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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

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Cholesterol and coronary heart disease: screening and treatment

- Despite the declining coronary heart disease (CHD) mortality rate, CHD remains a major cause of premature death and imposes high personal, social and economic costs.
- Blood cholesterol is an important risk factor for CHD but should be considered in the context of other risk factors such as smoking, raised blood pressure and physical inactivity.
- Blood cholesterol alone is a relatively poor predictor of individual CHD risk. The majority of CHD events occur in people with average or low blood cholesterol levels. Consequently, cholesterol screening is unlikely to reduce mortality and can be misleading or even harmful.
- Cholesterol lowering using statins is effective at reducing CHD mortality and morbidity. Therapy should be targeted at people who are at high risk of coronary heart disease rather than be based upon cholesterol levels. In asymptomatic people, at low risk of coronary heart disease, the costs of cholesterol lowering using statins are high relative to the benefits and their use is contentious.
- Cholesterol lowering is one of a number of methods of reducing the risk of cardiovascular disease. The cost-effectiveness of some anti-hypertensives, aspirin and beta-blockers is greater than statins.
- Greater priority should be given to the appropriate use of other drug treatments and non-pharmacological interventions in the primary and secondary prevention of coronary heart disease.

The contents of this bulletin are likely to be valid for around one year, by which time significant new research evidence may have become available.

A. Coronary heart disease

A.1 The importance of CHD: CHD is a major cause of morbidity and mortality in the UK, accounting for just under one quarter of all deaths in 1995: 27% among men and 21% among women.[1] While many CHD deaths occur among elderly people, CHD accounts for 31% of male and 13% of female deaths within the 45–64 age group.

CHD leads to obstruction of blood flow through the coronary arteries to the heart muscle, due to atherosclerosis (fibro-fatty deposits) and associated blood clots. This can lead to sudden death, heart attack (myocardial infarction) which may be fatal, angina or heart failure.

CHD imposes high social costs, including impaired quality of life and reduced economic activity. A large share of NHS resources are also accounted for by CHD.[2] However, CHD rates have been declining in the UK for almost 20 years (Fig. 1) and this needs to be taken into account when making projections of the population benefits flowing from interventions to reduce CHD such as cholesterol lowering. Declining CHD mortality rates are only partly explained by reductions in established cardiovascular risk factors[3, 4, 5] and it is probable that general social and economic improvement over time has contributed to this trend.[6] However, it is noteworthy that these benefits have not been observed in the lowest socio-economic groups.[7]

Because of the importance of CHD, considerable effort has been made to identify the major risk factors associated with the disease and to modify them by drugs, lifestyle and environmental change in order to prevent CHD occuring (primary prevention) or preventing death or (further) coronary events in people with established disease (secondary prevention). One approach to disease prevention requires identification of people at high risk of CHD and the subsequent application of interventions which will reduce their risk factors. Such targeted strategies require efficient means of identifying those at highest risk and effective interventions once they have been identified.

In contrast, a population approach focuses more on trying to reduce levels of risk factors in the population as a whole. The logic here is that even though CHD risk for any individual may be lowered by only a small amount, the population effect could be substantial because so many people are affected. Furthermore, a large percentage of events occur in people who are at only average risk and who would otherwise be missed by approaches targeted at those at high risk. Public health policy is based on a combination of population and targeted approaches.

One CHD risk factor is serum cholesterol. Much attention has been focused on screening people to identify those with raised cholesterol levels and then trying to lower these levels through diet and/or medical treatment. This topic was covered in a previous issue of *Effective Health Care*.[8] However, since then a new class of cholesterol lowering drugs – the statins – has been developed and evaluated.

The expenditure on statin drugs was over £20 million in 1993 and by 1997 had risen to over £113 million (Fig. 2). Expenditure on other lipid-lowering drugs is still increasing but at a much slower rate and in 1997 amounted to £21 million, resulting in a total of £134 million.

This bulletin 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 for reducing CHD.

A.2 Cholesterol and other risk factors: Cholesterol is a fatty substance which is manufactured in the body – particularly in the

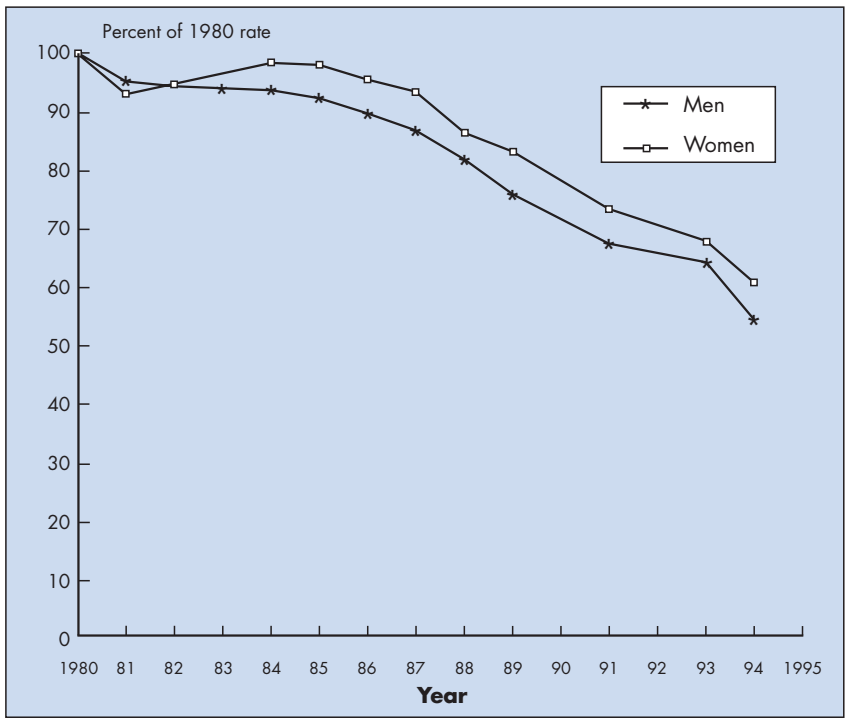

Fig. 1 CHD death rate as a percentage of 1980 rate among men and women aged 55–64 years, England & Wales, 1980–1995

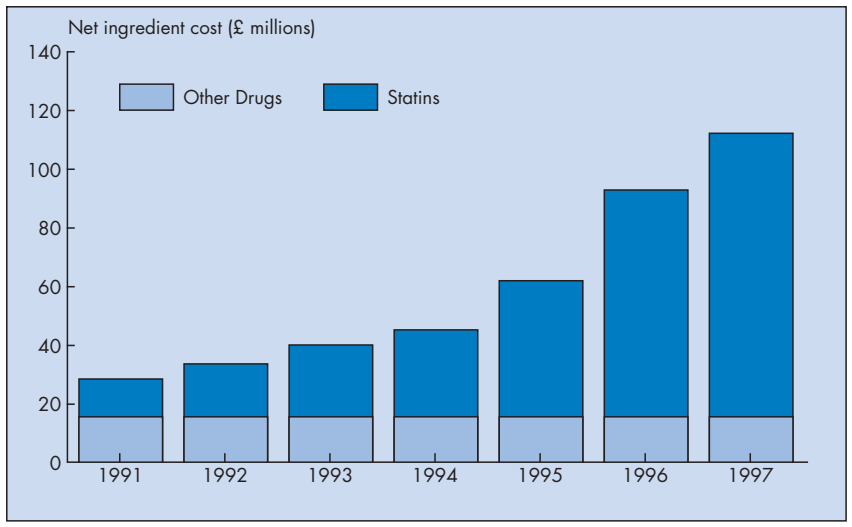

Fig. 2 Prescribing trends for cholesterol lowering drugs in England, 1993–1997
Source: Department of Health, Statistics Division 1E, Prescription Cost Analysis system

liver – and plays a vital role in the functioning of cell membranes. Cholesterol is found in several forms in the body and, when bound to proteins, forms lipoproteins. Cholesterol and other fatty blood components are often referred to collectively as 'blood lipids'.

Blood lipids can be divided into different fractions or components: low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol and triglycerides. High levels of LDL and low levels of HDL are associated with increased risk of CHD. The ratio of plasma total (or LDL) cholesterol to HDL cholesterol is often used in risk calculations. The higher the ratio the higher the CHD risk.

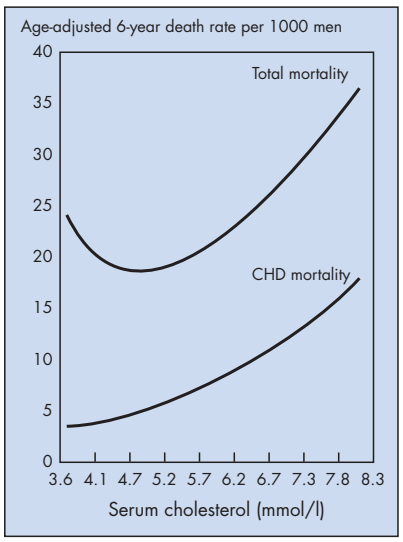

Fig. 3 Age-adjusted 6-year CHD and total mortality per 1,000 men screened for MRFIT according to serum cholesterol

The average level of blood cholesterol within a population is an important determinant of the CHD risk of the population. In countries where the average cholesterol levels of the population are low, CHD tends to be uncommon. Prospective studies show that groups of individuals with lower levels of cholesterol run less risk of developing CHD. The association between cholesterol level and future risk of CHD is graded and continuous: there is no threshold above which CHD risk begins to increase (Fig. 3).

There has been some concern that low levels of blood cholesterol increase the risk of mortality from causes other than CHD, including cancer, respiratory disease, liver disease and accidental/violent death. Fig. 3 shows a U-shaped curve in which men with the lowest cholesterol levels have higher rates of total mortality than men with higher (but still well below average) levels. Several studies have now demonstrated that this phenomenon is mostly, or entirely, due to the fact that this group of people with low cholesterol levels includes a disproportionate number whose cholesterol has been reduced by illness – early cancer, respiratory disease, gastrointestinal disease and alcoholism, among others.[9, 10, 11] Thus it is the pre-existing disease which causes both the low cholesterol and raised mortality and not the low cholesterol levels themselves which produce the elevated mortality rates.[12]

Differences in average levels 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 average cholesterol levels.[13] Randomised controlled trials (RCTs) in institutional settings demonstrate that if components of the diets of individuals are changed substantially then large changes in blood cholesterol levels can be achieved.[14]

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. Fig. 4 shows the relationship between blood cholesterol and CHD rates in British men; only 42% of those who will suffer an event over 15-years have blood cholesterol over 6.5 mmol/l. This is further illustrated in Fig. 5 which shows that the distribution of blood cholesterol in British men aged 40–59 who subsequently went on to suffer from CHD and in those who did not, overlap considerably.

Other major independent risk factors (e.g. smoking, high blood pressure, diabetes, physical inactivity, and obesity) also exist and should be considered in defining individual risk of CHD. Fig. 6 shows the importance of considering risk factors together. Smokers with high blood pressure have three times the risk of dying of CHD compared to non-smokers with low blood pressure where both have the same level of blood cholesterol. Risk scoring systems developed from the British Regional Heart Study were no more accurate in predicting who suffered from coronary heart disease with blood cholesterol

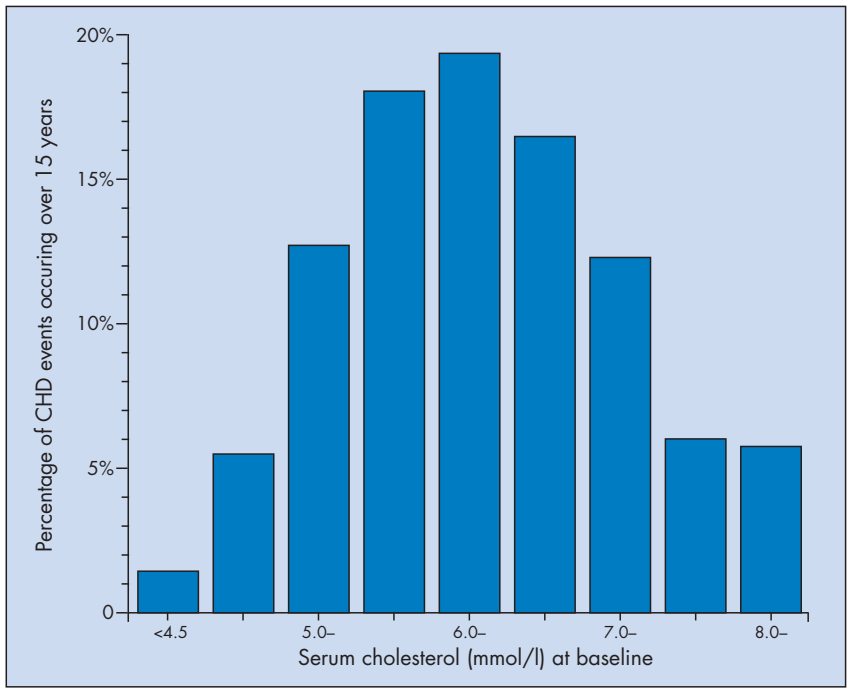

Fig. 4 Blood cholesterol distribution and percentage of CHD events occuring at each level over 15 years follow up Source: British Regional Heart Study

included than without, highlighting the importance of these other major risk factors.[15]

B. Detecting raised cholesterol

Cholesterol screening may be done either by testing the entire adult population or by making use of routine contacts in primary health care (opportunistic screening). Both these methods are essentially untargeted, giving equal priority to both high and low CHD risk individuals. In a recent survey two-thirds of British general practitioners said they offered some form of cholesterol testing.[16] In England, the Health Survey shows that 28% of people aged 45–64 have had their blood cholesterol measured in the last 3 years.[17]

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 level due to measurement error (bias and imprecision) and natural biological variation in cholesterol levels within an individual. These sources of error can result in misclassification and lead to incorrect diagnosis and the possibility of unnecessary treatment.

B.1 Measurement error: 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.[18] For example, a UK study found that laboratory equipment systematically overestimated cholesterol levels by over 4% at the cut off of 7.8 mmol/l.[19] 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 by using good equipment and repeat analyses. A National Initiative on Cholesterol Accuracy, Methods and Standardisation has been launched which aims to improve the standardisation of cholesterol measurement.

The increasing use of compact measuring devices such as desk top analysers in GP surgeries and their spread to high street chemist and health food stores, is of potential concern. They are less accurate,[20, 21, 22] making it difficult to distinguish confidently between people with raised and normal cholesterol levels,[23] 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.[24,25]

Availability of analysers was associated with a three-fold increase in cholesterol estimation, although the value of this extra information was not assessed.[26]

Even when evaluated in optimal conditions the performance of some machines has been inadequate,[27] although more recent disposable devices have achieved reasonable accuracy and precision.[28] Home cholesterol testing kits using such disposable devices, which have not been evaluated under the circumstances for which they are marketed, are unlikely to perform well.[29]

B.2 Biological variability: In any individual the blood cholesterol concentration is not constant over time. This random biological variation is quite large and results in considerable misclassification. Estimates of within-person variation show a coefficient of variation for measurements made one-year apart of 7% which is large compared with the between-person coefficient of variation of 15%. In British men, the implication of this biological variation is that 28% of men classified as having a raised blood

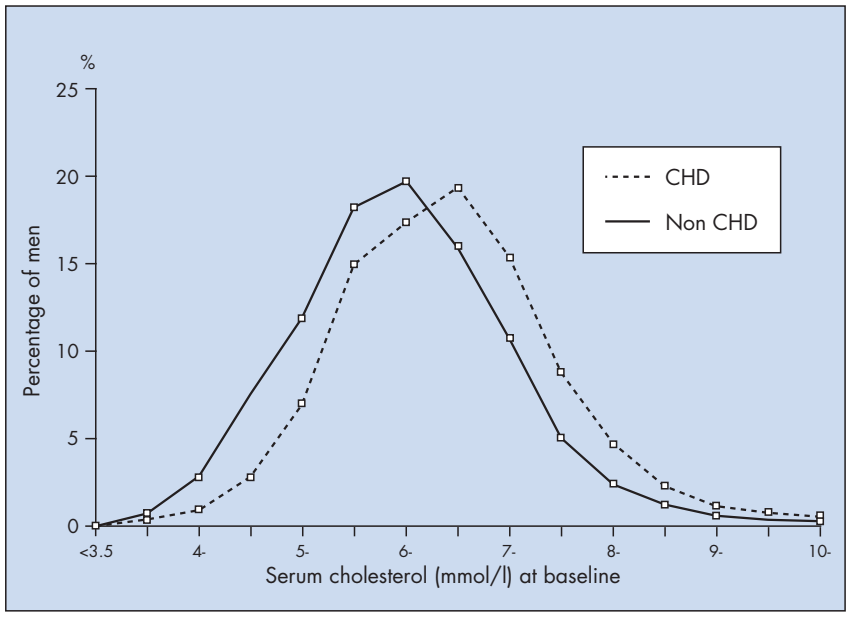

Fig. 5 Distributions of blood cholesterol among British men who did and did not develop coronary heart disease over 15 years follow up Source: British Regional Heart Study

cholesterol on a single testing will have a normal long-term blood cholesterol.[30] In order to reduce misclassification several (at least two) measurements should be made separated by a few weeks, and clinical decisions should be based upon the average of several readings rather than a single measurement.

B.3 Effect of screening on cholesterol levels: 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 RCT's in the USA and Britain show that untargeted general population screening coupled with dietary advice have little effect on cholesterol levels.[31, 32, 33]

An Australian study demonstrated that the majority (61%) of 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 levels were all right. This suggests that screening may interfere with general public health strategies to reduce the dietary fat intake of the whole population.[34]

B.4 Other effects of screening: Screening, either by mass approaches 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 behaving as if they were sick (adopting a sick role) with adverse consequences for the individual and society. It is also possible that knowledge of the absence of a risk factor may result in adverse life-style choices.

It has been shown that classifying people as 'suffering with hypertension' is associated with increased sickness absence and adoption of the sick role – a labelling phenomenon.[35] The negative effects of labelling people as hypertensive have not been found in all studies and it has been suggested that professional support, individualised care and follow up, and attention to compliance-improving strategies, may overcome adverse labelling effects.[36] Only limited evidence is available to determine the potential influence of blood cholesterol screening on labelling with case studies showing similar effects to those seen in hypertension.[37] However, a trial and a before–after study failed to demonstrate any adverse effects.[38, 39]

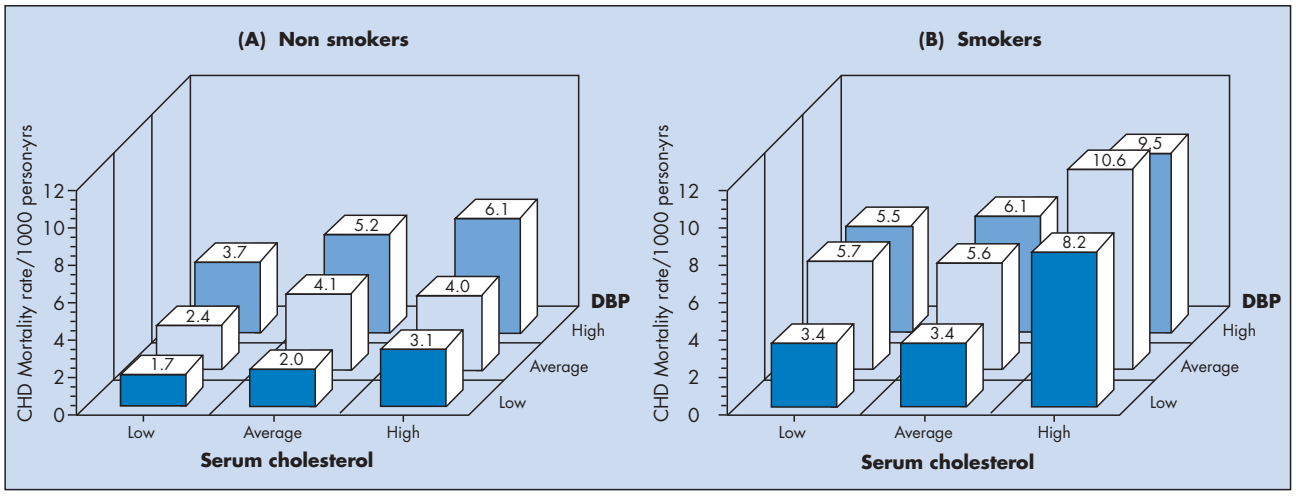

Fig. 6 CHD mortality among British men according to their levels of blood cholesterol, diastolic blood pressure and smoking behaviour

C. Cholesterol lowering interventions

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

Diet

C.1 Low fat diets: Changes in individual dietary intake of saturated fats and cholesterol have been studied extensively (Table 1). The effectiveness of low fat diets depend 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 can be expected to produce substantial reductions in blood cholesterol, though no clinical event data have been reported.[14] However, studies in the general population have shown only small changes in cholesterol.[40] 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%), and the effect on clinical events has been shown to be disappointing (OR = 0.96; 95% CI: 0.89 – 1.04).[41]

The effects of dietary interventions used alone following myocardial infarction demonstrated a greater fall in blood cholesterol than the other dietary trials,[44] 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 CHD mortality risk reduction (RR = 0.94; 95% CI: 0.84 – 1.06).[44]

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.[43] This reduces total cholesterol but leaves the more important LDL/HDL ratio unaffected and so does not reduce CHD risk.[14] This highlights the fact that the real aim should be to lower CHD risk rather than focusing on lowering serum cholesterol levels *per se*, which is relatively ineffective.

C.2 Garlic, oats and soy protein: 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 – 0.76) or around 10%.[45] However, some of the trials are severely flawed and, therefore, the evidence is not reliable. Systematic reviews of studies evaluating the effects of consuming oats[46] or psyllium-enriched cereals[47] show a small cholesterol lowering effect of around 2–5% respectively. A meta-analysis of 38 trials of soy protein as a substitute for meat protein also demonstrated a net fall in cholesterol of 0.60 mmol/l (95% CI: 0.35 - 0.85), which was greater in people with high baseline cholesterol levels.[48]

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

	Blood cholesterol reduction (percent)	
Multiple risk factor intervention trials[41]	0.14mmol/l	(2%)
Dietary interventions		
(i) general population		
Brunner[42]	0.22mmol/l	(3%)
(ii) including high risk		
Ebrahim & Davey Smith[44]	0.65mmol/l	(9%)

However, all these dietary trials were of relatively short duration and did not consider clinical endpoints. Therefore there is no evidence that they lower CHD risk.

Drugs

C.3 The statins: Over the last few years a new class of more powerful cholesterol lowering drugs – the statins (HMG CoA reductase inhibitors) – has become available which is able to reduce LDL cholesterol levels by more than 20%.

A total of 22 published RCTs of cholesterol lowering in which clinical outcomes were recorded were identified 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% (see Table 2). The trials which contributed most to the pooled estimates were the West of Scotland Coronary Prevention Study (WOSCOPS),[49] the Scandanavian Simvastatin Survival Study (4S),[50] the Cholesterol and Recurrent Events (CARE) trial,[51] and the recently reported Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial.[52]

C4. Statins compared to other cholesterol lowering drugs: The efficacy (relative risk) of statins in primary and secondary prevention is summarised for a range of endpoints in Table 3. For comparative purposes similar information for fibrates (clofibrate and bezafibrate) is also given.

Older drugs (e.g. fibrates) are not as effective as the newer statins in lowering blood cholesterol and in reducing CHD event rates. The overall efficacy of older cholesterol lowering drugs is strongly related to the baseline level of coronary heart disease risk. 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.[53]

Table 2 Summary of major trials of statins

Trial	CHD death rate*	Patient group	Treatment	Follow up (yr.)	Sex (mean age)	Number T/C	Base-line CHO	Total/CHD mortality odds ratio (95% CI)
WOSCOPS (1995)[49]	3.8	No CHD evidence cho: 6.5+mmol/l	Pravastatin 40mg vs placebo	4.9	Men only (55)	3302 vs 3293	7.03	0.78 (0.60–1.00) 0.67 (0.45–0.99)
4S trial (1994)[50]	15.7	Post MI or angina, cho: 5.5–8.0mmol/l	Simvastatin 20–40mg vs placebo	5.4	Men 81% (60)	2221 vs 2223	6.74	0.69 (0.56–0.84) 0.75 (0.64–0.88)
CARE (1996)[51]	11.5	Post MI 3–20 mths cho: <6.2mmol/l	Pravastatin 40mg vs placebo	5.0	Men 86% (59)	2081 vs 2078	5.40	0.91 (0.74–1.12) 0.80 (0.61–1.05)
LIPID (1997)[52]	13.8	Post MI/ unstable angina 3– 36 mths, cho: 4.0–7.0mmol/l	Pravastatin 40mg vs placebo	6.0	Men 83% (31–75)	4512 vs 4502	5.60	0.76 (0.67–0.86) 0.75 (0.64–0.88)

* Control group CHD mortality rate per 1000 patient years; CHO = cholesterol level T = Treatment group C = control group

Pravastatin and simvastatin appear to be equally effective in reducing CHD event rates. However, less data from large scale trials are currently available for fluvastatin, atorvastatin and cerivastatin and consequently their clinical efficacy is not yet proven, although they lower LDL cholesterol to an extent similar to or greater than other statins.

Further important trial results are awaited which appear likely to extend the range of indications for use of statins. The next trial to report will be 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 levels. This trial was stopped early after finding a 36% reduction in a combined fatal and non-fatal CHD endpoint.[54]

C.5 Statins in women: The efficacy of statin treatment among women is less certain due to limited data.[55] A meta-analysis for this bulletin of the recently published data on women from the 4S,[56] LIPID study (preliminary data),[52] CARE study[51] and pooled data from several pravastatin trials[57] shows that if both fatal and non-fatal coronary heart disease events are considered, women have an on-treatment relative risk of 0.77 (95% CI: 0.64 – 0.92), which is similar to men (no significant interaction effect for gender $P=$ 0.46). 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 three studies shows no association with breast cancer (RR = 1.0; 95% CI: 0.44 – 2.24).

C.6 Statins and older people: Statin treatment in older people is as effective as in middle-aged adults. The sub-group 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 sub-group analyses from the major statin trials (CARE, 4S, WOSCOPS, pooled pravastatin trials) carried out for this bulletin, demonstrates a relative risk of combined fatal and non-fatal CHD events of 0.70 (95% CI: 0.62 – 0.79) for older people. People in their late 70s and 80s, while 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.

Table 3 The relative efficacy of treatment with cholesterol lowering drugs+

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

+ Figures are pooled relative risk estimates (95% confidence intervals).

D. Non-cholesterol lowering alternatives

Cholesterol lowering is only part of the repertoire of possible effective interventions to reduce CHD risk and not necessarily the most important. CHD risk can also be significantly reduced by changes in lifestyle (e.g. smoking cessation, exercise and the use of non-cholesterol lowering diets) and drug treatments (e.g. to lower

blood pressure, beta-blockers after a myocardial infarction (MI), and aspirin). A recent *Effective Health Care* bulletin on Stable Angina (1997, vol 3 no.5) reviewed the use of invasive treatments such as coronary artery bypass grafting (CABG) and angioplasty (PTCA).

D.1 Smoking cessation: Smoking cessation advice 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 – 3%) of those given personal advice during one routine consultation stopped smoking and did not relapse up to 1-year later.[58] The use of nicotine gum increases the quit rates to about 4% (95% CI: 2 - 6%). This will lead to approximately a 1 – 2% overall reduction in mortality and morbidity. The effect is much larger in those who quit, but only a small percentage quit with simple advice.

Advice to stop smoking is much more effective among those people who have suffered a myocardial infarction, with up to 36% stopping.[59] This results in over a 30% reduction in the mortality risk. The next issue of *Effectiveness Matters* published by the NHS Centre for Reviews and Dissemination will summarise reviews of the effectiveness of interventions to promote smoking cessation. A future *Effective Health Care* bulletin will examine the effectiveness of ways to prevent the uptake of smoking in young people.

D.2 Oily fish and Mediterranean diets: Increased intake of oily fish has been shown to reduce cardiovascular mortality after heart attack without reducing cholesterol levels (RR = 0.65 95% CI: 0.5–0.9). In the DART trial[60] 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 MI, which also had no effect on cholesterol levels (RR = 0.24 95% CI: 0.1–0.8).[61, 62] The most prominent change in the intervention group was an increase in consumption of alpha-linolenic acid from rapeseed 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 following myocardial infarction. The effect of these interventions in people at lower risk of CHD is not known.

D.3 Exercise: Lack of physical activity has been shown to be a strong independent risk factor for death from CHD.[63] It is estimated that a sedentary lifestyle doubles the risk of CHD mortality (95% CI: 1.6 – 2.2). 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.[64] A recent review found that a proportion of patients did respond positively to exercise advice given in a primary care setting.[65]

A computer simulation based on the epidemiological evidence of the association between exercise and CHD mortality 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.[66]

D.4 Multiple interventions: Trials of multiple risk factor interventions for primary prevention in workplace settings and primary care show very small and non-significant effects on CHD mortality (RR = 0.96; 95% CI: 0.89 – 1.04).[41] This is probably due to poor adherence to non-pharmacological interventions, the use of drugs which may have had adverse effects and generally, the variable quality of the programmes.

Evidence from trials of post-MI rehabilitation are also relevant as many of these included smoking cessation together with increases in physical activity. Trials that attempted to modify several risk factors, including smoking, and not just increase physical activity, showed reductions in CHD mortality (RR = 0.63; 95% CI: 0.51 – 0.80) and total mortality (RR = 0.77; 95% CI:.0.64 – 0.94).[44] The absolute levels of CHD mortality in these trials were of the order of 4% per year in the control group, giving a number needed to treat of about 13 people for 5 years to avoid one CHD death. A future *Effective Health Care* bulletin will provide a more comprehensive summary of the research evidence about cardiac rehabilitation.

D.5 Aspirin: In primary prevention aspirin does not reduce all-cause mortality significantly.[67] However, the participants in both of the large primary prevention trials were physicians – a group at very low risk of CHD. Aspirin appears to reduce mortality among people who have not yet had a heart attack but who are at high risk of such an event (e.g. unstable angina, stable angina and peripheral vascular disease).[68]

D.6 Lowering raised blood pressure and beta-blockers post MI: Systematic reviews of RCTs show that for people with high blood pressure, anti-hypertensive medication reduces the risk of CHD and all-cause mortality.[69]

Epidemiological studies among survivors of cardiovascular disease show that the relationship between blood pressure and both total and CHD mortality follows a U-shaped relationship. This has caused concern that treating high blood pressure following MI may cause, rather than prevent, mortality. However, new evidence shows that the poor prognosis in those with

Table 4 Relative treatment effects (ie. vascular deaths) and a number needed to treat for five years to avoid one event for alternative treatments for the prevention of coronary heart disease at a range of baseline levels of CHD risk.

Treatment	Relative risk (95% CI)	Number of people needed to treat for 5 years to avoid one event by their annual percent risk of CHD 0.1%	0.5%	1.5%	3.0%	4.0%	6.0%
Primary prevention							
Smoking advice[58]	0.99 (0.98–1.0)	20,000	4000	1333	666	500	333
Nicotine replacement[58]	0.98 (0.98–0.99)	10,000	2000	667	333	250	166
Aspirin[72]	0.98(0.78–1.18)*	10,000	**2000**	**667**	333	250	166
Anti-hypertensive drugs[67, 73, 74]							
<60 yrs	0.79 (0.71–0.87)	950	**190**	63	31	24	16
60+yrs	0.75 (0.64–0.88)	800	160	53	**26**	**20**	13
Statins	0.68 (0.46–1.00)	625	**125**	**41**	21	16	10
Secondary prevention							
Aspirin[72]	0.82 (0.76–0.88)	–	222	74	37	**28**	**18**
Beta-blockers[75]	0.78 (0.71–0.87)	–	181	61	30	23	**15**
Statins	0.74 (0.66–0.83)	–	154	51	**26**	**19**	13
Smoking advice[59]	0.68 (0.57–0.79)	–	125	42	21	16	10
Oily Fish[60]	0.65 (0.5–0.9)	–	114	38	19	14	**9**
Mediterranean diet[61, 62]	0.24 (0.1–0.8)	–	52	17	9	**7**	4

– Risk level too high for primary prevention or too low for secondary prevention
* Not a statistically significant treatment effect
NNTs in bold are those that equate to range of CHD event rates occuring in randomised controlled trials or meta-analysis

low blood pressure is due to damaged heart muscle and not the low blood pressure.[70] This evidence, taken in conjunction with the trials of beta-blockers conducted in post-myocardial infarction patients suggest that treatment is beneficial.[71, 76]

D.7 Numbers needed to treat: Table 4 presents some summary information on the potential effects of some of these interventions in terms of numbers needed to be treated (NNTs) for 5 years to avoid a vascular death. A range of different baseline risks is used to compare NNTs which correspond to the differences that might be expected in primary and secondary care settings among men and women.

The NNT for 5 years of different drug treatment options, shows considerable variation. Interventions generally considered to be worthwhile (aspirin for secondary prevention and anti-hypertensive treatment in older people) have NNTs rather greater than those for statins. The 5-year NNTs for smoking cessation advice are very high but are not strictly comparable with drug NNTs as treatment is very cheap, is only given once and the CHD events

Table 5 Costs per year of life gained (£PLYG) for a range of different interventions+

Drug interventions	£PLYG, gross (95% CI)	£PLYG, net
Statins		
- Simvastatin 27mg/day (1.37/day)	£8,240 (£6,220, 11,280)	£7,240
Anti-hypertensives (bendrofluazide 2.5mg, 0.1p/day)*		
- middle-aged	£ 70 (£ 40–130)	£ 580 (saved)
- elderly@	£ 45 (£ 30–180)	£ 870 (saved)
Anti-hypertensives (combined regimen of bendrofluazide, atenolol, enalapril, 53p/day)*		
- middle-aged	£1,510 (£940–3,050)	£ 860
Aspirin (300mg/day,# 0.5p/day)	*£ 50 (£ 30–320)	£ 407(saved)
Aspirin (150mg) + dipyridamole (400mg, 24p/day)*	£2,800 (£1,500–17,080)	£2,340
Beta-blockers (atenolol 50mg, 3.8p/day)*	£ 230 (£170–410)	£ 130
Dietary interventions*		
Fish diet, advice only (£41/yr)	£ 560 (£330–2,220)	£ 610
Fish diet + 20mg maxepa/week (£57/yr)	£ 780 (£460–3110)	£ 830
Mediterranean diet (£52/yr)	£ 290 (£200–1,980)	£ 180

+ Figures are £ (1998) per life year gained with discounting of costs and benefits at 6% for patients with an absolute baseline risk of CHD events of 3% per year.
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% per year.
# aspirin dose used in post myocardial infarction trials was 1.2gm/day but current practice would favour a lower dose.

prevented are counted over a lifetime rather than the 5-year period. Nonetheless, they provide some indication of the relative effects of different types of intervention. A better guide to policy however is provided by looking at the relative cost-effectiveness of these options.

E. Cost-effectiveness

E.1 The model: The cost-effectiveness estimates of various interventions based on a life table model developed by the University of Sheffield are shown in Table 5. More details on the methods used are given in the Appendix. The costs per life year gained in primary and secondary prevention with statins are very similar to previous estimates based on the WOSCOPS trial[77] and by the 4S investigators,[78] suggesting that the methods used in the Sheffield model are robust.

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 hospitalisation. For example, analyses of the 4S trial data showed that hospital costs among the simvastatin treated group were 32% lower than the placebo group,[79] and that almost 90% of the drug costs were off-set by savings in hospital admissions.[80] However, because the rates of revascularisation in the UK 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.

E.2 The importance of the level of CHD risk: The baseline level of CHD risk has a major impact on the absolute effect or impact of interventions and should therefore, be taken into account when deciding who should receive which treatment.[81] This is illustrated in Table 4 and Fig. 7 which show how the NNT and cost of achieving an extra year of life increase as people with lower initial CHD risk are treated. A recent economic evaluation of lipid lowering in primary care in patients with moderately raised risk doubted whether drug treatment as primary prevention is cost effective.[82]

E.3 Alternatives to cholesterol lowering: A major advantage of the analyses presented in Table 5 is that they provide comparable cost-effectiveness estimates for a range of interventions. This demonstrates that the role of cholesterol lowering drugs must be considered alongside other appropriate options. It can be seen that several other interventions are more cost-effective than using statins.

Smoking cessation interventions 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.[83] The additional cost per life year gained of brief counselling or the use of nicotine substitutes (e.g. gum), over and above brief advice, is approximately £2,500 if costs to smokers as well as the NHS are taken into account.

If more people at increased CHD risk were appropriately treated with aspirin and anti-hypertensive drugs, helped to stop smoking and change their diet, then a large number (possibly over half) would have their CHD risk sufficiently reduced to make statin treatment unnecessary or relatively cost-ineffective.[84]

E.4 Which statin: The net cost per life year gained with statins of around £7,000 (for patients with an annual CHD event risk of about 3%), though quite high, 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. In such cases one of the issues to be considered is which one to use.

Fig. 8 shows the cholesterol lowering effects of a range of statins, both as the total percentage reduction, and the annual average drug costs per percentage reduction for each drug, in LDL cholesterol.

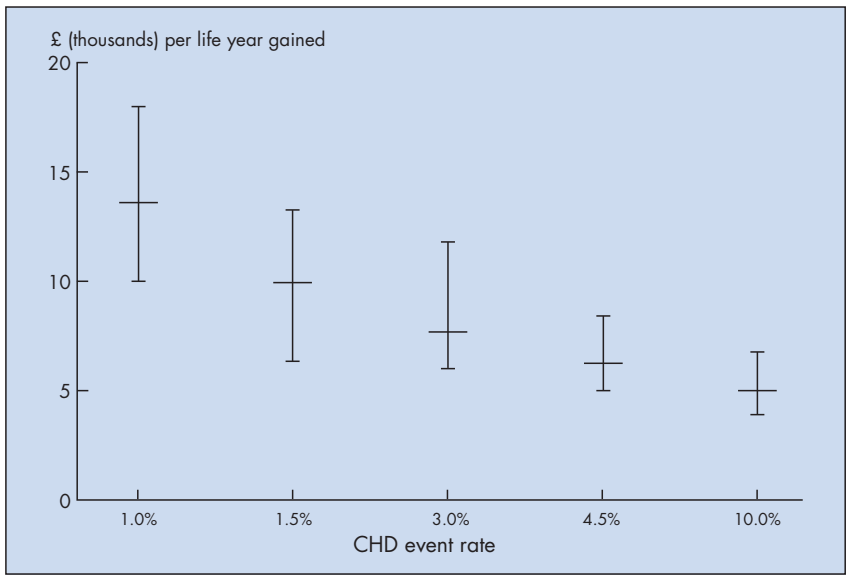

Fig. 7 Cost per life year gained with statins by initial CHD risk

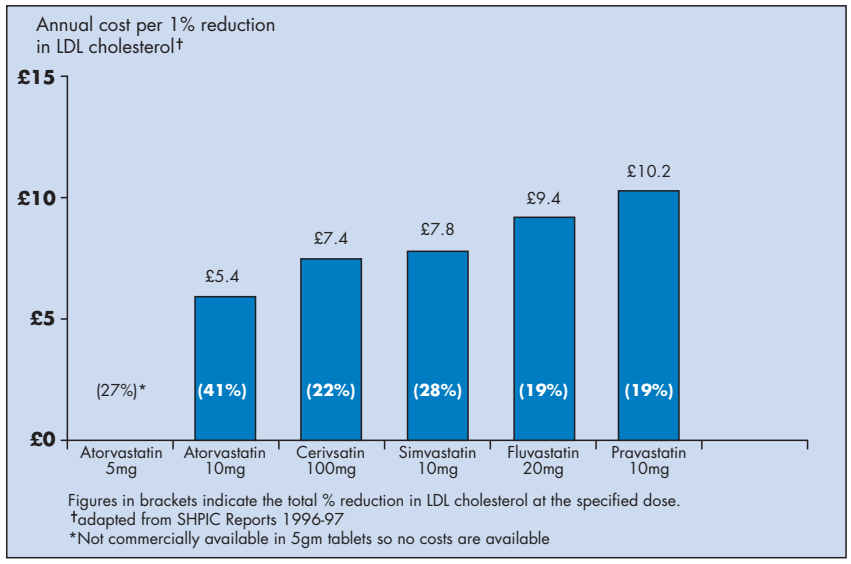

Fig. 8 Efficiency of Statins at lowering cholesterol

Atorvastatin is the most cost-effective way to reduce LDL cholesterol. Though the manufacturers recommend a 10mg starting dose, a 5mg dose, which has been shown to reduce LDL cholesterol by 29%,[85] would probably be more cost-effective.

If the different statins are equally efficacious and safe then those drugs having the lowest cost per percentage reduction in cholesterol would appear preferable. However, the only two statins sold in the UK which have been the subject of trials evaluating their effect on clinical outcomes (rather than just cholesterol levels) are simvastatin and pravastatin. Of these, simvastatin is more cost-effective.

Lovastatin has also been shown to produce clinical benefits. However, despite being used in the USA it is not licensed in the UK. Because its patent is due to expire soon, much cheaper generic forms of lovastatin may prove to be more cost-effective than other, branded, statins in countries where it is licensed. Therefore if Lovastatin were licensed in the UK considerable savings could be made.

Because the clinical effects of the cheaper statins have not been evaluated, the extent to which they will reduce CHD mortality and morbidity is uncertain. If their clinical effectiveness is significantly less than for simvastatin the cheaper statins would be less cost effective. Cost-effectiveness is sensitive to drug costs as well as clinical effects; if the price of simvastatin or pravastatin were to be significantly reduced, they would become the more cost-effective choice.

E.5 Population approaches: In population prevention the aim is to reduce the mean level of risk factors; this could result in a much greater overall benefit as well as reducing the prevalence of people at high risk in a population.[86] Estimates of the cost-effectiveness of population dietary interventions typified by the Stanford Five-City Project and Three-Community Study, and the North Karelia Study have been published recently.[87] These show, despite the very small cholesterol reductions achieved, a cost-effectiveness of around £2,000 per year of life gained. However, this work must be viewed with some caution as the estimates of benefit were derived from modelling the effect of cholesterol change on clinical events derived from observational studies, rather than RCTs. Meta-analysis of the available RCTs does not show evidence of clinical benefit.[41]

F. Implications

F.1 Screening: Universal cholesterol screening is unlikely to be cost-effective for the following reasons: treatment to reduce risk factors is most cost-effective when targeted at people who are at high risk of CHD events; most people who are at high risk will have a combination of easily detectable risk factors (e.g. smoking, high blood pressure or physical inactivity); the level of cholesterol by itself is generally too poor a predictor of coronary heart disease. Finally, cholesterol lowering confers significant benefits to people who are at high risk of CHD, even if they have average levels of cholesterol by British standards.

By focusing too heavily on levels of cholesterol it is likely that a significant proportion of those at high risk would be missed and that treatment could be offered to people who are not at significantly high risk but who have moderately elevated cholesterol levels. 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 in order to monitor serum lipid changes in patients on cholesterol lowering therapies or diets.

F.2 Cost-effective secondary prevention: 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 therapies and lifestyle changes, which may produce net savings of health care resources. It is of concern therefore, that people who might benefit from antiplatelet agents, beta-blockers following MI and treatment for hypertension are not receiving these treatments.

A recent survey of hospitals in the UK by the British Cardiac Society examined the extent to which

secondary prevention had been implemented in over 2,500 patients at high risk of CHD mortality because of a history of a CABG, PTCA, or acute MI.[88] This showed that the recording of risk factors in hospital notes was highly variable and that many risk factors remained unmanaged. For example, over 25% of patients remained hypertensive, up to 25% were still smokers, 75% remained obese, only one in three were taking beta-blockers after an MI and up to 20% of those with evidence of myocardial ischaemia were not taking aspirin at follow-up. This demonstrates 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.

F.3 Targeted use of statins in primary prevention: Cost-effectiveness considerations mean that statins should only be used for people who are at high risk after using other, more cost-effective, interventions (see Table 5). A similar, targeted risk approach has also been recommended for the management of raised blood pressure.[89] It should be noted that in older people baseline risk is significantly raised so a large percentage of people over 70 have an annual CHD event risk greater than 3%. It may not be desirable or cost-effective to use a single risk threshold irrespective of age. It may be more sensible in the case of older people to consider CHD risk over and above the average for people at the same age.

The level of CHD risk 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 within the NHS.

A recent statement by the Standing Medical Advisory Committee (SMAC) to health authorities and general practitioners on the use of statins recommended prioritising treatment for secondary prevention and noted that treating people with an annual risk of a CHD event of under 3% is unlikely to give value for money. The implications of this for the drug budget nationally and locally will depend on the degree to which lower priced statins are prescribed, and lower starting dosages followed by titration of dosages are used, the rates of case identification and compliance. If the decision to use statins were based on a threshold of a 3% annual coronary event risk, about 3.4% of those aged 35 to 69 in England (around 700,000 people) would be eligible for statins in addition to those who have had a CHD event.[90]

If used for people with CHD event risks below 3%, many more people would have to be treated for much less health gain than in secondary prevention. Widespread prescribing of statins would be very expensive for the NHS and represent poor value for money. However, pressure to treat people with statins at lower coronary event risk levels (e.g. 1.5 – 2% per year) is high and is likely to grow further. If the threshold for treatment is dropped to 1.5%, then almost 20% of people aged 35 to 69 would require primary prevention treatment, which in addition to the 5% who might benefit from statins for secondary prevention, would result in almost 5 million people requiring treatment.

Various scoring systems are available to help estimate an individuals overall CHD risk. One of the best known is the Sheffield Tables,[91] which are simple to use and can help clinicians make treatment decisions on the basis of CHD risk. These tables probably under-estimate the risk of CHD and the benefits of treatment with statins in people with diabetes[92, 93] and, in common with other scoring systems, do not take into account the increased risk associated with certain ethnic groups (e.g. South Asians) or low socio-economic class. Research is needed to develop and evaluate an easy to use and more accurate risk formula which can be used on a primary care computer system not only to calculate risk but to assess the likely effect of modifying risk factors for each patient.

F.4 Patient choice: One component generally missing in CHD prevention practice and policy is the views of patients. It is possible that some patients will prefer to make lifestyle changes than accept lifelong drug treatment. Methods which permit the discussion of a patient's risk and the effects of interventions other than cholesterol lowering to be emphasised both to the doctor and patient may have advantages.[94] Research on patient preferences for different treatment options is required.

Conclusion

There is a need to distinguish population from clinical strategies for the primary prevention of coronary heart disease. Pressing primary care clinicians into providing general dietary advice to a large proportion of their patients is of limited value.[95] In clinical terms, the most important issue is to concentrate on secondary prevention and to reserve drugs, such as statins, for those at high risk of disease following the management of other risk factors.

In public health terms, the major approaches to lowering population levels of risk factors remain the control of tobacco, reducing levels of hidden fats and calories in the diet, and encouraging and extending facilities available for physical activity throughout life.

Appendix: Methods used in the cost-effectiveness model

The cost-effectiveness estimates shown in Table 5 were produced for this *Effective Health Care* bulletin by the University of Sheffield using the life table method.[96] Particular attention was paid to the calculation of life-years gained, the calculation of costs of interventions and the savings produced by the interventions.

Calculation of life-years gained: The estimates of efficacy of interventions used were obtained from meta-analyses. Since the dietary trials of oily fish and of a Mediterranean diet have not been replicated however, data from the individual trials have been used to evaluate cost effectiveness.

The annual probability of dying at any age was calculated from age-specific mortality rates for men in the UK population provided by the Government Actuary's Department. The data on mortality of men on placebo during the years of the trial were used to determine the ratio of mortality in the placebo group to that of men of the equivalent average age in the UK general population. This ratio was assumed to remain constant for life. The annual probability of dying in any given year in the cohort treated with the drug or other intervention was calculated by multiplying the annual probability in the placebo cohort by the relative risk of all-cause mortality observed for treated men in the relevant trial or group of trials. Again this was assumed to remain constant for life.

The survival curves for placebo and treated patients were used to calculate life-years gained (LYG) with treatment by extrapolating the survival curves beyond the end of the trials, assuming that treatment would be lifelong. The Sheffield model therefore makes more optimistic (and realistic) estimates of the duration of benefit continuing for the rest of the life expectancy of the participant, rather than truncating treatment effects and survival at 10 years as in other models.[97]

In order to allow for the downward secular trends in coronary heart disease and all-cause mortality, the absolute benefits of treatment for earlier trials have been adjusted by 1% per annum on the basis of a fall of 2% per year for men in all-cause mortality since 1980.

Calculation of costs and savings: The total drug costs were calculated as the number of treatment years multiplied by the annual cost of drugs per patient. For each trial or set of trials examined, the cost per life-year gained was estimated assuming treatment with drugs at the average dose used in the relevant trial. Drug costs were taken from the British National Formulary. Excluded were any costs relating to medical, nursing or laboratory services.

Dietary interventions were assessed using data provided by the Dart (Oily Fish) and 'Mediterranean diet' studies. Costs for clinical nursing and dietician time were taken from Netton and Dutton's work on the costs of community care.[98]

For all the dietary estimates, the cost of changes in diet were assumed to be cost neutral as substitution of dietary items led to reductions in usually consumed food. The estimates for the 'oily fish and maxepa' are based on the costs of giving 22% of people supplements at the dose described in the DART trial. For all the dietary interventions, costs are based on the dietician (and doctor) visits described in the trials and the assumption was made that these visits were repeated throughout the duration of treatment. These assumptions make the comparison between dietary and drug interventions fairer than if it were assumed that the intervention was only given once (or for the period of the trial) and then stopped.

It should be noted that the costs for the diets themselves are borne by the patients rather than the health service. They are thus qualitatively different from the costs for the pharmacological interventions. Implicitly, the perspective of the evaluation is not the same and these costs are, therefore, not directly comparable with other cost-effectiveness estimates produced here.

Drug costs for treating hypertension are based on bendrofluazide which is one of the least expensive drugs available and for a more costly combination of drugs. The use of the much more expensive antiplatelet agents as well as aspirin is also included.

Cost-effectiveness may be calculated as *gross* cost per life-year gained, which ignores any savings to the health service, or *net*, which takes account of savings which may accrue. In many trials the rate of MI, CABGs and PTCAs are reduced by treatment, and a corresponding reduction in hospital admissions is expected. Health service savings on procedures and admissions may offset some or all of the costs of drug treatment. The costs used were: CABG, £5,725; PTCA, £2,436 (where trial data combine CABG and PTCA numbers we have assumed 75% CABG and 25% PTCA); admission for MI, £2,306; and admission for stroke, £8,823. These costings were applied to events as reported in the relevant trials.

Comparisons of net costs made between different prevention options may be less reliable as data on revascularisation procedures avoided were not available for all of the interventions. Thus the figures in the last column of Table 5 will tend to overestimate the net costs per life-year gained with anti-hypertensive drugs, aspirin and beta-blockers, and dietary interventions. However, these drug treatments show overall cost savings despite lack of data on potential savings due to avoided treatment.

Costs and benefits occuring in the future may be valued less than those occuring now. The cost-effectiveness estimates were therefore calculated using a 6% per annum discount rate for drug costs, potential savings and life-years gained, as recommended for public expenditure by the UK Treasury.

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