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Smith, G.D., Payne, N., Pickin, M. et al. (7 more authors) (1998) Cholesterol and coronary heart disease: screening and treatment. *Quality in Health Care*. pp. 232-239. ISSN 0963-8172

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Cholesterol and coronary heart disease: screening and treatment

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Accepted for publication
8 September 1998

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the United Kingdom, accounting for just under one quarter of all deaths in 1995: 27% among men and 21% among women.¹ Although many CHD deaths occur among elderly people, CHD accounts for 31% of male and 13% of female deaths within the 45–64 age group.

Coronary heart disease imposes high social costs, including impaired quality of life and reduced economic activity. A large share of National Health Service (NHS) resources are also accounted for by CHD.² One CHD risk factor is serum cholesterol concentration. Much attention has been focused on screening people to identify those with raised cholesterol concentrations and then trying to lower these concentrations through diet or medical treatment. This paper is an edited version of a recent *Effective Health Care* bulletin, Vol 4, No 1, February 1998, which considers whether cholesterol screening is worthwhile and examines the effectiveness and cost effectiveness of the statins and a range of other interventions to reduce CHD. It aims to provide a summary of the research evidence which can be used to establish cost effective policies.

This topic was covered in a previous issue of *Effective Health Care*.^{3,4} However, since then a new class of cholesterol lowering drugs—the statins—has been developed and evaluated. The expenditure on statin drugs in England was over £20 million in 1993 and by 1997 had risen to over £113 million.

The average concentration of blood cholesterol within a population is an important determinant of the risk of CHD in the population. In countries where the average cholesterol concentrations of the population are low, CHD tends to be uncommon. Prospective studies show that groups of people with lower concentrations of cholesterol run less risk of developing CHD. The association between cholesterol concentration and future risk of CHD is graded and continuous: there is no threshold above which CHD risk begins to increase. There has been some concern that low concentrations of blood cholesterol increase the risk of mortality from causes other than CHD, including cancer, respiratory disease, liver disease, and accidental or violent death.

Several studies have now shown that this mostly, or entirely, is due to the fact that people with low cholesterol concentrations include a disproportionate number whose cholesterol has been reduced by illness—early cancer, respiratory disease, gastrointestinal disease, and alcoholism, among others.⁵⁻⁷ Thus it seems to be the pre-existing disease which causes both the low cholesterol and raised mortality.⁸

Differences in mean concentrations of blood cholesterol between communities or populations are largely determined by differences in diet. Countries with high dietary saturated fat intake and a low ratio of polyunsaturated to saturated fatty acids have high mean cholesterol concentrations.⁹ Randomised controlled trials (RCTs) in institutional settings show that if components of the diets of individuals are changed substantially then large changes in blood cholesterol concentrations can be achieved.¹⁰ Animal experiments and metabolic ward studies carried out over half a century show that we should not be surprised by substantial declines in cholesterol concentration in someone who is locked in a room and fed lettuce. The results of trials of externally regulated dietary intake have, inappropriately, been taken to be directly translatable into public health terms. Understanding what can be achieved in real life settings by dietary intervention requires studies of dietary changes capable of being sustained by ordinary people leading normal lives.

Although blood cholesterol is an important risk factor, by itself it is a relatively poor predictor of who will go on to have a CHD event. Figure 1 shows the relation between blood cholesterol and CHD rates in British men; only 42% of those who will have an event over 15 years have blood cholesterol over 6.5 mmol/l. This is further illustrated in figure 2 which shows that the distribution of blood cholesterol in British men aged 40–59 who subsequently went on to have CHD and those who did not overlaps considerably.

Other major independent risk factors (smoking, high blood pressure, diabetes, physical inactivity, and obesity) also exist and should be considered in defining individual risk of CHD. Figure 3 shows the importance of considering risk factors together. Smokers with high blood pressure have three times the risk of dying of

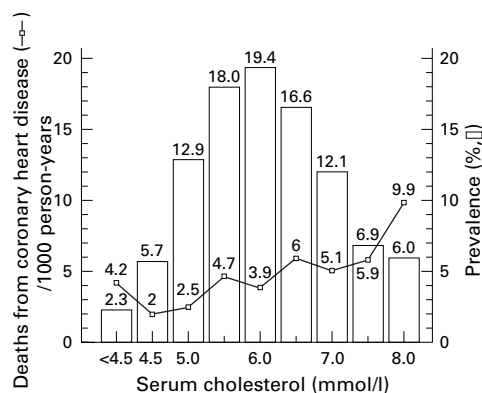


Figure 1 Coronary heart disease events and cholesterol concentration.

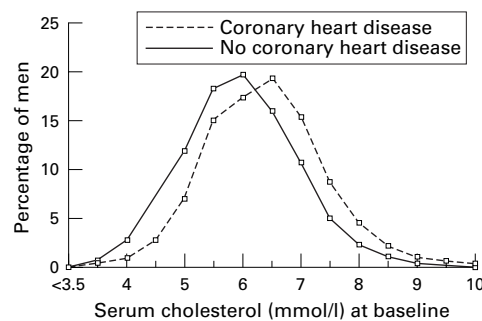


Figure 2 Blood cholesterol in British men aged 40–59 and coronary heart disease events.

CHD compared with non-smokers with low blood pressure when both have the same concentration of blood cholesterol. Risk scoring systems developed from the British Regional Heart Study were no more accurate in predicting who had coronary heart disease with blood cholesterol included than without, highlighting the importance of these other major risk factors.¹¹

Detecting raised cholesterol

The main screening test for blood cholesterol is the measurement of total blood cholesterol in blood samples obtained by either venepuncture or finger prick. Cholesterol measurements may not accurately reflect the true cholesterol concentration due to measurement error (bias and imprecision) and natural biological variation in cholesterol concentrations within a person. These sources of error can result in misclassification and lead to the incorrect diagnosis and the possibility of unnecessary treatment.

Measurement error can be the result of bias (the degree to which a reading systematically differs from a gold standard or reference value) or imprecision (where measurements are subject to random measurement error). There is considerable evidence that different laboratory analysers can give different readings for the same blood sample.¹² For example, a United Kingdom study found that laboratory equipment systematically overestimated cholesterol concentrations by over 4% at the cut off of 7.8 mmol/l.¹³ This would result in a 50% increase in the number of people tested subsequently being recommended for treatment. Bias can be reduced in laboratory equipment by regular calibration against a standard, and precision increased with good equipment and repeat analyses.

The increasing use of compact measuring devices such as desk top analysers in general practitioners' surgeries and their spread to high street chemist and health food stores, is of potential concern. They are less accurate,^{14 15} making it difficult to distinguish confidently between people with raised and normal cholesterol concentrations,¹⁶ and are less amenable to national initiatives for quality assurance. Studies of the use of such analysers in general practice suggest that quality control is a major problem due to lack of time, poor technique, and the use of outdated test strips.^{17 18} Availability of analysers was associated with a three-fold increase in cholesterol estimation, although the value of this extra information was not assessed.¹⁹

Even when evaluated in optimal conditions the performance of some machines has been inadequate,²⁰ although more recent disposable devices have achieved reasonable accuracy and precision.²¹ Home cholesterol testing kits with such disposable devices, which have not been evaluated under the circumstances for which they are marketed, are unlikely to perform well.²²

In any person the blood cholesterol concentration is not constant over time. This random biological variation is quite large and results in considerable misclassification. Estimates of variation within a person show a coefficient of variation for measurements made 1 year apart of 7% which is large compared with the coefficient of variation between people of 15%. In British men, the implication of this biological variation is that 28% of men classified as

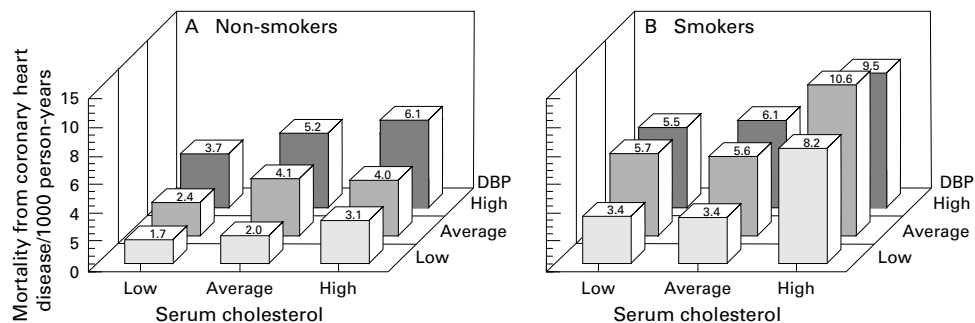


Figure 3 Mortality from coronary heart disease in British men related to blood cholesterol, diastolic blood pressure, and smoking.

having a raised blood cholesterol on a single testing will have a normal long term blood cholesterol.²³ To reduce misclassification several (at least two) measurements should be made separated by a few weeks, and clinical decisions should be based on the mean of several readings rather than a single measurement.

EFFECT OF SCREENING ON CHOLESTEROL CONCENTRATIONS

Early enthusiasm in the United States for a patient centred approach—the “know your number” campaign—resulted in many people being screened and given dietary advice. However, evidence from randomised controlled trials in the United States and Britain show that untargeted screening of the general population coupled with dietary advice have little effect on cholesterol concentrations.^{24–26}

OTHER EFFECTS OF SCREENING

Screening—either large scale or opportunistically—is never entirely without the risk of harm. Knowledge of the presence of a risk factor may result in people who previously felt well thinking that they are sick, as has been found in hypertension.^{27–28} Only limited evidence from case studies is available to determine the potential influence of blood cholesterol screening on labelling, and showed similar effects to those seen in hypertension.²⁹ However, a trial and a before-after study did not show any adverse effects.^{30–31}

Another possible adverse effect of population cholesterol screening is that being informed that one’s cholesterol concentration is normal may result in adverse lifestyle choices, so interfering with the general public health strategies. An Australian study showed that most (61%) people who had their blood cholesterol tested by case finding were unwilling to make dietary changes to their fat intakes on the grounds that their cholesterol concentrations were “all right”.³²

Cholesterol lowering interventions

Cholesterol concentrations can be lowered by several types of interventions, diet and drugs being the most important.

Diet

Changes in individual dietary intake of saturated fats and cholesterol have been studied extensively (table 1). The effectiveness of low fat diets depends critically on how restrictive they are and the degree of adherence. In settings where patients’ diets are controlled by others—such as in metabolic wards—where adherence to diets is likely to be high, dietary changes have produced substantial reductions in blood cholesterol.¹⁰ However, studies in the general population have shown only small changes in cholesterol.^{33–36} These studies suggest that the extent of cholesterol reduction which may be expected from recommending lipid lowering diets is likely to be very small (1–5%)^{35–36} and the effect on clinical events has been shown to be disappointing (OR=0.96; 95% CI 0.89 to 1.04).³⁷

Table 1 The effect of lipid lowering diets in reducing blood cholesterol concentrations

	Blood cholesterol reduction (mmol/l (%))
Multiple risk factor intervention trials ³⁴	0.14 (2)
Dietary interventions:	
General population:	
Brunner <i>et al</i> ³⁵	0.22 (3)
Tang <i>et al</i> ³⁶	0.31 (5)
Including high risk:	
Ebrahim and Davey Smith ³⁷	0.65 (9)

The effects of dietary interventions used alone after myocardial infarction showed a greater fall in blood cholesterol than the other dietary trials,³⁷ probably because the participants were more motivated to follow strict diets or lived in institutions where control over diet was much greater. However, despite the greater fall in blood cholesterol, the meta-analysis failed to find any significant reduction in risk of CHD mortality (RR 0.94; 95% CI 0.84 to 1.06).³⁷

The generally poor performance of some lipid lowering diets may be partly explained by the fact that they often substitute complex carbohydrates for total fat resulting in a reduction in both HDL as well as LDL cholesterol. This reduces total cholesterol but leaves the LDL/HDL ratio unaffected and so may not reduce the risk of CHD.¹⁰ This highlights the fact that the real aim should be to lower the risk of CHD rather than focusing on lowering serum cholesterol concentrations by themselves.

A systematic review of trials suggested that garlic may exert a cholesterol lowering effect with falls of 0.65 mMol/l (95% CI 0.53 to 0.76) or around 10%.³⁸ However, some of the trials are severely flawed and, therefore, the evidence is not reliable. Systematic reviews of studies evaluating the effects of consuming oats³⁹ or psyllium enriched cereals⁴⁰ show a small cholesterol lowering effect of around 2%–5%. A meta-analysis of 38 trials of soy protein as a substitute for meat protein also showed a net fall in cholesterol of 0.60 mMol/l (95% CI 0.35 to 0.85), which was greater in people with high baseline cholesterol concentrations.⁴¹ However, all these dietary trials were of relatively short duration and did not consider clinical end points. Therefore, there is no evidence that they lower the risk of CHD.

Drugs

THE STATINS

Over the past few years a new class of more powerful cholesterol lowering drugs—the statins (HMG CoA reductase inhibitors)—has become available. These are able to reduce LDL cholesterol concentrations by more than 20%. A total of 22 published RCTs of cholesterol lowering in which clinical outcomes were recorded were identified for the bulletin and their results pooled to give an overall estimate of treatment effect. Overall, these trials show that statins reduce the risk of CHD mortality by around 25% (table 2). The trials which contributed most to the pooled estimates were the West of Scotland coronary prevention study

Table 2 Summary of major trials of statins

Trial	CHD death rate*	Patient group	Treatment	Follow up (y)	Sex (mean age or range)	Number T/C	Baseline cholesterol	Total: CHD mortality OR (95% CI)
WOSCOPS (1995) ⁴⁹	3.8	No CHD evidence cholesterol: ≥ 6.5 mmol/l	Pravastatin 40 mg v placebo	4.9	Men only (55)	3302 v 3293	7.03	0.78 (0.60 to 1.00); 0.67 (0.45 to 0.99)
4S trial (1994) ⁵⁰	15.7	Post MI or angina, cholesterol: 5.5–8.0 mmol/l	Simvastatin 20–40 mg v placebo	5.4	Men 81% (60)	2221 v 2223	6.74	0.70 (0.58 to 0.85); 0.58 (0.46 to 0.73)
CARE (1996) ⁵¹	11.5	Post MI 3–20 mths cholesterol: < 6.2 mmol/l	Pravastatin 40 mg v placebo	5.0	Men 86% (59)	2081 v 2078	5.40	0.91 (0.74 to 1.12); 0.80 (0.61 to 1.05)
LIPID (1997) ⁵²	13.8	Post MI/unstable angina 3–36 mths, cholesterol: 4.0–7.0 mmol/l	Pravastatin 40 mg v placebo	6.0	M 83% (31–75)	4512 v 4502	5.60	0.76 (0.67 to 0.86); 0.75 (0.64 to 0.88)

*Control group CHD deaths/1000 patient-years.

CHD=coronary heart disease; MI=myocardial infarction; T=treatment group; C=control group.

(WOSCOPS),⁴² the Scandinavian Simvastatin survival study (4S),⁴³ the cholesterol and recurrent events (CARE) trial,⁴⁴ and the recently reported long term intervention with pravastatin in ischaemic disease (LIPID) trial.⁴⁵

STATINS COMPARED WITH OTHER CHOLESTEROL LOWERING DRUGS

The efficacy (relative risk) of statins in primary and secondary prevention is summarised for a range of end points in table 3. For comparative purposes similar information for fibrates (clofibrate and bezafibrate) is also given. Older drugs—for example, fibrates—are not as effective as the newer statins in lowering blood cholesterol and in reducing rates of CHD events. The overall efficacy of older cholesterol lowering drugs is strongly related to the baseline level of risk of coronary heart disease. In high risk populations ($>3\%$ annual CHD death rate), treatment benefits outweigh treatment risk whereas in lower risk populations there is no place for these older drugs, which may do harm.⁴⁶

Further important trial results are awaited which seem likely to extend the range of indications for use of statins. The latest trial to report was the Air Force/Texas coronary atherosclerosis prevention study of lovastatin in 6605 people (15% women) with no evidence of coronary heart disease and with average blood cholesterol concentrations. This trial was stopped early after finding a 36% reduction in a combined fatal and non-fatal CHD end point (study published subsequent to the publication of the *Effective Health Care* bulletin) mainly due to reductions in the rates of revascularisation.⁴⁷

Pravastatin and simvastatin seem to be equally effective in reducing the rates of CHD events. Interestingly in the AF/TexCAPS trial neither total mortality nor CHD mortality were reduced by lovastatin treatment (table 3). However, less data from large scale trials are currently available for fluvastatin, atorvastatin,

and cerivastatin and consequently their clinical efficacy is not yet established, although they lower LDL cholesterol to an extent similar to or greater than other statins.

A meta-analysis of the recently published data on women from the 4S,⁴⁸ LIPID study (preliminary data), CARE study, AF/TexCAPS,⁴⁷ and pooled data from several pravastatin trials⁴⁹ shows that if both fatal and non-fatal coronary heart disease events are considered, women have an on treatment relative risk of 0.70 (95% CI 0.60 to 0.81), which is similar to men (no significant interaction effect for sexes $p=0.45$). A report of an increased risk of breast cancer among treated women in the CARE study was not confirmed in the 4S or the LIPID studies. The pooled results from the four major studies show no association with breast cancer (RR 1.2; 95% CI 0.66 to 2.13).

Statin treatment in older people is as effective as in middle aged adults. The subgroup analyses of those aged ≥ 55 and ≥ 65 years within individual trials have reported risk reductions at least as good as, if not better than, those among younger participants. Pooling of these subgroup analyses from the major statin trials (CARE, 4S, WOSCOPS, AF/TexCAPS pooled pravastatin trials), shows a relative risk of combined fatal and non-fatal CHD events of 0.73 (95% CI 0.67 to 0.80) for older people. People in their late 70s and 80s, although obviously at increased absolute risk of coronary heart disease, have not been studied in the recent statin trials. Treating people in this age group with statins must, therefore, remain a matter of clinical judgement until the anti-hypertensive, lipid lowering after heart attack trial (ALLHAT), which is examining the efficacy of statin treatment in older people, reports in 2002.

Non-cholesterol lowering alternatives

Cholesterol lowering is only part of the repertoire of possible effective interventions to reduce the risk of CHD and not necessarily the most important. The risk of CHD can also be significantly reduced by changes in lifestyle—for example, stopping smoking, exercise, and the use of non-cholesterol lowering diets) and drug treatments—for example, to lower blood pressure, β blockers after a myocardial infarction, and aspirin). The effectiveness of these

Table 3 The relative efficacy of treatment with drugs that lower cholesterol*

	Primary prevention with statins	Secondary prevention with statins	Secondary prevention with fibrates
Total mortality	0.77 (0.60 to 0.99)	0.79 (0.73 to 0.86)	0.97 (0.90 to 1.05)
CHD mortality	0.68 (0.46 to 1.00)	0.74 (0.66 to 0.83)	0.93 (0.85 to 1.01)
Non-fatal MI	0.68 (0.56 to 0.84)	0.70 (0.61 to 0.80)	0.57 (0.28 to 1.11)
Net cholesterol lowering (%)	20	21	9.5

*Figures are pooled relative risk estimates (95% CI).

Table 4 Relative treatment effects for alternative treatments

Treatment	Relative risk (95% CI)
Primary prevention:	
Smoking advice ⁵⁰	0.99 (0.98 to 1.0)
Nicotine replacement ⁵⁰	0.98 (0.98 to 0.99)
Aspirin ⁶⁰	0.98(0.78 to 1.18)*
Antihypertensive drugs: ^{62 63}	
<60 y	0.79 (0.71 to 0.87)
≥60 y	0.75 (0.64 to 0.88)
Statins	0.68 (0.46 to 1.00)
Secondary prevention:	
Aspirin ⁶⁰	0.82 (0.76 to 0.88)
β Blockers ⁶⁴	0.78 (0.71 to 0.87)
Statins	0.74 (0.66 to 0.83)
Smoking advice ⁵¹	0.68(0.57 to 0.79)
Oily fish ⁵²	0.65 (0.5 to 0.9)
Mediterranean diet ^{53 54}	0.24 (0.1 to 0.8)

*Not significant effect of treatment.

non-cholesterol lowering alternatives is briefly summarised here and in table 4.

Advice on stopping smoking, given in primary care settings, has a small but important effect on long term behaviour. Pooled estimates from 188 trials show that around 2% (95% CI 1% to 3%) of those given personal advice during one routine consultation stopped smoking and did not relapse up to 1 year later.⁵⁰ The use of nicotine gum increases the stop rates to about 4% (95% CI 2% to 6%). This will lead to about a 1%–2% overall reduction in mortality and morbidity. The effect is much larger in those who stop, but only a small percentage stop with simple advice.

Advice to stop smoking is much more effective among those people who have had a myocardial infarction, with up to 36% stopping.⁵¹ This results in over a 30% reduction in the risk of mortality.

Increased intake of oily fish has been shown to reduce cardiovascular mortality after heart attack without reducing cholesterol concentrations (RR 0.6 95% CI 0.5 to 0.9). In the DART trial⁵² 22% of participants did not like oily fish and consequently were given maxepa supplements. Significant reductions in CHD were also found in a trial of Mediterranean diet in people after myocardial infarction, which also had no effect on cholesterol concentrations (RR 0.24 95% CI 0.1 to 0.8).^{53 54} The most prominent change in the intervention group was an increase in consumption of α -linolenic acid from rape seed margarine (used as the participants found it difficult to consume high intakes of olive oil). The striking findings of the trials of oily fish and Mediterranean diet certainly require replication, and if substantiated, these diets would have an important role in reducing mortality after myocardial infarction. The effect of these interventions in people at low risk of CHD is not known.

Lack of physical activity has been shown to be a strong independent risk factor for death from CHD.⁵⁵ It is estimated that a sedentary lifestyle doubles the risk of mortality from CHD. However, there are no reliable trials examining the impact on survival of interventions solely aimed at promoting exercise and there is considerable debate about the level or intensity of exercise which confers cardiovascular benefit.⁵⁶ A recent review found that a proportion of patients did respond positively to

exercise advice given in a primary care setting.⁵⁷ A computer simulation based on the epidemiological evidence of the association between exercise and mortality from CHD has estimated that if the proportion of the population undertaking moderate activity were increased by 25%, the number of life-years gained would be similar to a 2% reduction in the proportion of smokers.⁵⁸

Trials of interventions for multiple risk factors for primary prevention in workplace settings and primary care show very small and non-significant effects on mortality from CHD (RR 0.96; 95% CI 0.89 to 1.04).^{34 59} This is probably due to poor adherence to non-pharmacological interventions, the use of drugs which may have had adverse effects, and the variable quality of the programmes.

Evidence from trials of rehabilitation after myocardial infarction are also relevant as many of these included stopping smoking together with increases in physical activity. Trials that attempted to modify several risk factors, including smoking, and not just increased physical activity, showed reductions in mortality from CHD (RR 0.63; 95% CI 0.51 to 0.80) and total mortality (RR 0.77; 95% CI 0.64 to 0.94).³⁷ The absolute levels of mortality from CHD in these trials were of the order of 4% a year in the control group, giving a number needed to treat of about 13 people for 5 years to avoid one CHD death.

In primary prevention aspirin does not reduce all cause mortality significantly.⁶⁰ However, the participants in both of the large primary prevention trials were physicians—a group at very low risk of CHD. Aspirin seems to reduce mortality among people who have not yet experienced a myocardial infarction but who are at high risk of such an event—for example, unstable angina, stable angina, and peripheral vascular disease.^{60 61}

Systematic reviews of RCTs show that for people with high blood pressure anti-hypertensive medication reduces the risk of CHD and all cause mortality^{62 63} including people after myocardial infarction.⁶⁵

To help develop the most efficient policies for reduction of CHD, the relative cost effectiveness of these options was estimated. The results are given in the next section, and more details can be obtained from the *Effective Health Care* bulletin and associated *Health Technology Assessment Report*.

Cost effectiveness

The cost effectiveness estimates of various interventions based on a life table model developed by the University of Sheffield are shown in table 5. As the cost per life-year gained is influenced by the level of risk of the patients being treated, the values in table 5 were calculated for a group of patients with the same average risk of CHD events of 3% a year to aid comparison.

The costs per life-year gained in primary and secondary prevention with statins are very similar to previous estimates based on the WOSCOPS trial⁶⁶ and by the 4S investigators⁶⁷ suggesting that the methods used are valid.

Table 5 Costs per year of life gained (£PLYG) for a range of different interventions in patients with an absolute baseline risk of CHD events of 3%/y in primary prevention or secondary prevention after myocardial infarction

	£PLYG, gross (95% CI)	£PLYG, net
Drug interventions:		
Statins:		
Simvastatin 27 mg/day (1.37p/day)	£8240 (£6220 to 11280)	£7240
Antihypertensive drugs (bendrofluazide 2.5 mg, 0.1p/day):*		
Middle aged	£70 (£40 to 130)	£580 (saved)
Elderly†	£45 (£30 to 180)	£870 (saved)
Antihypertensive drugs (combined regimen of bendrofluazide, atenolol, enalapril, 53 p/day):*		
Middle aged	£1501 (£940 to 3050)	£860
Aspirin (300 mg/day, ‡0.5 p/day)*	£50 (£30 to 320)	£407 (saved)
Aspirin (150 mg) + dipyridamole (400 mg, 24p/day)*	£2800 (£1500 to 17080)	£2340
β Blockers (atenolol 50 mg, 3.8 p/day)*	£230 (£170 to 410)	£130
Dietary interventions:*		
Fish diet, advice only (£41/year)	£560 (£330 to 2220)	£610
Fish diet + 20 mg maxepa/week (£57/year)	£780 (£460 to 3110)	£830
Mediterranean diet (£52/year)	£290 (£200 to 1980)	£180

CHD=coronary heart disease; PLYG=per life-year gained. Figures are £ (1998) PLYG with discounting of costs and benefits at 6% for patients with an absolute baseline risk of CHD events of 3%/y. Net costs take into account projected savings from reduced admissions and treatment for clinical events avoided.

*No data on revascularisation procedures avoided by treatment, hence potential savings are underestimated.

†CHD event rate for elderly people was derived from trials and was equivalent to 4.5%/y.

‡Aspirin dose used in postmyocardial infarction trials was 1.2 g/day but current practice would favour a lower dose.

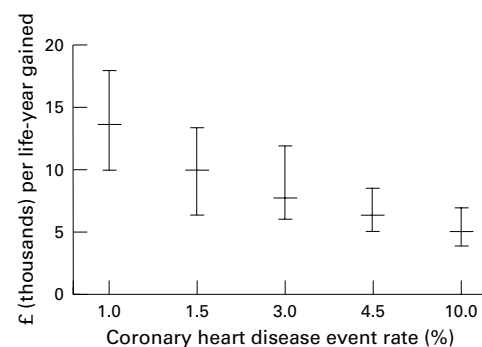


Figure 4 Cost per life-year gained with statins by initial risk of coronary heart disease.

The final column in table 5 shows the net cost per life-year gained which takes into account potential savings due to avoiding CHD events and associated costs of treatment and admissions to hospital. For example, analyses of the 4S trial data showed that hospital costs among the simvastatin treated group were 32% lower than the placebo group,⁶⁸ and that almost 90% of the drug costs were off-set by savings in hospital admissions.⁶⁹ However, because the rates of revascularisation in the United Kingdom are lower than in Scandinavia (where the trial was carried out), the savings are unlikely to be as great. However, more effective treatment of people at high risk of CHD events may reduce pressure for increasing the rates of revascularisation.

Because the baseline level of risk of CHD has a major impact on the absolute effect or impact of interventions it should be taken into account when deciding who should receive which treatment. This is illustrated in figure 4 which shows how the cost of achieving an extra year of life increase as people with lower initial risk of CHD are treated. A recent economic evaluation of lipid lowering in primary care in patients with moderately increased risk doubted whether drug treatment as primary prevention is cost effective.⁷⁰

The data in table 5 provide comparable cost effectiveness estimates for a range of interventions. It can be seen that several other interventions are more cost effective than stat-

ins. Interventions that stop smoking have also been shown to be highly cost effective. The costs per life saved are low and have been estimated to be about £500 per life-year gained.⁷¹ The additional cost per life-year gained of brief counselling or the use of nicotine substitutes—for example, gum—over and above brief advice, is about £2500 if costs to smokers as well as the NHS are taken into account.

If more people at increased risk of CHD were appropriately treated with aspirin and antihypertensive drugs, helped to stop smoking, and changed their diet, then many (possibly over half) would have their risk of CHD sufficiently reduced to make statin treatment unnecessary or relatively cost ineffective.⁷²

The net cost per life-year gained with statins of around £7 000 (for patients with an annual risk of a CHD event of about 3%) compares favourably with several other interventions currently provided by the NHS, including those in the management of coronary heart disease. If a patient is still at sufficiently high risk after using other more cost effective options, the use of a statin may be appropriate. If the different statins are equally efficacious and safe then the use of the drugs with lowest cost per percentage reduction in cholesterol would seem to be preferable.

Implications

Universal cholesterol screening is unlikely to be cost effective because treatment to reduce risk factors is most cost effective when targeted at people who are at high risk of CHD events and most people who are at high risk will have a combination of easily detectable risk factors—for example, smoking, high blood pressure, or physical inactivity. The concentration of cholesterol by itself is generally too poor a predictor of CHD. Finally, cholesterol lowering confers considerable benefits to people who are at high risk of CHD even if they have average concentrations of cholesterol by British standards.

By focusing too heavily on concentrations of cholesterol it is likely that a considerable proportion of those at high risk would be missed and that treatment could be offered to people who are not at high risk but who have

moderately increased cholesterol concentrations. It is probably only worth measuring cholesterol in patients who have either a strong family history of CHD or other easily identifiable risk factors, and to monitor serum lipid changes in patients on cholesterol lowering treatments or diets.

In people with cardiovascular disease or diabetes, who are at high risk of CHD events, the evidence for the effectiveness of statins is strong. However, the cost per life-year gained is high compared with some other drug treatments and lifestyle changes, which may produce net savings of healthcare resources. It is of concern, therefore, that people who might benefit from treatment after myocardial infarction are not being treated. A recent survey of hospitals in the United Kingdom showed that secondary prevention in patients at high risk of mortality from CHD because of a history of a coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or acute myocardial infarction was highly variable and that many risk factors remained unmanaged.⁷³ This shows the considerable potential for the cost effective reduction of risks in patients with established coronary disease. A first priority must be to ensure that appropriately targeted interventions that are clearly more cost effective are used in practice. Cost effective considerations mean that statins should only be used for people who are at high risk after using other, more cost effective, interventions (table 5).

The level of risk of CHD above which it is decided that the use of statins is sufficiently cost effective as to justify routine use, however, is not a technical issue but a question of policy. This depends on the valuation of treatment benefits, the resources available, and the cost effectiveness of alternative uses of those resources. Various scoring systems are available to help estimate a person's overall risk of CHD—such as the Sheffield tables.^{74 75} However, they all have weakness and they do not take into account the increased risk associated with certain ethnic groups—for example, south Asians—or low socioeconomic status. Research is needed to develop and evaluate an easy to use and more accurate risk formula which can be used in primary care not only to calculate risk but to assess the likely effect of modifying risk factors for each patient. This will also make it possible for patients to make informed decisions on the basis of individual and valid estimates of their risk and trade offs with benefits of different interventions.⁷⁶

This paper is based on work funded in part by the NHS Health Technology Assessment programme.

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