is increasing. For example, scrips for lipid-lowering drugs in the UK more than doubled from 1986 to 1990.[16] In addition, with the development of the HMG CoA reductase inhibitors, which are more easily tolerated and produce a greater fall in serum cholesterol, it is likely that prescriptions for lipid lowering drugs will increase yet further. Given the increasing pressures on health care resources, there is growing interest in the assessment of the relative value for money from such health care interventions.

Estimates of the cost-effectiveness of different lipid-lowering drugs are available for a number of other countries.[18,19] In one recent study Kristiansen et al.[20] reported that for a Norwegian population the extra costs of adding drugs in 50% of subjects with serum cholesterol concentrations > 8.0 mmol/L would be £111,600 per life-year gained (£125,860 per QALY gained). They argued that the widely recommended intervention limits should be adjusted to include only a small proportion of the population and that the use of drugs should be reserved for subjects with genetic hypercholesterolaemia or those who are

otherwise at very high risk of arteriosclerotic disease.

Therefore, the objective of this paper is to assess the incremental costs and consequences (in life-years gained) of lifetime drug therapy for individuals of different ages and pretreatment cholesterol levels of 6.5 mmol/L and above in the UK, so as to inform the debate about the rational use of medicines.

METHODS

Form of economic evaluation

The form of economic evaluation employed was cost-effectiveness analysis, where the costs of interventions are compared with their consequences, measured in natural units, such as life-years gained.[21] The costs considered were those of the drugs themselves, the costs of associated medical care (such as visits to the lipid clinic or general practitioner, plus tests to monitor therapy) and the costs of treating side effects. In addition the averted costs of treating CHD events were also considered and deducted from the cost of the interventions.

All future treatment costs and changes in life expectancy were discounted to present values at a real annual rate of 6%, the rate currently advised by the UK Treasury. The rationale for discounting has been fully discussed elsewhere.[21] It causes higher values to be attached to treatment costs and changes in life expectancy early in the course of treatment, and lower values when they occur much later in life.

Alternative interventions considered

All assessments related to individuals with known cholesterol level in excess of 6:5 mmol/L, for whom dietary measures had failed (i.e. serum-cholesterol remaining above 6.5 mmol/L after a reasonable length of time). Two alternatives were considered in the primary assessment (i) no drug therapy, (ii) lifelong treatment with a HMG CoA reductase inhibitor (simvastatin 20 mg daily). The selected dosage for simvastatin represented the midpoint of the currently recommended dosage range. The selected pretreatment level was that for which simvastatin is licensed in the United Kingdom. In addition, other drugs and dosages were considered and these are discussed later.

Estimates of effectiveness

Effectiveness needs to be considered in two components: the relation between changes in cholesterol level and CHD risk, and the relation between drug intake and reduction in cholesterol level.

A cohort-based statistical model[22] was used to evaluate the effects of alternative cholesterol-lowering treatments on lifetime coronary risks. In this Coronary Heart Disease Risk Assessment Model (CHD-RAM), logistic risk equations based on the Framingham Heart Study[23] were used to estimate the five-year likelihood of developing CHD for any given cholesterol level among British men and women with age- and gender-specific average coronary risk characteristics. (These are described below in Epidemiological Sources.) From these five-year risk probabilities, the likelihood of developing CHD to age

75 and the expected loss in years of life due to CHD were obtained. Standard incidence–based cost–of–illness techniques were combined with the CHD event probabilities to estimate direct costs of CHD. The effect of cholesterol–lowering therapy was obtained by estimating reductions in the five year CHD risk resulting from the cholesterol lowering effects of the therapy. In the model, no reduction in coronary risk is experienced during the first two years of therapy, representing the expected time lag to therapy benefit. After the second year it is assumed that a patient received 90% of the maximum benefit of lowering cholesterol, given by the difference in naturally–occurring coronary risk estimated at baseline and post–intervention cholesterol levels.[18] The cost–effectiveness was measured as the ratio of the present value of the expected cost of drug therapy (net of the reduced expected direct medical costs of treating CHD) to the gain in life expectancy.

The Framingham Heart Study was used as the basis for the estimations since it has the longest follow–up, includes men and women and, in addition, the logistic equations are freely available. Doubts that the Framingham data are not transferable to other populations have been partly dispelled by the work of Schulte,[24] who showed that the Framingham logistic equations closely predicted the CHD experience of the PROCAM Study population. In addition, the use of mean values of age– and gender–specific risk factors in the estimation, although not entirely accurate, introduces a conservative bias owing to the non–linear relation between risk factors and CHD incidence.

The second aspect of the calculation of effectiveness concerns the relation between drug intake and reduction in total serum cholesterol level. The estimate for simvastatin 20mg (27% reduction) was taken from an overview based on clinical studies with 3500

patients, of whom 350 had been treated for 18 months or more.[25]

Epidemiological sources

The epidemiological data relevant to the CHD-RAM included age- and gender-specific mortality (expressed as the probability of dying in a five year period conditional on being alive at the start of the period), and estimates of sudden death, unstable angina and the prevalence of risk factors specified by the model. Full details of epidemiological issues and sources of data are given elsewhere[26] but are also summarised below.

Mortality: National age- and gender-specific death rates were used to calculate conditional probabilities.[27]

Sudden death: This was defined as death of unknown cause occurring within one hour of the onset of symptoms. Using this definition the proportion of fatal heart attacks that were sudden were derived from a community survey.[28]

Unstable angina as a proportion of non fatal CHD: Estimates were obtained from a national survey of consultation in general practice.[29]

Proportion of the population with left ventricular hypertrophy: Estimates were derived for men from the Whitehall Survey using the Minnesota Code 3.1 (tall R waves on ECG). The same proportions have also been applied to women. In the Medical Research Council Trial of Mild Hypertension estimates of LVH incidence were similar in men and women.[30]

Proportion of the population with glucose intolerance: Glucose intolerance was defined by a random blood sugar test > 120 mg/dl, and age- and gender- specific estimates derived from a community survey.[31]

Proportion of current smokers: A variety of studies provide data on the percentage of current smokers. The General Household Survey was used since it was the most representative.[32]

Mean systolic blood pressure: The mean casual systolic pressures were derived up to the age of 59 from a multicentre survey of 12,000 subjects attending general practitioners in the United Kingdom,[33] and for 60 years and over from a community survey of the elderly.[34]

Cost estimates

The daily costs for simvastatin 20 mg (£1.11) and other drug therapies were estimated from published NHS costs. The cost of a lipid clinic visit (£30) was obtained from the Hammersmith Hospital,[35] the cost of a general practitioner visit (£6.37) from the Compendium of Health Statistics[36] and the costs of tests (£5) from a locally-conducted costing study. The total annual cost of accompanying medical care, to monitor therapy and to treat minor side effects, was £100, around 25% of drug costs. An additional therapy initiation cost of £95 was included in the first year, representing the need for extra visits and tests when patients are first placed on a new drug.

The costs of treating CHD events were calculated by asking a Delphi panel, consisting of 6 cardiologists representing a range of clinical practice in the United Kingdom, to specify the likely clinical care for patients experiencing the five end points reported in the Framingham Heart Study (sudden death, non-sudden death, acute myocardial infarction, angina and unstable angina). In particular they were asked to specify the percentage of patients undergoing expensive procedures such as CABG and PTCA. This, together with an analysis of the literature, enabled a clinical flow diagram to be constructed for the immediate and follow-up care.

The expected average treatment cost for each of the five events was then estimated using data from detailed costing studies previously conducted in the UK.[37,38,39] These studies give basic costs in general wards, coronary care units, intensive therapy units, plus the unit costs of CABG, valve replacements, pacemaker implants, adult catheterisation and PTCA. The resulting costs were £1270 for myocardial infarction, £2160 for angina, £1950 for unstable angina, £300 for sudden death and £320 for non-sudden death. (Fuller details of the costing methods are available from the authors. In so far as the estimates of the costs of treating CHD are lower than the actual costs, this is conservative in relation to assessing the benefits of primary prevention.)

Because it is possible that not all the costs of treating CHD events would be averted if some events were prevented by drug therapy, marginal costs were also obtained by identifying which costs were variable (i.e. relating to the number of patients treated) and which were fixed. All costs were expressed in 1989-90 prices.

Sensitivity analysis

The sensitivity of the cost–effectiveness results to a number of parameters was explored. These included the costs of drug therapy, the compliance with therapy and the extent of savings (marginal or average) from averting CHD events.

Also, the other (non–cardiology) health care costs that would be incurred in added years of life were also considered, on the grounds that individuals who would have died prematurely of a fatal CHD event would require treatment for other diseases in old age. An average annual cost of £500 was used, based on the average per capita health care expenditure in the NHS, inflated to allow for the fact that individuals surviving beyond 65 years old would incur higher health care costs in older age.[36]

A further sensitivity analysis considered impacts on quality of life. An assessment of treatment effectiveness in terms of life years gained may be an underestimate in that it ignores the benefits of reducing morbidity from CHD. On the other hand, it may be an overestimate if there is a slight reduction in the quality of life through being on drug therapy. Therefore, additional analyses were performed using the health state values derived by Kind et al.[40] and used by Williams[41] in his assessment of screening for elevated cholesterol.

Based on the earlier studies, it was assumed that a year of life following a non–fatal CHD event was equivalent to 0.9 quality–adjusted life–years (QALYs) post angina and 0.7 QALYs post myocardial infarction or unstable angina.[41] (The relative proportions

of these events were given by the CHD-RAM.) The other key assumption related to the QALYs for a year on drug therapy. This was assumed to be 0.995 for an individual on long-term therapy experiencing few side effects, corresponding to the health state valuation reported by Kind et al.[40] for the state no disability with mild distress. The construction and use of QALYs is currently the subject of considerable controversy and debate.[42,43] Therefore, they are included in this study as a secondary analysis.

RESULTS

Table 1 gives the epidemiological data inputs to the CHD-RAM. Table 2 shows the gains in life years predicted by the model for various cohorts of men and women with different pretreatment cholesterol levels. (The life years gained are undiscounted and are for a 27% reduction in cholesterol level, equivalent to that expected with a 20 mg daily dose of simvastatin). It can be seen that a cohort of 1000 men aged 40-44 with a pretreatment level of 8.00 mmol/L, the level where most treatment guidelines suggest therapy should be considered even in the absence of other risk factors, would gain in excess of 1000 life-years in total if placed on therapy to age 75. Life-years gained are greater with higher pretreatment levels, but lower for women and for the treatment of older age cohorts.

Table 3 shows the incremental costs per life year gained for simvastatin, compared with the baseline of no drug therapy. It can be seen that these vary by the age of individuals, their pretreatment cholesterol level and gender, the cost-effectiveness ratios for women being greatly inferior to those of men. The minimum point of the cost-

effectiveness ratios is for men of age 55–59. This does not correspond to the point that maximises years of life gained, since initiation of therapy for younger age cohorts means that these costs are borne earlier and for a longer period. However, cost per year of life gained varies only around 20% between the 2 cohorts aged 45–49 and 55–59 years.

The sensitivity of results to variations in assumptions can be explored by considering the incremental cost–effectiveness ratio for men aged 50–54 with a pretreatment cholesterol level of 8 mmol/L. This is £21050 per life year gained for simvastatin (20 mg daily) using base case assumptions. The use of marginal, rather than average, cost estimates for the treatment of CHD events makes little difference to the results, giving an equivalent cost–effectiveness ratio of £21200, a change of only 0.6% Essentially this is because these costs, many of which occur far into the future, are heavily discounted. A similar result is obtained when other health care costs in added years of life are included. This adds approximately 2% to the cost–effectiveness ratios, a constant arithmetic shift regardless of age or pre–treatment level.

Schulman et al.[44] have pointed to the importance of considering compliance when assessing the cost–effectiveness of reducing high blood cholesterol with drugs. However, in this instance, differing assumptions about compliance with therapy lead to only minor changes in cost–effectiveness ratios. For example, if only 75% of patients comply with therapy, the cost–effectiveness ratio is changed by only 0.1%, since many of the costs of life–long therapy are averted as well as effectiveness being reduced.

The cost–effectiveness ratios are most sensitive to the cost of the intervention, as is to be expected for a life–long therapy. For example, a 5% change in therapy cost, resulting from either a change in drug price or in the annual costs of the associated medical care, would change the cost–effectiveness ratios by approximately the same amount.

When the impact of therapy on quality of life was considered, the incremental cost per QALY of treatment by simvastatin (20 mg daily) for men aged 50–54 with a pre–treatment level of 8 mmol/L was found to be £19800, or £1250 lower than the base case estimate of £21050.

When other risk factors are considered, the cost–effectiveness ratios are reduced. Table 4 shows that the cost–effectiveness ratios fall at two pre–treatment levels as individual risk factors are added. Cholesterol lowering in smokers produces the most favourable ratios.

DISCUSSION

This study has shown that the incremental cost per life year gained for men from primary prevention with simvastatin 20 mg daily ranges from £11900 to £56650 depending on age and pre–treatment cholesterol. Cost–effectiveness ratios for women were substantially higher.

In judging whether this constitutes a rational use of scarce NHS resources, comparisons need to be made with other health care interventions. Williams[45] has ranked a number of interventions, in terms of their cost per quality-adjusted life-year gained. Recently Maynard[46] has published an updated 'league table' containing 21 interventions ranging from cholesterol testing and diet therapy only (all adults, aged 40-69) at £220 per QALY to erythropoietin treatment for anaemia in dialysis patients (assuming no increase in survival) at £126,290 per QALY. The use of league tables is currently subject to considerable methodological controversy and debate.[47] Therefore, decision makers should exercise extreme caution in interpreting these data.[48] However, it can be seen that the cost-effectiveness results for drug therapy for primary prevention of hypercholesterolaemia in men fall in the upper half of the range. The ratios for men with high pre-treatment levels or with other risk factors compare favourably with those for a number of current health care interventions.

Another way to improve value for money would be to use cheaper drug regimens, or lower doses of simvastatin. However, if the aim is to achieve target levels of cholesterol for those individuals with high pre-treatment levels, the alternatives to simvastatin are more expensive, and hence less cost-effective. For example, the combination therapy of cholestyramine and bezafibrate evaluated by Curtis et al.[49] would cost in excess of £30000 per life year gained for a 50-54 year old man. One of the cheaper fibrates, bezafibrate (400 mg daily) has been shown in a number of studies to give an average cholesterol reduction of 17%.[50] The analysis suggests that bezafibrate would have a cost per life year gained of £12300 for a 50-54 year old man with a pre-treatment level of 8.0 mmol/L. However, physicians working towards target levels of cholesterol

may consider this to be unsatisfactory, as the final cholesterol level would still be 6.6 mmol/L. Simvastatin (20 mg daily) would bring cholesterol almost to the target level, although the implication is that the additional life years gained by attaining the target level, over and above those gained from using bezafibrate, are being bought at an incremental cost of £38550 each. Lower doses of simvastatin can also be considered as an alternative to fibrates. A daily 10 mg dose gives a cholesterol reduction of 21% at a cost per life year gained (50–54 year old man with pre-treatment level of 8.0 mmol/L) of £17350.

In addition, the estimation of the effectiveness of drug interventions for hypercholesterolaemia by a modelling approach raises an important methodological issue. Namely, while most drug primary prevention trials show a statistically significant reduction in CHD events and CHD mortality, none show a reduction in overall mortality owing to an increase in non-CHD deaths. Therefore, it might be argued that this finding is inconsistent with using a model like the CHD-RAM, which uses data from population-based surveys to attribute changes in CHD risk to reductions in cholesterol level. The main difficulty in interpreting the intervention studies with respect to overall mortality is that these studies were designed (in terms of sample size and duration) to detect a statistically significant reduction in CHD events. Therefore, they do not account for the fact that some CHD, while not fatal immediately, does alter life expectancy. While the CHD-RAM does project an increase in deaths from causes other than CHD, it is based on a competing risk argument, and as such, it is assumed that non-CHD deaths are not causally linked to reduction in cholesterol. Further trials are underway with adequate power to assess whether the previously reported increase in non-CHD deaths in intervention studies is a chance finding or not.[51]

Therefore, these data support an approach to the treatment of hypercholesterolaemia based on a rational consideration of risk factors, with diet being used as first line therapy.[52] The cost–effectiveness of drug therapy varies with age, gender, pre–treatment cholesterol level and other CHD risk factors. The incremental cost–effectiveness ratios, of instituting drug therapy when dietary measures fail, are lowest for individuals with very high pre–treatment levels or having other risk factors, in particular being a smoker.

The government's target of a 30% reduction in CHD by the year 2000 requires a range of interventions. This paper helps determine the role of cholesterol–lowering drugs within the broader strategy. Whether or not drugs lower overall mortality is still being debated. The issue of cost–effectiveness is also complex with cost–effectiveness ratios being influenced by a number of factors. However, when individuals have high pre–treatment levels or other risk factors, the cost–effectiveness of drug therapy compares favourably with that for a number of current health care interventions.

Finally, this study illustrates how crucially dependent economic evaluations are upon the available medical evidence relating to the interventions concerned.

TABLE 1: EPIDEMIOLOGICAL DATA

	Age	Mean systolic BP	Percent smokers	Percent glucose intolerance	Percent LVH	Conditional mortality probability	Sudden death as a % of CHD death	% of CHD (excl. MI and CHD death) that is unstable angina
MALES	35-39	125.9	39.00	.56	.07	.0075	.5000	.7140
	40-44	125.9	39.00	.74	.07	.0126	.5000	.7140
	45-49	131.7	39.00	.74	.07	.0233	.5000	.7160
	50-54	131.7	39.00	2.41	.06	.0427	.5000	.6710
	55-59	138.5	39.00	2.41	.06	.0702	.5000	.6220
	60-64	156.2	30.00	2.38	.10	.1150	.5000	.5000
	65-69	156.2	30.00	2.38	.10	.1792	.5000	.5000
	70-74	159.0	30.00	4.63	.10	.2747	.4700	.5300
FEMALES	35-39	120.3	36.00	.44	.07	.0052	.4700	.4620
	40-44	120.3	36.00	.47	.07	.0088	.4700	.4620
	45-49	129.6	36.00	.47	.07	.0153	.4700	.4810
	50-54	129.6	39.00	1.35	.06	.0252	.4700	.4810
	55-59	139.1	39.00	1.35	.06	.0382	.4700	.4810
	60-64	161.8	23.00	2.02	.10	.0601	.4700	.4810
	65-69	161.8	23.00	2.02	.10	.0929	.4700	.4900
	70-74	164.7	23.00	3.79	.10	.1509	.4400	.4900

TABLE 2: LIFE YEARS GAINED (UNDISCOUNTED) PER 1000 INDIVIDUALS FOR A 27% REDUCTION IN CHOLESTEROL

Cholesterol Level mmol/L		AGE GROUP (YEARS)								
From	To	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	
6.5	4.7	792	729	640	531	420	290	151	53	
7.0	5.1	922	843	735	606	477	327	170	59	
7.5	5.5	1057	960	831	682	534	365	188	65	
8.0	5.8	1201	1086	934	762	594	405	208	72	MEN
8.5	6.2	1363	1225	1047	850	661	450	231	80	
9.0	6.6	1523	1363	1160	938	727	495	253	87	
9.5	6.9	1687	1504	1275	1029	796	541	277	95	
10.0	7.3	1860	1654	1398	1126	872	593	303	104	
6.5	4.7	394	376	351	316	275	215	135	54	
7.0	5.1	463	440	408	365	316	245	153	61	
7.5	5.5	539	509	468	416	358	276	171	68	
8.0	5.8	626	587	536	473	404	309	191	76	WOMEN
8.5	6.2	734	681	616	539	457	347	213	84	
9.0	6.6	854	784	702	608	511	385	235	93	
9.5	6.9	995	902	799	685	570	427	258	102	
10.0	7.3	1171	1046	915	774	638	473	284	112	

TABLE 3: INCREMENTAL COST PER LIFE YEAR GAINED (£s) SIMVASTATIN 20mg DAILY
(DISCOUNTED AT 6% PER ANNUM)

MEN

Cholesterol level mmol/L		AGE GROUP (YEARS)							
From	To	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
6.5	4.7	56650	45200	37400	32500	28950	28450	35950	54400
7.0	5.1	47150	37950	31700	27850	25050	24800	31700	48300
7.5	5.2	39800	32300	27200	24150	21900	21900	28200	43400
8.0	5.8	33800	27650	23500	21050	19300	19400	25250	39200
8.5	6.2	28600	23600	20250	18350	16950	17150	22600	35300
9.0	6.6	24500	20350	17600	16150	15050	15350	20400	32100
9.5	6.9	21100	17650	15400	14250	13400	13750	18450	29300
10.0	7.3	18100	15300	13450	12550	11900	12300	16650	26700

WOMEN

Cholesterol levels mmol/L		AGE GROUP (YEARS)							
From	To	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
6.5	4.7	164150	128300	10150	81100	65150	55750	55950	68200
7.0	5.1	134150	106300	84800	68950	56000	48400	49100	60250
7.5	5.2	110600	89050	72000	59350	48700	42500	43600	53900
8.0	5.8	91050	74550	61200	51200	42550	37500	38900	48450
8.5	6.2	73900	61800	51650	43950	37000	33000	34650	43500
9.0	6.6	60450	51650	40000	38100	32550	29350	31150	39400
9.5	6.9	49200	43100	37450	33050	28650	26150	28150	35800
10.0	7.3	39450	35500	31550	28500	25100	23250	25350	32500

TABLE 4: COST PER LIFE-YEAR GAINED FOR MEN AGED 50-54 YEARS BY NATURE OF RISK
SIMVASTATIN, 20MG DAILY

Cholesterol Level mmol/L		NATURE OF RISK		
From	To	Systolic BP > 140 mm Hg	Smoker	Smoker with systolic BP>140 mm Hg
6.5	4.7	£32,200	£25,350	£24,900
8.0	5.8	£20,500	£16,650	£16,000

REFERENCES

1. World Health Statistics Annual. World Health Organization, Geneva 1988.

2. Goldman, L., Cook, E.F. Reasons for the decline in coronary heart disease mortality: medical intervention versus life-style changes. P.67-75 in Trends in coronary heart disease mortality. The influence of medical care. Eds. Higgins, M.W., Luepker, R.V. Oxford University Press, 1988.

3. Tunstall-Pedoe, H., Smith, W.C.S., Tavendale, R. How-often-that-high graphs of serum cholesterol. Findings from the Scottish heart health and Scottish MONICA studies. Lancet 1989; i: 540-542.

4. Department of Health. The health of the nation. London, HMSO, 1991.

5. Risk assessment: its role in the prevention of coronary heart disease: recommendations of the scientific and medical advisory committee of the Coronary Prevention Group. B.M.J. 1987; 295: 1246.

6. Tunstall-Pedoe, H. Coronary heart disease. B.M.J. 1991; 303: 701-4.

7. Shepherd, J., Betteridge, D.J., Durrington, P., Laker, M., Lewis, B., Mann, J., Miller, J.P., Reckless, J.P.D., Thompson, G.R. Strategies for reducing coronary heart disease and desirable limits for blood lipid concentrations: guidelines of the British Hyperlipidaemia Association. Br. Med. J. 1987; 295: 1245-1246.

8. Study Group. European Atherosclerosis Society. The recognition and management of hyperlipidaemia in adults: a policy statement of the European Atherosclerosis Society. Eur. Heart J. 1988; 9: 571-600.

9. Tunstall-Pedoe, H. Who is for cholesterol testing. B.M.J. 1989; 298: 1593-1594.

10. Blood cholesterol measurement in the prevention of coronary heart disease. Consensus statement. The Sixth King's Fund Forum, 1988, London.

11. Department of Health. Blood cholesterol testing: the cost effectiveness of opportunistic cholesterol testing. Report by the Standing Medical Advisory Committee to the Secretary of State for health. London, Department of Health, 1990.

12. Ramsey, L.E., Yeo, W.W., Jackson, P.R. Dietary reduction of serum cholesterol concentration: time to think again. B.M.J. 1991; 303: 953-7.

13. Peto, R., Yusuf, S, Collins, R. Cholesterol lowering trial results in their epidemiological context. Circulation 1985; 72: 451.

14. Muldoon, M.F., Manuck, S.B., Matthews, K.A. Lowering cholesterol concentrations and mortality: a quantative review of primary prevention trials. B.M.J. 1990; 301: 309–314.

15. Rossouw, J.E., Lewis, B., Rifkind, B.M. The value of lowering cholesterol after myocardial infarction. New Engl. J. Med. 1990; 323: 1112–9.

16. Smith, G.D., Pekkanen, J. Should there be a moratorium on cholesterol lowering drugs? British Medical Journal 1992; 304: 411–414.

17. Oliver, M.F. Might treatment of hypercholesterolaemia increase non cardiac mortality. Lancet 1991; 337: 1529–1531.

18. Oster, G., Epstein, A.M. Primary prevention and coronary heart disease: The economic benefits of lowering serum cholesterol. Am. J. Public Health 1986; 76: 647–656.

19. Martens, L.L., Rutten, F.F.H., Erkelens, D.W. and Ascoop, C.A.P.L. Cost effectiveness of cholesterol–lowering therapy in the Netherlands. American Journal of Medicine 1989; 87 (Suppl. 4A), 54–58.

20. Kristiansen, I.S., Eggen, A.E., Thelle, D.S. Cost effectiveness of incremental programmes for lowering serum cholesterol concentration: is individual intervention worthwhile? British Medical Journal 1991; 302: 1119–1122.

21. Drummond, M.F., Stoddart, G.L. and Torrance, G.W. Methods for the economic evaluation of health care programmes. Oxford, Oxford University Press, 1987.

22. Glick, H. and Heyse, J., Thompson, D., Epstein, R.S., Stephenson, W.P., Smith, M.E. and Oster, G. The coronary heart disease risk assessment model. Leonard Davis Institute Management Discussion Paper, No. 73, University of Pennsylvania, Philadelphia, July 1990. (Forthcoming in the International Journal of Technology Assessment in Health Care.)

23. Abbott, R.D., McGee, D. Section 37: The probability of developing certain cardiovascular diseases in eight years at specified values of some characteristics. In: Kannell, W.B., Woolf, P.A., Garrison, R.J. eds. The Framingham study. An epidemiological investigation of cardiovascular disease. US Dept. of Health, Education, and Welfare publication NIH 87–2703. Bethesda, MD, Public Health Services, 1987.

24. Shulte, H., Assmann, G. CHD risk equations, obtained from the Framingham Heart Study, applied to the PROCAM study. Cardiovascular Risk Factors Issue No. 3. Madrid, Saned Publishers, 1991.

25. Walker, J.F. HMG CoA reductase inhibitors: current clinical experience. Drugs 1988; 36 (Suppl. 3): 83–86.

26. Fletcher, A. Epidemiology of coronary heart disease in the United Kingdom. Epidemiology Research Unit, Royal Postgraduate Medical School, 1989 (mimeo).

27. Office of Population Censuses and Surveys. Mortality Statistics. Review of the Registrar General on deaths in England and Wales, 1841–1985. Series DH1, No. 19. London: Her Majesty's Stationery Office, 1986.

28. McIlwaine, W.J., Donnelly, M.D.I., Mallaghan, M. et al. Deaths from ischaemic heart disease in Belfast. Br. Heart J. 1986; 55: 330–335.

29. Royal College of General Practitioners, Office of Population Censuses and Surveys, Department of Health and Social Security. Morbidity statistics from general practice 1981–1982. Series MB5 No. 1. London: Her Majesty's Stationery Office, 1986.

30. Miall, W.E. and Greenberg, G. Mild hypertension: is there pressure to treat? An account of the MRC trial. Cambridge University Press, 1987.

31. Sharp, C.L. Diabetes survey in Bedford 1962. Proc. Roy. Soc. Med. 1964; 57: 193–202.

32. Office of Population Censuses and Surveys, Social Survey Division. Series GHS No. 14. General Household Survey 1984. London, Her Majesty's Stationery Office, 1986.

33. Mann, J.I., Lewis, B., Shepherd, J. et al. Blood Lipid concentrations and other cardiovascular risk factors: distribution, prevalence and detection in Britain. Br. Med. J. 1988; 296: 1702–1706.

34. Grimley Evans, J. Blood pressure and stroke in an elderly English population. J. Epidemiol. and Comm. Health 1987; 41: 275–282.

35. Thompson, G. Personal communication, 1990.

36. Office of Health Economics. Compendium of health statistics. London, OHE, 1989.

37. Buxton, M.J. et al. Costs and benefits of the heart transplant programmes at Harefield and Papworth Hospitals. London, HMSO, 1985.

38. Oxford Health Authority. Cardiology costing study. Oxford, 1988.

39. Trent Regional Health Authority. Cardiothoracic costing study. London, Price Waterhouse for Trent RHA, 1987.

40. Kind, P., Rosser, R.M., Williams, A.H. Valuation of quality of life: some psychometric evidence. In M.W. Jones-Lee (ed.) The value of life and safety. Amsterdam, Elsevier/North, Holland, 1982.

41. Williams, A.H. Screening for risk of CHD: is it wise use of resources? In M. Oliver, M. Ashley-Miller, D. Wood (eds.) Screening for Risk of Coronary Heart Disease. John Wiley and Sons Ltd., 1987.

42. Loomes, G., McKenzie, L. The use of QALYs in health care decision making. Social Science and Medicine 1989; 28: 299-308.

43. Mehrez, A., Gafni, A. Quality-adjusted life-years, utility theory and healthy years equivalents. Medical Decision Making 1989; 9: 142-149.

44. Schulman, K.A., Kinosian, B., Jacobson, T.A. et al. Reducing high blood cholesterol level with drugs. Journal of the American Medical Association 1990; 264 (23): 3025-3033.

45. Williams, A.H. Economics of coronary artery bypass grafting. British Medical Journal 1985; 291: 326-9.

46. Maynard, A. Developing the health care market. The Economic Journal 1991; 101: 1277-1286.

47. Drummond, M.F. Output measurement for resource allocation decisions in health care. Oxford Review of Economic Policy 1989; 5(1): 59-74.

48. Gerard, K., Mooney, M. QALY league tables: three points for concern - goal difference counts. HERU Discussion Paper 04/92. Departments of Public Health and Economics, University of Aberdeen, 1992.

49. Curtis, L.D., Dickson, A.C. et al. Combination treatment with cholestyramine and bezafibrate for heterozygous familial hypercholesterolaemia. British Medical Journal 1988: 173-175.

50. Hunninghake, D.B., Peters, J.R. Effect of fibric acid derivatives on blood lipid and lipoprotein levels. American Journal of Medicine 1987; 83 (Suppl. 5B): 44-49.

51. Jones, P.H. Lovastatin and simvastatin prevention studies. American Journal of Cardiology 1990; 66: 39B-43B.

52. Oliver, M.F. Doubts about preventing coronary heart disease. British Medical Journal 1992; 304: 393-394.