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The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin

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Abstract

Objective: To estimate the economic efficiency of using pravastatin to prevent the transition from health to cardiovascular disease in men with hypercholesterolaemia.

Design: Economic benefit analysis based on data from the West of Scotland coronary prevention study. Treatment specific hazards of developing cardiovascular disease according to various definitions were estimated. Scottish record linkage data provided disease specific survival. Cost estimates were based on extracontractual tariffs and event specific average lengths of stay calculated from the West of Scotland coronary prevention study.

Subjects: Men with hypercholesterolaemia similar to the subjects in the West of Scotland coronary prevention study.

Main outcome: Cost consequences, the number of transitions from health to cardiovascular disease prevented, the number needed to start treatment, and cost per life year gained.

Results: If 10 000 of these men started taking pravastatin, 318 of them would not make the transition from health to cardiovascular disease (number needed to treat, 31.4), at a net discounted

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cost of £20m over 5 years. These benefits imply an undiscounted gain of 2460 years of life, and thus £8121 per life year gained, or £20 375 per life year gained if benefits are discounted. Restriction to the 40% of men at highest risk reduces the number needed to treat to 22.5 (£5601 per life year gained (undiscounted) and £13 995 per life year gained (discounted)).

Conclusions: In subjects without evidence of prior myocardial infarction but who have hypercholesterolaemia, the use of pravastatin yields substantial health benefits at a cost that is not prohibitive overall and can be quite efficient in selected high risk subgroups.

Introduction

Prevention of coronary heart disease, the leading cause of death in the United Kingdom,[1][2] is one of the primary goals of the NHS.[3] The West of Scotland coronary prevention study[4] established that treating hypercholesterolaemia with pravastatin is an effective strategy for achieving this goal.[5] This study randomised 6595 Scottish men aged 45-64 years with a mean cholesterol concentration of 7.0 mmol/l and no evidence of previous myocardial infarction to either placebo or pravastatin 40 mg/day, both in addition to dietary advice. After an average 4.9 years of follow up the drug reduced the risk of non-fatal myocardial infarction or death from coronary disease by 31% (95% confidence interval 17% to 43%). In the light of this, physicians need to balance the important clinical benefits of treatment against the cost of its provision.[3] We aimed to weigh the prevention of cardiovascular disease with pravastatin against the costs to the NHS of such a strategy.

Definition of transition from health to cardiovascular disease, according to which events are considered

Definition	Description
1	Deaths from CHD
2	Deaths from CHD or from cardiovascular causes, including fatal stroke
3	Dealth from CHD or from cardiovascular causes or definite MI
4	Deaths from CHD or from cardiovascular causes; definite MI; or silent (unrecognised) MI
5	Deaths from CHD or from cardiovascular causes; definite MI; silent (unrecognised) MI; PTCA; or CABG
6	Deaths from CHD or from cardiovascular causes; definite MI; silent (unrecognised) MI; PTCA; CABG; or angiography
7	Deaths from CHD or from cardiovascular causes; definite MI, silent (unrecognised) MI; PTCA; CABG; angiography; or hospital admission for angina
8	Deaths from CHD or from cardiovascular causes; definite MI; silent (unrecognised) MI; PTCA; CABG; angiography; hospital admission for angina; or non-fatal stroke
9	Deaths from CHD or from cardiovascular causes; definite MI; silent (unrecognised) MI; PTCA; CABG; angiography; hospital admission for angina; non-fatal stroke; or TIA

CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting; TIA = transient ischaemic attack.

Methods

We created an economic model of prevention of cardiovascular disease (additional details of these definitions and other methodological aspects are available from the corresponding author). Its main premise is that an initial cardiovascular event constitutes an irreversible transition from health to sickness and that society values the avoidance of this transition. Several combinations of events were considered hierarchically as possibly defining this transition (box).

Effects

To estimate the effect of pravastatin on the rate of transition from health to cardiovascular disease, we reanalysed the data from the West of Scotland coronary prevention study according to the events used to define the transition. For each definition, we estimated average instantaneous transition rates (hazards) over the five years of the trial on an "intention to treat" basis (table 1). We also calculated the proportion of transitions due to each type of event within each definition.

We compared treatment with pravastatin to no primary intervention, each in addition to normal dietary advice. The model considers these two strategies in a population similar to that of the West of Scotland coronary prevention study, adjusting monthly for those who die of non-cardiovascular causes. To estimate the number of people making the transition to cardiovascular disease under each prevention strategy, we applied the relevant hazard to the survivors. At the end of each month we calculated the difference in the number of people who developed cardiovascular disease and classified this information according to the type of event specified by the definition. This process was carried out over 60 months. The net consequence of not using pravastatin was the cumulative difference in transitions.

We also expressed this consequence as the number needed to treat (the number of people who would have to start treatment to prevent one person making a transition from health to cardiovascular disease over five years). This definition considers starting treatment rather than continuing treatment (the standard definition)[6] because the benefit in the West of Scotland coronary prevention study was obtained despite many patients discontinuing treatment.

To determine the implications for life expectancy of making the transition to cardiovascular disease, the course of illness beyond the trial period must be considered—a process subject to assumptions. We estimated the life years gained as the difference between the age and sex specific cumulative survival curve for Scotland[7] and the event specific curves. The latter were derived from data obtained from the Scottish record linkage system on comparable cardiovascular events in Scotland between 1981 and 1994 (over 460 000).[8] This provided the first decade of each event specific survival curve. The full extent of each curve was derived by matching the corresponding average hazard observed during the final five years of the linkage data to known Scottish life table hazards and by using the implied subsequent course. The entire survival curves were derived to permit full discounting (at 6% a year, as recommended by the Treasury) of the life years gained.

Table 1 Hazards for transition from health to cardiovascular disease for various definitions of the latter, and for each transition definition, the percentage of transitions accounted for by each component of the definition

Definition*	Hazard/1000 person years		Transitions accounted for by:								
	Pravastatin	Placebo	CDD	CVD	NFM	SMI	RVS	CTH	ANG	NFS	TIA
1	2.6	3.9	100								
2	3.1	4.6	83	17							
3	9.9	15.1	24	5	71						
4	14.5	20.2	16	4	51	29					
5	16.4	23.0	14	4	45	26	13				
6	17.8	24.3	13	3	41	23	7	13			
7	22.7	29.6	10	2	32	19	4	8	25		
8	24.7	31.5	9	2	30	17	4	7	23	8	
9	26.4	33.9	9	2	28	16	4	7	21	8	7

*See box for details of definitions.
CDD=death from coronary heart disease; CVD=death from cardiovascular cause (including stroke); NFM=non-fatal definite myocardial infarction; SMI=silent (unrecognised) myocardial infarction; RVS=revascularisation (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty); CTH=cardiac catheterisation; ANG=admission for angina; NFS=non-fatal stroke; TIA=transient ischaemic attack.
Percentages do not always add up to 100% owing to rounding.

Duration was not adjusted by quality of life, owing to a lack of relevant data.[9]

Costs

The cost of a transition was based on the average direct 1996 cost of initial management of each type of event—for example, non-fatal myocardial infarction and stroke (table 2). These costs were derived by combining average cost estimates from extracontractual tariffs from a sample of over 200 trusts and event specific average lengths of stay calculated from data from the West of Scotland coronary prevention study. We did not consider management costs subsequent to the first admission to hospital, costs relating to "preadmission" management (for example, ambulances), costs borne by patients, or indirect costs. All costs were discounted at 6%.

The cost of using pravastatin (£1.66 per 40 mg tablet) was derived by considering the number of people receiving one tablet daily. This number was estimated monthly as the proportion of men not yet making the transition to cardiovascular disease, adjusted by the proportion in the West of Scotland coronary prevention study who had tablets dispensed at each visit. The cost of monitoring (liver function test, lipid profile, and a visit to the general practitioner every six months) was also included. As there was no evidence in the West of Scotland coronary prevention study of important side effects caused by pravastatin, no costs for their management were included.

Table 2 Estimates of cost of first hospital admission for management of each type of event and prevention with pravastatin

Cardiovascular event	Cost (£) 1996
Non-fatal myocardial infarction	2327
Silent (unrecognised) myocardial infarction	188
Fatal myocardial infarction	532
Admission for angina	978
Non-fatal stroke	5154
Fatal stroke	6118
Transient ischaemic attack	190
Coronary artery bypass grafting	6076
Percutaneous transluminal coronary angioplasty	3200
Angiography	1121
Pravastatin 40 mg	1.66
Monitoring per month	2.67

Subgroup analysis

To permit estimation of the effects in various subgroups of patients, the variables in the model were recalculated to give hazards adjusted according to various risk profiles for cardiovascular disease. These adjusted hazards were estimated with an exponential regression model derived from data from the West of Scotland coronary prevention study. The risk factors considered were age, diagnosis of hypertension, diastolic blood pressure, baseline high density lipoprotein cholesterol concentration, smoking status, electrocardiographic abnormality, family history of coronary heart disease, widow status, positive response on Rose questionnaire,[10] previous vascular disease, diabetes, and nitrate use.

The adjusted hazards were used to recalculate the number needed to treat. To translate this value for a high risk subgroup to costs per life year gained required the simplifying assumption that the factors that increase risk of cardiovascular disease have no other effect on life expectancy. This assumption was necessary because the data on risk factors essential to make these adjustments were not available in the Scottish record linkage database. This may lead to an overestimate of the life years gained in the high risk subgroup because many of the factors that increase risk of cardiovascular disease also have separate implications for both life expectancy and other cost components of the economic analysis. The life expectancy of older smokers with hypertension, for example, may be lower than the average used in this analysis owing to death from non-cardiovascular causes.

Sensitivity analyses

As any model involves assumptions and uncertainties, extensive sensitivity analyses were carried out. These included such factors as the discount rate, the initial risk of cardiovascular disease, the price of the drug, the costs of monitoring, the costs of subsequent care, the efficacy of prevention, and the age of subjects.

In addition, a Monte Carlo simulation was run for the factors and ranges shown in the box. In this type of analysis, which simultaneously considers the effect of varying several factors, each factor is varied within its range and the results are recalculated. By varying the factors at the same time, the effects of multiple changes in the model can be seen.

<table>
<tr><td colspan="2">Factors and ranges considered in multivariate sensitivity analysis</td></tr>
<tr><td><i>Factor</i></td><td><i>Range</i></td></tr>
<tr><td>Hazard of cardiovascular disease without pravastatin</td><td>0.001 to 0.1 (per person year)</td></tr>
<tr><td>Age</td><td>45-65 years</td></tr>
<tr><td>Subsequent costs (per event)</td><td>£0 to £6500</td></tr>
<tr><td>Monitoring costs per month</td><td>£0 to £10</td></tr>
<tr><td>Efficacy (% reduction in risk)</td><td>10% to 43%</td></tr>
<tr><td>Definition of cardiovascular disease</td><td>All definitions</td></tr>
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Results

Using pravastatin in men who have hypercholesterolaemia but no symptoms prevents substantial numbers of them from developing cardiovascular disease, regardless of the definition of the event (table 1). Taking the definition that includes all events, 318 men out of 10 000 would avoid cardiovascular disease over five years (undiscounted). Thus, to prevent one transition, 31.4 men need to started treatment. Of the 318 men avoiding cardiovascular disease, 33 would have died immediately from cardiovascular disease, 138 would have had a first non-fatal myocardial infarction, 68 would have been admitted to hospital for angina, 33 would have needed revascularisation, and 47 would have had a non-fatal stroke or transient ischaemic attack.

The implications of these transitions can be measured in several ways. Initial acute admission to hospital for these events would have occupied 2017 bed days. Apart from immediate deaths, an additional 35 men who survived their first event would have died over the five years. Taking this loss of life plus the shortened life span of those who make the transition to cardiovascular disease, 2460 years of life would have been lost without treatment with pravastatin.

Obtaining these benefits in a population of 10 000 men would cost the NHS £23 340 984 for the drug. This is offset by £529 214 in savings for the management of the events that are prevented. Thus the net cost would be £22 811 769 over the five years (undiscounted). Discounting at 6% annually, these costs amount to £19 973 401. If benefits are not discounted, this translates to a cost effectiveness ratio of £8121 per year of life gained; if they are, the ratio becomes £20 375 per life year gained. Results for other discounting rates and definitions are shown in figure 1.

Figure 2 shows the effect of the risk of cardiovascular disease over five years without treatment on the number needed to treat to prevent one transition from health to sickness. As risk increases, the number needed to treat drops. European guidelines recommend treatment when the 10 year risk of coronary heart disease is above 20%[11]; in the West of
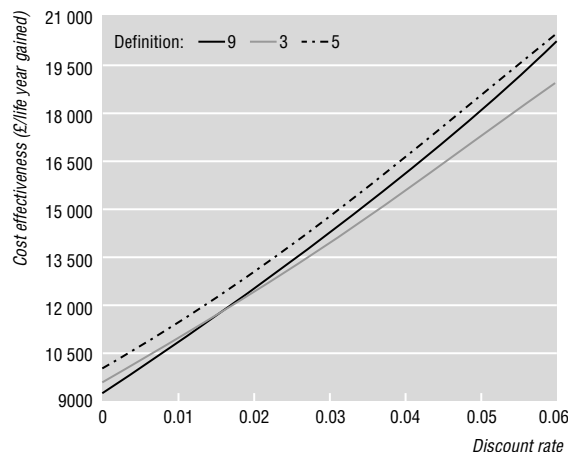

Fig 1 Cost per life year gained for various discounting rates applied equally to costs and benefits. Lines represent a range of definitions for the transition from health to cardiovascular disease (see first box for description of definitions)
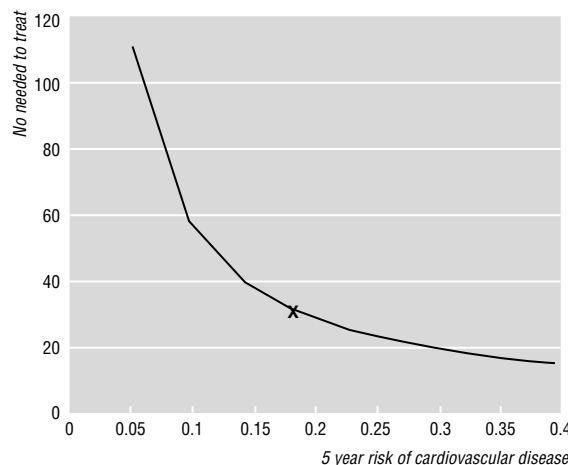

Fig 2 Number of men who need to started taking pravastatin to prevent one transition from health to cardiovascular disease as a function of the five year risk for men who are not treated. The baseline analysis is identified with an x

Scotland coronary prevention study slightly more than 40% of subjects met this criterion. Using the same proportional cut off, but on risk of cardiovascular disease, means that only 22.5 men need to start treatment to prevent one transition. Assuming that these higher risk men would have the same gain in life years as estimated for the entire population of the West of Scotland coronary prevention study, this number needed to treat translates to a cost per life year gained of £5601 (undiscounted). If the benefits are discounted (number needed to treat, 25.7), the estimate becomes £13 995.

The estimate of reduction in risk of cardiovascular disease shown in the West of Scotland coronary prevention study is subject to some statistical uncertainty. A sensitivity analysis of this value shows that at the lower limit of the 95% confidence interval (12% reduction) the cost effectiveness ratio is between £15 068 per life year gained (undiscounted) and £37 788 per life year gained (discounted), whereas at the upper limit (33%) it is between £5346 per life year gained and £13 419 per life year gained.

Table 3 Results of Monte Carlo multivariate sensitivity analysis showing percentage of combinations that yield cost effectiveness ratio between stated cut off points

Cut off points (per life year gained)	Discounting of benefits	
	No	Yes
Under £10 000	77.1	2.1
£10 000 to £20 000	20.6	41.8
£20 000 to £40 000	2.3	49.8
Over £40 000	0	6.3

Apart from the price of the drug, other factors and assumptions affect the results relatively little. The "off-setting" costs of managing cardiovascular events—that is, costs that can be offset against costs of treating with pravastatin—were estimated very conservatively by considering only the first hospital admission. However, even if the average discounted value of subsequent costs were as high as £10 000, the cost effectiveness ratio would drop by only 10.9%. Another variable—the cost of monitoring—was estimated on the basis of expert opinion. Still, if it is increased from £2.67 per compliant patient per month to £10, the cost effectiveness ratio would increase by only 14%.

The distribution of the results of the Monte Carlo multivariate sensitivity analysis according to various cut offs is provided in table 3. If benefits are not discounted most of the combinations fall below £10 000 per life year gained; even if benefits are discounted nearly half of the combinations remain below £20 000 per life year gained. The results of the analysis are quite robust from a health policy perspective.

Discussion

On the basis of the results of the West of Scotland coronary prevention study, using pravastatin in men with hypercholesterolaemia will prevent 1 in 31.4 of those who start treatment from making the transition to cardiovascular disease over five years, at an undiscounted cost over that time period to the NHS of about £2000 per person starting treatment, at the current drug price. This can be reduced to 1 in 22.5 if only men with higher risks consistent with European guidelines start taking pravastatin. In the West of Scotland coronary prevention study this threshold would have encompassed 42.2% of the study population.

Other studies

Although the measure "life years gained" does not fully account for the benefits of prevention, it does permit comparison with other analyses. With discounting of costs but not of benefits, the cost effectiveness ratio is £8121 per life year gained. If the benefits are discounted, the ratio rises to £20 375 per life year gained. These results are somewhat conservative. Only initial management of cardiovascular events was included, yet subsequent management can be costly—for example, emergency management of stroke represents only 7% of costs.[12]) Moreover, the reduction in quality of life due to cardiovascular disease and indirect costs (productivity losses) was not considered. Thus, the results obtained suggest that primary prevention with pravastatin represents relatively good value for money in Britain.

These results might seem surprising in the light of a recent paper estimating much higher cost effectiveness ratios.[13] That study, however, failed to consider the adverse implications of cardiovascular disease that do not result in death within the trial, thus severely underestimating the life years gained from prevention. This problem was compounded by the authors' assumption that all patients consumed the drug. All other studies addressing primary prevention were based on projections of the effect of cholesterol lowering rather than on actual data from a clinical trial.[14] Given the much

larger uncertainties in making these projections, those estimates should be superseded now.

Assumptions

Despite being based on trial data, this study required several assumptions. Notwithstanding analysis of substantial Scottish data, projections were required to complete the survival curves. The premise of shortened life expectancy following non-fatal cardiovascular disease should be generally acceptable, however. Another major assumption was that patients would be identified in the course of routine clinical practice. This is not intended to underestimate the costs of a screening programme—it simply accords with clinical reality.

Policy implications

The economic implications of using pravastatin to prevent cardiovascular disease depend on the underlying risk of the disease in the population. Restrictions to those at higher risk, however, are not clear cut as many factors that increase the risk of the disease may also affect other determinants of economic efficiency. These considerations are complex because multiple risk factors may not influence life expectancy or use of medical resources in an additive manner, and data reflecting these interactions are not currently available.

The extreme restriction is to abandon primary prevention altogether and focus on the higher risk patients who already have major manifestations of cardiovascular disease. Indeed, a recent economic analysis of secondary prevention, based on the Scandinavian simvastatin survival study,[15] estimated a cost per life year gained of £5502 (discounted). Comparison of primary and secondary prevention must be made cautiously, however, owing to differences in assumptions made in each analysis. For example, the analysis in the Scandinavian simvastatin survival study did not include monitoring and used a 5% discount rate, different treatment costs, and a much higher offsetting cost of £3267 per event (due in part to a costly heart

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Key messages

- The West of Scotland coronary prevention study showed that pravastatin can prevent cardiovascular disease in men with hypercholesterolaemia

- So far, reports have deemed this prevention unjustified due to adverse economic implications

- This analysis, based on data from the West of Scotland coronary prevention study and extensive data from the Scottish record linkage system, shows that using pravastatin in this way is worth considering because of its substantial clinical benefit at a reasonable cost

- Practitioners must now consider using pravastatin to prevent cardiovascular disease in men with hypercholesterolaemia

- Increased economic efficiency may be obtained by restricting prevention to patients with additional risk factors

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transplantation in the placebo group). When these values are used in this model the ratio for prevention through use of pravastatin drops to £11 893 per life year gained (discounted).

More importantly, these situations are not strictly comparable. The transition from health to cardiovascular disease (primary prevention) represents a much larger loss than that from one degree of illness to another (secondary prevention). A decision to focus only on the latter would force a healthy person to experience and survive a cardiovascular event in order to become eligible for treatment, and this experience entails more than just hospital costs and life years gained. When this fact is acknowledged, the benefits achieved with primary prevention are greater than those of secondary prevention.

Although widespread use of pravastatin for primary prevention may seem like an unjustified additional burden on already strained healthcare resources, the results of the West of Scotland coronary prevention study provide evidence that this intervention can be economically sound.

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Epileptic seizures after a first stroke: the Oxfordshire community stroke project

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Abstract

Objective: To describe the immediate and long term risk of epileptic seizures after a first ever stroke.
Design: Cohort study following up stroke survivors for 2 to 6.5 years; comparison with age specific incidence rates of epileptic seizures in the general population.
Setting: Community based stroke register.
Subjects: 675 patients with a first stroke, followed up for a minimum of 2 years.
Main outcome measures: Occurrence of single and recurrent seizures.
Results: 52 patients had one or more post stroke seizures; in 25 the seizures were recurrent. The 5 year actuarial risk of a post stroke seizure in survivors (excluding 19 patients with a history of epilepsy and 3 patients in whom the seizure occurred shortly before death from another cause) was 11.5% (95% confidence interval 4.8% to 18.2%). The relative risk of seizures, in comparison with the general population, was estimated at 35.2 in the first year after stroke and 19.0 in year 2. The risk of seizures was increased in survivors of subarachnoid and intracerebral haemorrhage (hazard ratio for intracranial haemorrhage v cerebral infarction 10.2 (3.7 to 27.9)). The risk of seizures after ischaemic stroke was substantial only in patients presenting with severe strokes due to total anterior circulation infarction. Only 9 of 295 patients (3%) independent one month after stroke suffered a seizure between 1 month and 5 years (actuarial risk 4.2% (0.1% to 8.3%)).
Conclusion: Stroke patients have about an 11.5% risk of single or recurrent seizures in the first 5 years after a stroke. Patients with more severe strokes or haemorrhagic strokes are at higher risk.

Introduction

Cerebrovascular disease is an important cause of epilepsy,[1] particularly in elderly people.[2] When seizures complicate a clinical stroke they have a devastating