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Review

What role for statins? A review and economic model

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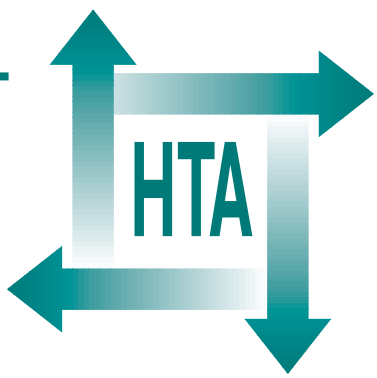
Health Technology Assessment
NHS R&D HTA Programme



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What role for statins? A review and economic model

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The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Pharmaceutical Panel and funded as project number 96/14/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature but the term has a constant meaning throughout this review.

Glossary

Discounting reducing the costs and benefits of treatment by a fixed annual amount to take account of declining value of assets over time.

Gross cost cost without taking potential savings to the NHS into account.

Net cost cost taking potential savings to the NHS into account.

Primary prevention treatments used in people without clinical evidence of cardiovascular disease.

Revascularisation coronary artery bypass graft or percutaneous transluminal coronary angioplasty.

Secondary prevention treatments used in people with evidence of cardiovascular disease.

List of abbreviations

4S	Scandinavian Simvastatin Survival Study
ACE	angiotensin-converting enzyme*
AFCAPS/ TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
BP	blood pressure*
CABG	coronary artery bypass graft
CARE	Cholesterol and Recurrent Events (trial)
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease*
DART	Diet and Reinfarction Trial
DBP	diastolic blood pressure*
df	degrees of freedom*
HDL	high density lipoprotein
ICD	International Classification of Diseases
LDL	low density lipoprotein
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease (trial)
MI	myocardial infarction*
NA	not applicable*
NNT(s)	number(s) needed to be treated
OR	odds ratio
PAD	peripheral artery disease*
PTCA	percutaneous transluminal coronary angioplasty
py	patient-years*
RCT	randomised controlled trial
RR	relative risk
TIA	transient ischaemic attack*
WOSCOPS	West of Scotland Coronary Prevention Study

* Used only in tables and figures

Executive summary

Background

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the UK. The social and health service costs are large, and CHD prevention remains a government high priority. The major preventative approach is the modification of common risk factors (tobacco smoking, high blood pressure, physical inactivity, unhealthy diet and high blood cholesterol). The statins are a new class of drugs that lower blood cholesterol. This review systematically examines the evidence for statins in the light of existing treatments and provides cost-effectiveness estimates for statins and other treatments.

Objectives

This review aimed to answer the following questions.

- By how much do low fat and other diets reduce blood cholesterol, and how effective are they in reducing CHD risk?
- Does treatment with statins reduce CHD events and are relative reductions in these events independent of the level of CHD risk?
- How effective are non-cholesterol lowering drug treatments for reducing CHD risk relative to dietary and cholesterol lowering drug treatments?
- What is the relative cost-effectiveness of different approaches to reducing cholesterol and/or CHD?

Methods

Data sources

A search of MEDLINE citations from 1993 to November 1997 was made using the standard randomised controlled trial (RCT) and meta-analysis filters. The references obtained, together with information supplied by investigators working in the field of cholesterol lowering, were used to compile a list of statin trials.

Study selection

The review included RCTs with ≥ 6 months follow-up in which clinical event outcomes were measured.

Data extraction and synthesis

A data abstraction form was developed. Effect sizes were estimated using the statistical computer package META97 and further analysis was conducted with the EGRET package using logistic regression models. Heterogeneity in fixed effects models was investigated by sensitivity analyses.

Estimates of statin effectiveness were made from pooled data. Effects of other CHD prevention treatments were taken from published meta-analyses and individual RCTs. Cost-effectiveness analyses were performed using a life-table approach which calculated the years of survival expected with and without treatment. Costs were direct costs of drugs and health service costs and were considered as gross and net (i.e. not taking account and taking account of potential NHS savings, respectively) and were presented as discounted and undiscounted. Costs per life-year gained were used as the cost-effectiveness index.

Results

Five major trials of statins were identified. Data from these and from another 18 RCTs demonstrated significant reductions in CHD events. In secondary prevention (i.e. prevention among people with evidence of cardiovascular diseases) the relative reductions in total and CHD mortality were 21% (95% CI, 14–27%) and 26% (95% CI, 17–34%), respectively. There were similar reductions for non-fatal myocardial infarctions and greater reductions for combined end-points (including revascularisation end-points). In primary prevention (i.e. among people without evidence of cardiovascular disease) there were significant reductions for combined end-points and non-fatal myocardial infarction, but not for total and CHD mortality. The primary prevention trials were too small to have adequate power to detect effects on mortality outcomes alone. Statins are effective across a wide range of levels of blood cholesterol, including levels considered normal in the UK.

Other treatments that reduce CHD risk were considered in this review. For primary prevention these were advice on smoking cessation, nicotine

replacement and antihypertensive drugs; other treatments considered for secondary prevention were advice on smoking cessation, aspirin, beta-blockers, oily fish diet and Mediterranean diet. Except for smoking interventions, these treatments have numbers needed to treat that are broadly similar to those for statins.

The cost-effectiveness of statins depends on the cost of the statin used and the CHD risk in the population treated. Gross, discounted estimates based on CHD risk in the trials considered ranged from £5400 to £13,300 per life-year gained at levels of risk expected in primary prevention, and from £3800 to £9300 at levels of risk consistent with secondary prevention. Use of low cost statins had the potential to reduce gross costs by 60%.

The cost-effectiveness of other treatments was much better than for statins. Gross discounted cost per life-year saved of aspirin (£53), bendrofluazide treatment for elderly people with hypertension (£45), low cost mixed drug antihypertensive regimens for middle-aged people (£1509), beta-blockers following myocardial infarction (£227) and Mediterranean diet following myocardial infarction (£293) were all lower than for statins.

Conclusions

Implications for health care

The evidence on efficacy supports the use of statins over a wide range of CHD risks covering both primary and secondary prevention. Although statins are less cost-effective than other treatments, there is consensus that their use in secondary prevention is acceptable because they achieve effects additional to those of other treatments. However, there is evidence that these other treatments are insufficiently used in the UK and that greater efforts are required to ensure that highly cost-effective treatments are used optimally.

The limited cost-effectiveness of statins in primary prevention indicates that their indiscriminate use might be a poor use of resources. Cost-effectiveness clearly improves with increasing baseline CHD risk. Scoring systems and guidelines have been developed to measure individual risk: most of these assume that 3% annual CHD risk marks the threshold between cost-effective and cost-ineffective use of statins. However, these scoring systems and guidelines have major weaknesses because they are derived from American data that are now out of date, and they do not consider variations between regional, ethnic or socio-economic groups.

The price of statins is a major determinant of their relative cost-effectiveness: lower cost statins are available and their use would improve cost-effectiveness to the levels of low cost anti-hypertensive regimens. As the price of drugs is agreed by the Department of Health, there may be a case for further examining the prices of statins, given the very large potential market for these drugs in primary prevention. Targeting statin treatment at people aged 55 years and older would further improve cost-effectiveness.

In public health terms, the major approaches to the primary prevention of CHD remain the fiscal and legislative control of tobacco, the reduction of hidden saturated fats and calories in the diet, encouraging and extending facilities available for physical activity throughout life, and the reduction of levels of poverty.

Recommendations for research

Areas of further research, which would help inform policy and practice in CHD prevention, include the following.

- Trials to examine the long-term effects of dietary modification with the oily fish or Mediterranean diet, both of which show promise but require stronger evidence of effect.
- Studies of the effects of different types of statin, and of the effects of statins in people aged 75 years and older.
- Continued surveillance of statin-treated patients for long-term adverse effects.
- Investigation of the translation of the effects of treatments found in trials to routine clinical practice.
- Evaluation of CHD risk prediction scoring systems in clinical practice (which will require longitudinal follow-up of patients to compare predicted and observed event rates) and the effects of risk scoring systems on professional and patient behaviour, risk levels and outcomes.
- Investigation of patient preferences (and their determinants) for specific types of treatment (e.g. drugs versus lifestyle modification) in primary and secondary prevention.

Chapter 1
Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the UK, accounting for just under one quarter of all deaths in 1996: 28% among men and 18% among women.[1] Although many CHD deaths occur among elderly people, CHD accounts for the deaths of 31% of men and 13% of women aged 45–64 years.

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] 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 dietary modifications with or without medical treatment.

A previous review found that medical approaches to lowering cholesterol achieved a reduction in all-cause mortality only among patients with a high initial overall risk of death from CHD. It was estimated that a net benefit was achieved only in people with a greater than 3% chance of dying from CHD over the next year.[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 it had risen to over £113 million.[5]

This report examines the effectiveness and cost-effectiveness of the statins and a range of other interventions in reducing CHD. It aims to provide a summary of the research evidence which can be used to establish cost-effective prevention policies.

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. 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. Several studies have now demonstrated that this is mostly, or entirely, due to the fact that people with low cholesterol levels include a disproportionate number whose cholesterol has been reduced by illness – early cancer, respiratory disease, gastrointestinal disease and alcoholism, among others.[6–8] Thus it appears to be the pre-existing disease which causes both the low cholesterol and raised mortality.[9]

Differences in average levels of blood cholesterol between communities or populations are largely determined by differences in diet. In countries where diets have high levels of saturated fat and a low ratio of polyunsaturated to saturated fatty acids are associated with high average blood cholesterol levels.[9]

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 relationship between blood cholesterol and CHD rates in British men; only 42% of those who will suffer an event over 15 years have a blood cholesterol level higher than 6.5 mmol/litre. This is further illustrated in *Figure 2*, which shows that in British men aged 40–59 years there is considerable overlap between the distribution of blood cholesterol concentrations in those who subsequently went on to suffer from CHD and the distribution in those who did not.

Other major independent risk factors (e.g. tobacco smoking, high blood pressure, diabetes, physical inactivity, familial hypercholesterolaemia and obesity) also exist and should be considered in defining individual risk of CHD. *Figure 3* shows the importance of considering risk factors together. At the same levels of blood cholesterol, tobacco smokers with high blood pressure have three times the risk of dying of CHD compared with non-smokers with low blood pressure. The importance of these other major risk factors is highlighted by the finding that risk scoring

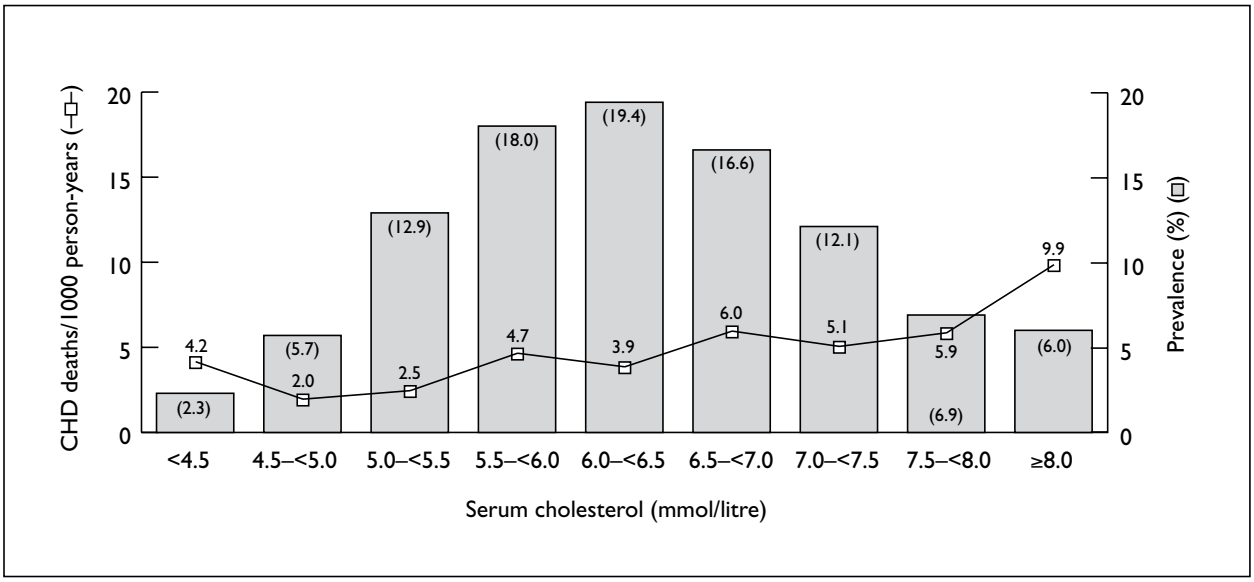

FIGURE 1 *Blood cholesterol distribution and percentage of CHD events occurring at each level over 15 years follow-up. Source: British Regional Heart Study*

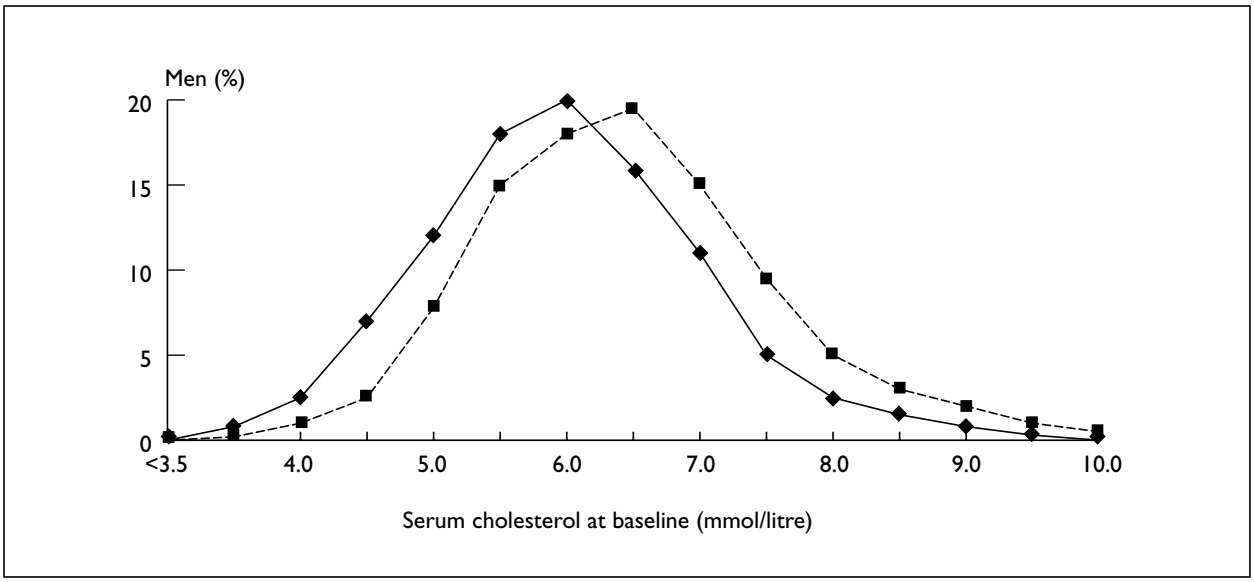

FIGURE 2 *Distribution of blood cholesterol among British men who did (–■–) or did not (–◆–) develop CHD over 15 years follow-up. Source: British Regional Heart Study*

systems developed from the British Regional Heart Study were no more accurate in predicting who suffered from CHD when blood cholesterol was included as a risk factor than when it was not.[10]

Because of the importance of other modifiable risk factors, the technology assessment reported here considers the role of cholesterol lowering using statins within the wider context of alternative drug and non-drug interventions.

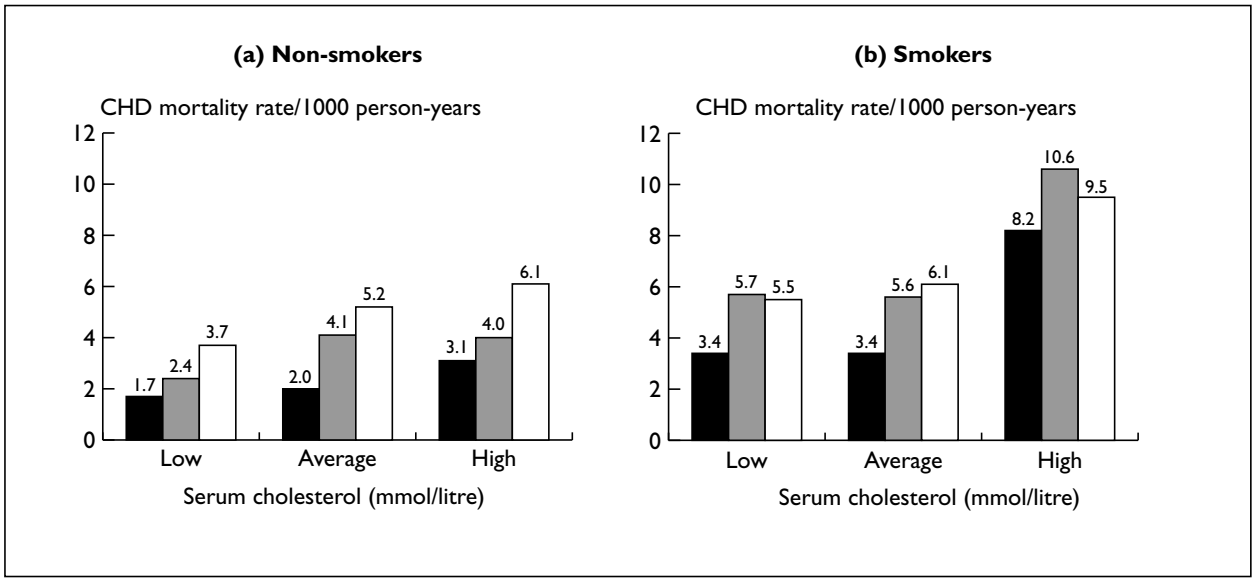

FIGURE 3 *CHD mortality among British men according to their tobacco smoking behaviour (a, non-smokers; b, smokers) and levels of blood cholesterol and diastolic blood pressure (■, low; ▨, medium; □, high). Source: British Regional Heart Study*

Chapter 2

Aims and methods

This review aimed to answer the following questions.

- By how much do low fat and other diets reduce blood cholesterol? And, how effective are such diets in reducing CHD risk?
- Does treatment with statins reduce CHD events and are relative reductions in these events independent of the level of CHD risk?
- How effective are non-cholesterol lowering drug treatments (i.e. aspirin, beta-blockers, and antihypertensives) for reducing CHD risk relative to dietary modifications and cholesterol lowering drug treatments?
- What is the relative cost-effectiveness of different approaches to reducing cholesterol and/or CHD?

Outcomes and effect modifiers

Clinical events were the primary outcomes of interest and include total mortality, CHD mortality, stroke mortality, non-fatal myocardial infarction and non-fatal stroke. In addition, surgical revascularisation end-points (i.e. coronary artery bypass surgery, percutaneous angioplasty) and regression of atheroma identified by angiography were also examined. Only those trials with published data on clinical events were included in this review because time did not permit information to be obtained directly from investigators.

The major effect modifiers were:

- the extent of cholesterol lowering expressed as the net change (i.e. control group changes subtracted from treatment group changes) between baseline and final measurement
- the level of CHD risk expressed as the control group risk.

Inclusion and exclusion criteria

Only randomised controlled parallel group trials were included in the review. Only those trials with at least 6 months follow-up were included, as this arbitrary time interval would seem to be the minimum reasonable for examining effects on clinical outcomes given the natural history of the disease. Studies that were excluded are shown in appendix 1.

Studies with non-random allocation to treatment groups were not included. Studies of children were not included.

Searching for studies

The search strategy is shown in appendix 2. The standard randomised controlled trial (RCT) and meta-analysis filters were used in MEDLINE and the Cochrane CENTRAL register, with review of reference lists of reviews and trials. Specific drug names of the various statins were applied, together with relevant disease groups. Citation searches were made from 1993 to November 1997. Reference lists of papers abstracted and of previous meta-analyses, together with replies from requests made to investigators working in the field of cholesterol lowering, were used to compile an up-to-date list of all statin trials. Original data from investigators were not sought and industry databases were not examined.

Data extraction and synthesis

A data abstraction form was developed. The data for each trial are shown in appendices 3–5. Effect sizes were estimated using the statistical package META97 and further analysis was conducted with the EGRET package using logistic regression models. Heterogeneity in fixed effects models was investigated by sensitivity analyses.

Economic modelling

Methods

Estimating the cost-effectiveness of treatments consisted of five separate calculations:

- calculation of life-years gained on treatment
- calculation of costs of treatments
- calculation of savings (i.e. reduced hospital admissions, fewer revascularisation procedures) produced by the treatments

- calculation of the gross cost-effectiveness (i.e. ignoring any savings to the health service)
- calculation of the net cost-effectiveness (i.e. taking account of any saving which may accrue).

These calculations used a spreadsheet model which contained the following methods and assumptions. This work is described in detail elsewhere.[11]

Calculation of life-years gained using the cohort life-table method

In these analyses the cost-effectiveness of treatment (in terms of cost per life-year gained) was calculated assuming that patients were treated for life, and that the relative risk of dying in the treatment and placebo groups remained constant throughout life at the level observed during the trials. It is improbable that benefit would increase after the trial period, and therefore life-years gained were unlikely to be greater than calculated. In practice, treatment would be unlikely to be stopped after the length of the trial period. We therefore considered that our assumptions would provide a realistic estimate of the duration of treatment and the health gain from treatment.

The life-table method was used to estimate the total number of life-years gained through different treatments in cohorts of patients of the same average ages as those in the relevant trials. Many of the trials recruited only men, and in others the number of women was too small to estimate reliably the effect of treatment on total mortality. Consequently, direct estimates of cost per life-year gained were only possible for men. However the relative risk reduction in coronary events in women was often at least as high as that in men, and the absolute benefit was therefore assumed to be independent of sex at any given level of absolute risk.

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 taking 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 with treatment by extrapolating the survival curves beyond the end of the trials, assuming that treatment would be lifelong.

The life-table method involves construction of a table to calculate the mortality experience of a cohort of people. The cohorts used were 1000 men of the same average age as patients in the relevant trial or group of trials. In each cohort the mortality experience predicted for men on treatment was compared with that of men on placebo. The life-years gained by treatment were the difference between the total life-years lived by those on treatment and those on placebo. In each instance, the 1000 men were assumed to be the same age. In the first year a small number of each cohort died; this number was calculated by multiplying the annual mortality rate for men of that age by the number alive at the beginning of the year. The number surviving at the beginning of the following year was then 1000 minus the number who died during the first year. The number dying during each of the following years was calculated in the same way. The number of life-years lived in each year was then the number of men who were alive at the end of each year plus half of the deaths during that year. The deaths in a given year occurred at various times, some early and some late in the year. It was assumed that deaths occurred half way through the year, on average, so that each death contributed half a year towards the total of life-years lived. The total life-years for each cohort was the sum of the life-years lived for each year. The life-years gained by treatment were the total life-years lived by the treatment cohorts minus the life-years lived by the placebo cohorts.

In order to take account of the decline in CHD mortality in the years since the trials reported, the baseline mortality risk was adjusted downwards by 5, 10 or 15%. The baseline mortality adjustments for each therapy are given in the input tables.

Calculation of cost of treatments

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.[12–14] Drug costs were taken from the British National Formulary, November 1997.[15] The drug doses were taken from the trials for simvastatin and pravastatin. The drug dose for atorvastatin was calculated as the equipotential dose for achieving the same cholesterol

reduction as simvastatin or pravastatin as appropriate. Costs relating to medical, nursing or laboratory services were excluded.

Dietary interventions were assessed using data provided by the DART (oily fish) and Mediterranean diet studies.[16,17] After consideration of the diets it was decided that the net impact on the total cost of food was likely to be zero, as substitution of different foods was likely to occur.

Costs for clinical nursing and dietician time were taken from Netton and Dutton's work on the costs of community care.[18]

Calculation of possible savings

In many trials myocardial infarction, the numbers of coronary artery bypass grafts (CABGs) and angioplasties (PTCAs) were reduced by treatment, and a corresponding reduction in hospital admissions was expected. In principle, health service savings on procedures and admissions can be used to partly offset the costs of drug treatment.

The costs of events (see below) were taken from work by Buxton and colleagues,[19] except for the cost of a stroke, which was taken from a report to the Public Accounts Committee.[20] Costs were indexed to 1997 prices using the Health Service Pay and Prices Index. These were unit costs and did not take account of long-term resource use driven by differences in effectiveness. The costs are given in *Table 1*.

These costs were applied to events as reported in the relevant trials. Where trials reported combined CABG and PTCA rates, a CABG:PTCA ratio of 75%:25% was used to calculate the expected cost savings. This ratio was reported in the Hospital Episode Statistics for September 1996.[21]

Calculation of gross and net cost-effectiveness

The gross cost-effectiveness of each treatment was calculated as the total cost of therapy divided by the predicted number of life-years gained from therapy. No account was taken of any potential health service savings in these estimates.

TABLE 1 *Costs of events avoided used to calculate savings due to therapy*

Event	Cost (£)
CABG	5725
PTCA	2436
Admission for MI	2306
Admission for stroke	8823

Source: McKenna, et al., *1997;[19] Spackman, 1991[20]*
MI, myocardial infarction

The net cost-effectiveness of each treatment was calculated by dividing the total cost of therapy minus the total value of the events avoided, by the predicted number of life-years gained from therapy. Thus, potential health service savings were included in these estimates.

Discounting of costs and benefits

Costs and benefits occurring in the future may be valued less than those occurring 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.[20]

Considerable debate over whether health benefits should be discounted continues,[22,23] and therefore the undiscounted estimates were also presented.

Other economic considerations

No attempts were made to adjust cost-effectiveness estimates for intangible costs (e.g. due to suffering) or indirect costs (e.g. loss of employment, patient costs of attending hospital). While it was recognised that the effects of treatment might be delayed by 1 or 2 years, that drug doses might be reduced, that compliance will vary and that quality of life will differ depending on clinical status, a robust and simple model was required. Taking account of these and other factors would require many assumptions to be made.

Chapter 3

Interventions to reduce CHD: review findings

Cholesterol levels can be lowered by several types of treatment, diet and drugs being the most important. The review findings on the effectiveness of cholesterol lowering diets and drugs, and of non-cholesterol lowering interventions, in reducing risk of CHD are presented in this chapter. Data on the relative effectiveness and cost-effectiveness of different interventions are also shown.

Cholesterol lowering diets

Low fat diets

The effects of changes in individual dietary intake of saturated fats and cholesterol have been studied extensively (appendix 5 and *Table 2*). The effectiveness of low fat diets depends critically on how restrictive they are and the degree of adherence. 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.[24] Animal experiments and studies carried out in hospital metabolic wards 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.

TABLE 2 *The effect of lipid lowering diets in reducing blood cholesterol levels derived from published meta-analyses*

Intervention	Blood cholesterol reduction (% fall)
Diet alone	
General population:	
Brunner, *et al.*, 1997[27]	0.22 mmol/litre (3%)
Tang, *et al.*, 1998[28]	0.31 mmol/litre (5%)
After MI (high risk):	
Ebrahim & Davey Smith, 1996[30]	0.65 mmol/litre (9%)
Multiple risk factor	
Primary care and occupational settings:	
Ebrahim & Davey Smith, 1997[26]	0.14 mmol/litre (2%)

Studies in the general population have shown only small changes in cholesterol.[25–28] These studies suggest that the extent of cholesterol reduction that may be expected from recommending lipid lowering diets is likely to be very small (1–5%).[27,28] Such reductions are clinically trivial for an individual patient – although some patients undoubtedly benefit from lipid-lowering diets because of high levels of motivation and compliance, and achieve closer to institutional levels of cholesterol reduction. At a population level, a fall in blood cholesterol of 1–5% (i.e. a fall of 0.05–0.3 mmol/litre) would equate to a reduction in CHD mortality of between about 0.3 and 10%.[29] In the UK, this would represent avoiding 200 to 6000 deaths under the age of 75 years. A systematic review of RCTs of primary prevention involving many tens of thousands of participants and using multiple interventions including diet found a blood cholesterol reduction of only 2% and a correspondingly small, and non-significant, effect on CHD mortality (odds ratio (OR) = 0.96; 95% confidence interval (CI), 0.89–1.04).[26] The trial evidence could not exclude an effect on CHD mortality as large as the 10% predicted from epidemiological models, but suggests that the true effect is considerably smaller, and may be negligible.

The effects of dietary interventions used alone following myocardial infarction demonstrated a greater fall in blood cholesterol than the other dietary trials,[30] 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 (OR = 0.94; 95% CI, 0.84–1.06).[30] Lowering blood cholesterol by 9%, equivalent to about 0.6 mmol/litre, would result in a predicted CHD mortality reduction of 20% – but a difference of this size was excluded by the CIs of the pooled risk reduction.

In an observational study of American nurses, unhydrogenated monounsaturated and polyunsaturated fat intake, but not total fat intake, was correlated with CHD mortality.[31] These

relationships suggested that substituting unsaturated fats for saturated fats would be beneficial. 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 cholesterol as well as LDL cholesterol. This reduces total cholesterol, but leaves the LDL:HDL ratio unaffected and so may not reduce CHD risk.[24] This highlights the fact that the real aim should be to lower CHD risk rather than focusing on lowering serum total cholesterol levels *per se.*

Garlic, oats and soya protein

A systematic review of trials suggested that garlic may exert a cholesterol lowering effect, with falls of 0.65 mmol/litre (95% CI, 0.53–0.76) or about 10%.[32] However, some of the trials were severely flawed and, therefore, the evidence is unreliable. Systematic reviews of studies evaluating the effects of consuming oats[33] or psyllium-enriched cereals[34] showed a small cholesterol lowering effect of 2% and 5%, respectively. A meta-analysis of 38 trials of soya protein as a substitute for meat protein also demonstrated a net fall in cholesterol of 0.60 mmol/litre (95% CI, 0.35–0.85), which was greater in people with high baseline cholesterol levels.[35]

However, all of these dietary trials were of relatively short duration and did not consider clinical end-points. Therefore there is no evidence that such diets lower blood cholesterol levels in the long-term, or that they reduce CHD risk.

Cholesterol lowering drugs

The statins

Over the last few years a new class of more powerful cholesterol lowering drugs – the statins – has become available. Statins are able to reduce LDL cholesterol levels by more than 20%. Data from a total of 23 published RCTs of cholesterol lowering in which clinical outcomes were recorded (appendix 3) were pooled to give an overall estimate of treatment effect (appendix 6). Overall, these trials show that statins reduce the risk of CHD mortality by about 27% (see *Table 3*). The trials which contributed most to the pooled

TABLE 3 *Summary of major trials of statins*[*]

Trial	CHD death rate[†]	Patient group	Treatment	Follow-up (years)	Sex (mean age, years)	Numbers treated vs. controls	Baseline cholesterol (% fall)	Total mortality and CHD mortality OR (95% CI)
Primary prevention trials								
WOSCOPS (Shepherd, *et al.*, 1995[13])	3.8	No CHD Cholesterol: ≥ 6.5 mmol/litre	Pravastatin 40 mg vs. placebo	4.9	Men only (55)	3302 vs. 3293	7.03 (20%)	0.78 (0.60–1.00) 0.67 (0.45–0.99)
AFCAPS/ TexCAPS (Downs, *et al.*, 1997[37])	0.9	No CHD Cholesterol: 4.6–6.8 mmol/litre	Lovastatin 20–40 mg vs. placebo	5.2	Men 85% (58)	3301 vs. 3304	5.71 (18%)	1.04 (0.75–1.45) 1.36 (0.59–3.18)
Secondary prevention trials								
4S trial (4S Study Group, 1994[12])	15.7	Post MI/angina Cholesterol: 5.5–8.0 mmol/litre	Simvastatin 20–40 mg vs. placebo	5.4	Men 81% (60)	2221 vs. 2223	6.74 (25%)	0.70 (0.58–0.85) 0.58 (0.46–0.73)
CARE (Sacks, *et al.*, 1996[14])	11.5	Post MI Cholesterol: < 6.2 mmol/litre	Pravastatin 40 mg vs. placebo	5.0	Men 86% (59)	2081 vs. 2078	5.40 (20%)	0.91 (0.74–1.12) 0.80 (0.61–1.05)
LIPID (LIPID Study Group, 1997[36])	13.8	Post MI/ unstable angina Cholesterol: 4.0–7.0 mmol/litre	Pravastatin 40 mg vs. placebo	6.0	Men 83% (31–75[‡])	4512 vs. 4502	5.60 (18%)	0.76 (0.67–0.86) 0.75 (0.64–0.88)

[*] *These trials contribute 95% of the data to pooled estimates of the efficacy of statins shown in* Table 5
[†] *Control group CHD mortality per 1000 person-years*
[‡] *Age range*

estimates were the West of Scotland Coronary Prevention Study (WOSCOPS; 8% weighting),[13] the Scandinavian Simvastatin Survival Study (4S; 21% weighting),[12] the Cholesterol and Recurrent Events (CARE; 16% weighting) trial,[14] the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID; 48% weighting) trial,[36] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS; 2% weighting).[37] The AFCAPS/TexCAPS trial was stopped early after finding a 36% reduction in a combined fatal and non-fatal CHD end-point, and although the final study report was published after the search period for the current review, its findings were reported in abstract form at the same time as those of the LIPID trial, and consequently have been included.

Comparisons between statins

The statins belong to the hydroxymethylglutaryl co-enzyme A reductase inhibitor class of drugs, which all appear to be very effective at lowering blood cholesterol. Comparison of the effects of different types of statin in reducing clinical events is limited by the available trial evidence. Effects on CHD mortality and composite end-points for those statins with sufficient data are shown in *Table 4*.

TABLE 4 *Comparison of the effects of different statins on CHD mortality and composite primary end-points*

Drug	OR on treatment (95% CI)	
	CHD mortality	Composite primary end-point
Pravastatin	0.77 (0.68–0.87)	0.69 (0.53–0.90)
Simvastatin	0.60 (0.48–0.75)	0.68 (0.49–0.93)
Lovastatin	1.02 (0.60–1.73)	0.62 (0.49–0.77)

In the case of lovastatin, apparent lack of a class effect on CHD mortality is probably determined by the primary care clinical settings of the major trials which recruited only low risk patients. In these trials, the main aim was to detect an effect on a combined vascular end-point outcome, including revascularisation procedures. Consequently, the trials of lovastatin were underpowered to detect effects on CHD mortality. For all three statins, the 95% CIs of the effects on CHD mortality overlap, suggesting that the effects on both CHD mortality and on composite end-points are consistent with a class effect, rather than being specific to a type of statin.

However, fewer data from large-scale trials are currently available for fluvastatin, atorvastatin and cerivastatin, and consequently their clinical efficacy is not yet proven. Available data for atorvastatin and cerivastatin indicate that they lower LDL cholesterol to an extent similar to or greater than that of other statins.

Statins compared with other cholesterol lowering drugs

The efficacy (in terms of relative risk on treatment) of statins in primary and secondary prevention is summarised for a range of end-points in *Table 5* (also see appendix 6). For comparative purposes, similar information for fibrates (clofibrate and bezafibrate) is also given (*Table 5*; see also appendix 7). Fibrates are not as effective as the newer statins in lowering blood cholesterol and in reducing rates of CHD events. The overall efficacy of the older cholesterol lowering drugs is strongly related to the baseline level of CHD 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.[3]

TABLE 5 *The efficacy of treatment with cholesterol lowering drugs*

Outcome	Statins		Fibrates	
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention
Total mortality*	0.89 (0.73–1.08)	0.79 (0.73–0.86)	1.25 (0.05–1.50)	0.97 (0.90–1.05)
CHD mortality*	0.76 (0.54–1.06)	0.74 (0.66–0.83)	1.09 (0.82–1.44)	0.93 (0.85–1.01)
Non-fatal MI*	0.64 (0.53–0.77)	0.70 (0.61–0.80)	–	0.57 (0.28–1.11)
Net cholesterol lowering	20%	21%	9%	10%

* *OR (95% CI)*

Primary and secondary prevention with statins

There is no doubt about the efficacy of statins in secondary prevention. The pooled effects on total and CHD mortality and non-fatal events are highly significant. In primary prevention, the efficacy of statins is much more dependent on the outcomes considered. As discussed earlier, the primary prevention trials were powered to detect differences in composite end-points, including revascularisation procedures. Indeed, AFCAPS/TexCAPS was stopped early because of such a clear-cut difference in the composite end-point between treated and placebo groups.[37] The use of composite end-points which include health service utilisation outcomes presents problems in generalising the results, because procedures may differ markedly between locations.

Unlike the older cholesterol lowering drugs, for statins there does not appear to be any relationship between baseline level of CHD risk and effect of treatment. Statins are effective in reducing clinical events across a wide range of baseline CHD mortality risks – from 0.4% per annum (WOSCOPS) to 1.6% per annum (4S). At the very low risk levels seen in the AFCAPS/TexCAPS trial (0.1% per year), more data are required to determine whether statins are clinically effective.

Effect of statins in women

A meta-analysis of the recently published data on women from the 4S,[38] LIPID,[36] CARE,[14] and AFCAPS/TexCAPS[37] trials and pooled data from several pravastatin trials[39] (see appendix 8) shows that if both fatal and non-fatal CHD events are considered, women have an on-treatment relative risk (RR) of 0.70 (95% CI, 0.60–0.81), which is similar to that of men (no significant interaction effect for gender, $p = 0.45$). A report of an increased risk of breast cancer among women treated with pravastatin in the CARE study was not confirmed in the 4S or the LIPID study. The pooled results from the major pravastatin studies show no association with breast cancer (RR = 1.2; 95% CI, 0.66–2.13).

Effect of statins in older people

Statin treatment in older people is as effective as in middle-aged adults. Sub-group analyses of participants aged 55 years or older or 65 years or older 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 study, 4S, WOSCOPS, AFCAPS/TexCAPS, pooled pravastatin trials) (see appendix 9) demonstrates an RR of combined fatal and non-fatal CHD events of 0.70 (95% CI, 0.62–0.78) for older people. People in their late 70s and 80s, while obviously at increased absolute risk of CHD, have not been recruited into 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, which is examining the efficacy of statin treatment in older people, reports in 2002.

Statins in combination with other treatments

The major trials of statins differed in their approach to use of other treatments, reflecting differences in entry requirements, clinical settings and the time at which they were initiated. *Table 6* shows the extent of use of with potentially important treatments in each of the five major statin trials.

In the WOSCOPS trial, at least 16% of participants had evidence of cardiovascular disease and a similar proportion reported hypertension. The protocol for the study did not define management strategies for these additional risk factors, nor was any systematic smoking cessation advice given to participants. By contrast, participants in the AFCAPS/TexCAPS trial were taking relevant co-treatments for reduction of cardiovascular risk. It is possible that the potential for reducing CHD deaths in these participants was reduced by these co-treatments, whereas in the WOSCOPS trial significant effects on mortality were found but there was very little use of co-treatments, as shown in *Table 6*.

In secondary prevention, the LIPID and CARE trials demonstrate clear benefits from use of statins even in the face of high levels of prescribing of effective drugs. This suggests that the effects of statins are **additional** to the effects obtained by other treatments.

Non-cholesterol lowering alternatives

Cholesterol lowering is only part of the repertoire of possible effective interventions to reduce CHD risk and it is 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

TABLE 6 *Use of treatments for lowering cardiovascular risk in the major statin trials*

Treatment	Percentage on treatment in statin group in trial:				
	WOSCOPS[13]	**AFCAPS/TexCAPS[37]**	**CARE[14]**	**4S[12]**	**LIPID[36]**
Aspirin	16*	17	83	37	83
ACE inhibitors	–	7	15	–	16
Beta-blockers	–	4	41	57	46
Calcium antagonists	–	5	40	30	35
Diuretics	16*	6	11	7	16
Nitrates	2	–	32	31	35
Fish oil	–	–	–	13	–
Eligible for smoking advice†	44	13	21	24	9

* *Percentage reporting past cardiovascular disease and therefore eligible for aspirin or reporting hypertension and therefore eligible for antihypertensives*

† *Percentage of current smokers*

ACE inhibitors, angiotensin-converting enzyme inhibitors

lowering diets) and by drug treatments (e.g. to lower blood pressure, beta-blockers after a myocardial infarction, and aspirin). The effectiveness of these non-cholesterol lowering alternatives is briefly summarised in this section and in *Table 7*.

Smoking cessation advice

Advice on stopping tobacco smoking given in primary care settings has a small but important effect on long-term smoking rates. Pooled estimates from 188 trials show that about 2% (95% CI, 1–3%) of those given personal advice during one routine consultation stopped smoking and had not relapsed up to 1 year later.[40] The use of nicotine chewing gum increases the quit rates to about 4% (95% CI, 2–6%). This will lead to an approximately 1–2% overall reduction in vascular mortality and morbidity. The effect is much larger in those who quit, but only a small percentage quit with simple advice.

Advice about how to stop tobacco smoking is much more effective among people who have suffered a myocardial infarction, with up to 36% stopping.[46] This should result in over a 30% reduction in the mortality risk.

Non-cholesterol lowering diets

In the DART trial,[16] increased intake of oily fish was shown to reduce cardiovascular mortality after heart attack (OR = 0.6; 95% CI, 0.5–0.9) (appendix 5), although serum cholesterol levels were not reduced. In the trial, 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 who had had a myocardial infarction (OR = 0.24; 95% CI, 0.1–0.8), although again there was no effect on cholesterol levels.[17,47] The most prominent change in the intervention group was an

TABLE 7 *Effects on cardiovascular mortality (i.e. circulatory deaths, International Classification of Diseases [ICD] 390–459) of other treatments that have a role in lowering CHD risk*

Treatment	RR, cardiovascular deaths (95% CI)
Primary prevention	
Tobacco smoking advice[40]	0.99 (0.98–1.0)
Nicotine replacement[40]	0.98 (0.98–0.99)
Aspirin[41]	0.98 (0.78–1.18)*
Anti-hypertensive drugs:	
Patients aged < 60 years[42]	0.79 (0.71–0.87)
Patients aged ≥ 60 years[43]	0.75 (0.64–0.88)
Statins	0.68 (0.46–1.00)
Secondary prevention	
Aspirin[44]	0.82 (0.76–0.88)
Beta-blockers[45]	0.78 (0.71–0.87)
Statins	0.74 (0.66–0.83)
Tobacco smoking advice[46]	0.68 (0.57–0.79)
Oily fish[16]	0.65 (0.5–0.9)
Mediterranean diet[17,47]	0.24 (0.1–0.8)

* *Not a statistically significant treatment effect*

increase in consumption of alpha-linolenic acid from rapeseed margarine (used because the participants found it difficult to consume large amounts of olive oil).

The striking findings of the trials of the oily fish diet and the 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 low risk of CHD is not known. The other treatment arms of the DART trial were dietary fat restriction and increase in dietary fibre; neither of these treatments proved effective compared with the control group.

Exercise

Lack of physical activity has been shown to be a strong independent risk factor for death from CHD.[48] It is estimated that a sedentary lifestyle doubles the risk of CHD mortality. 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 that confers cardiovascular benefit.[49] A recent review found that a proportion of patients did respond positively to exercise advice given in a primary care setting.[50] 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 that from a 2% reduction in the proportion of smokers.[51]

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) (see appendix 4).[26,52] This is probably due to poor adherence to non-pharmacological interventions, the use of drugs that may have had adverse effects and the variable quality of the programmes.

Cardiac rehabilitation

Evidence from trials of post-myocardial infarction 'rehabilitation' are also relevant because 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).[30] 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 be treated (NNT) of about 13 people for 5 years to avoid one CHD death.

Aspirin

In primary prevention aspirin does not reduce all-cause mortality significantly.[44] 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 experienced a myocardial infarction but who are at high risk of such an event (e.g. people with unstable angina, stable angina or peripheral vascular disease).[41,44]

Lowering blood pressure

Systematic reviews of RCTs show that for people with high blood pressure, anti-hypertensive medication reduces the risk of CHD, stroke and all-cause mortality.[42,43] There is a lack of evidence from trials among people who have had a myocardial infarction. Long-term follow-up of cohorts of patients after myocardial infarction shows they have a similar graded increased risk of mortality and recurrent vascular events with increasing systolic and diastolic blood pressure.[45,53] This suggests that lowering blood pressure would be associated with reductions in risk, and trials are being planned to establish whether this is so.

Relative effectiveness of different interventions and number needed to treat

Table 8 presents summary information on the potential effects of some interventions in terms of NNTs for 5 years to avoid a cardiovascular 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 for 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 prevented are counted over a lifetime rather than the 5-year period. Nonetheless, they provide some

TABLE 8 *Relative treatment effects for vascular deaths (i.e. circulatory deaths ICD 390–459) and NNT for 5 years to avoid one vascular death for alternative treatments for the prevention of CHD at a range of annual baseline levels of cardiovascular mortality risk*

Treatment	RR (95% CI)	NNT for 5 years to avoid one vascular death at an annual risk of vascular death of:					
		0.1%	0.5%	1.5%	3.0%	4.0%	6.0%
Primary prevention							
Tobacco smoking advice[40]	0.99 (0.98–1.0)	20,000	4000	1333	666	500	333
Nicotine replacement[40]	0.98 (0.98–0.99)	10,000	2000	667	333	250	166
Aspirin[41]	0.98 (0.78–1.18)*	10,000	2000	667	333	250	166
Anti-hypertensive drugs:							
Patients aged < 60 years[42]	0.79 (0.71–0.87)	950	190	63	31	24	16
Patients aged ≥ 60 years[43]	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[44,45]	0.82 (0.76–0.88)	NA	222	74	37	28	18
Beta-blockers[45]	0.78 (0.71–0.87)	NA	181	61	30	23	15
Statins	0.74 (0.66–0.83)	NA	154	51	26	19	13
Tobacco smoking advice[46]	0.68 (0.57–0.79)	NA	125	42	21	16	10
Oily fish[16]	0.65 (0.5–0.9)	NA	114	38	19	14	9
Mediterranean diet[17,47]	0.24 (0.1–0.8)	NA	52	17	9	7	4

* *Not a statistically significant treatment effect*

NA, not applicable (in this case because the risk level is too low for secondary prevention)

indication of the relative effects of different types of intervention.

It is clear that statins compare favourably with many other widely used interventions. It is important to emphasise that the data on dietary interventions is far weaker than that for drug treatments. The very small NNTs for the oily fish diet and the Mediterranean diet are due to the large effects found in these two trials. Replication of these studies is urgently required.

Cost-effectiveness

While the NNT analyses indicate that statins appear to produce considerable health gain for relatively small NNTs, a better guide to policy is provided by looking at the relative cost-effectiveness of these various treatment options.

Cost-effectiveness has been assessed as the cost per life-year gained using methods developed for examining the statin drugs and published previously.[11] In the current new analyses for this review, these methods have been applied to a wide range of treatment options. These analyses, performed using the same methods, provide fair comparisons of the cost-effectiveness of different treatments.

The input values used in the economic model are shown for each therapy in a series of tables in appendix 11. Separate tables are presented for each therapy. An additional set of results is presented in which the same baseline total mortality risk has been set at 1.5% per annum for a selection of the interventions, in order to aid direct comparison.

Because the baseline level of CHD risk 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. The baseline risks presented in this review are of **total and CHD mortality** and not of **combined fatal and non-fatal CHD event rates**, as are now widely used in guidelines for treatment thresholds. Total and CHD mortality rates have been used because these data are available for earlier trials of other treatments, which allows comparisons to be made with statins. Furthermore, the combined fatal and non-fatal event rate may be difficult to interpret and compare because it varies depending on which cardiovascular events are included (e.g. should new diagnoses of angina

and revascularisations be included or not?) and how carefully events are ascertained.

The comparison of CHD event and mortality rates shown in *Table 9* demonstrates that the commonly used threshold of a 3% annual CHD event rate equates to a CHD mortality rate of between 1% and 1.5% and a total mortality rate of 2%.

The costs per life-year gained for a range of interventions, considering baseline level of total mortality and statin and other drug costs, are shown in *Tables 10–17*. Throughout these tables a decline in CHD mortality of 5% per year is assumed. The costs per life-year gained in primary and secondary prevention with statins (*Table 11*) are very similar to previous estimates based on the WOSCOPS trial[54] and those made by the 4S investigators,[55] suggesting that the methods used in this review to make comparisons between treatments are valid.

TABLE 9 *Fatal and non-fatal CHD event rates and total mortality and CHD mortality rates in the placebo groups of the major statin trials*

Trial	Annual combined fatal + non-fatal CHD event rate (%)	Annual total mortality rate (%)	Annual CHD mortality rate (%)
WOSCOPS (Shepherd, *et al.*, 1995[13])	1.58	0.82	0.38
AFCAPS/ TexCAPS (Downs, *et al.*, 1998[37])	1.28	0.44	0.09
CARE (Sacks, *et al.*, 1996[14])	2.64	1.89	1.15
4S (4S Study Group, 1994[12])	4.03	2.13	1.57
LIPID (LIPID Study Group, 1998[36])	2.64	2.35	1.38

Tables 10–17 show not only the gross costs per life-year gained (i.e. not including any NHS savings) but also the net cost per life-year gained (i.e. taking into account potential savings due to avoiding CHD events and associated costs of treatment and hospitalisation). Such net cost analyses are important. For example, analyses of the 4S trial data showed that hospital costs among the simvastatin treated group were 32% lower than for the placebo group,[56] and that almost 90% of the drug costs were off-set by savings in hospital admissions.[57] 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.

The summary data in *Tables 16* and *17* provide comparable cost-effectiveness estimates for a range of interventions. 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-year saved are low and have been estimated to be about £500 per life-year gained.[58] 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 £2500 if costs to smokers as well as the NHS are taken into account.

The effects of baseline level of risk are illustrated in *Figure 4* which shows how the cost of achieving an extra year of life increases as people with lower risk are treated. A recent economic evaluation of lipid lowering in primary care among patients with moderately raised risk doubted whether drug treatment for primary prevention is cost-effective.[59]

TABLE 10 *Cost-effectiveness, in terms of cost per life-year gained, of statins at different baseline levels of total mortality*

Annual total mortality rate	Estimate	Cost (£) per life-year gained (95% CI)	
		Discounted	**Undiscounted**
Trial data – 1.86%	Gross	7515 (5682–10,280)	4527 (3417–6202)
	Net	6391 (4833–8742)	3850 (2906–5274)
0.5%	Gross	13,260 (9998–18,184)	5575 (4188–7669)
	Net	12,727 (9596–17,453)	5351 (4020–7361)
1%	Gross	9780 (7379–13,401)	5073 (3812–6974)
	Net	8992 (6785–12,322)	4665 (3505–6412)
1.5%	Gross	8239 (6225–11,277)	4742 (3574–6503)
	Net	7242 (5471–9912)	4168 (3141–5716)
3%	Gross	6228 (4717–8508)	4144 (3135–5664)
	Net	4727 (3580–6457)	3145 (2379–4299)
6%	Gross	4802 (3649–6542)	3589 (2727–4890)
	Net	2480 (1885–3379)	1854 (1409–2526)

A decline in CHD mortality of 5% per year has been assumed throughout

Pooled estimates of RR reduction have been held constant for all baseline risk estimates

TABLE 11 *Cost-effectiveness, in terms of cost per life-year gained, of statins of different costs*

Statin cost category*	Estimate	Cost (£) per life-year gained (95% CI)	
		Discounted	**Undiscounted**
Primary prevention (0.5% total mortality per year)			
Low	Gross	5389 (2969–129,696)	2589 (1409–63,092)
	Net	4889 (2694–117,663)	2348 (1278–57,239)
Intermediate	Gross	10,952 (6035–263,586)	5261 (2863–128,225)
	Net	10,452 (5759–251,554)	5021 (2732–122,371)
High	Gross	13,267 (7310–319,299)	6373 (3468–155,327)
	Net	12,767 (7035–307,266)	6133 (3337–149,473)
Secondary prevention (3% total mortality per year)			
Low	Gross	3785 (2912–5746)	2368 (1820–3599)
	Net	2188 (1683–3322)	1369 (1052–2081)
Intermediate	Gross	7692 (5918–11,677)	4813 (3698–7315)
	Net	6096 (4689–9253)	3814 (2930–5796)
High	Gross	9318 (7168–14,145)	5830 (4480–8861)
	Net	7721 (5940–11,721)	4831 (3712–7343)

* *Taken as annual costs as follows: low cost statin: atorvastatin 10 mg, £246; intermediate cost statin: simvastatin 27 mg, £500; high cost statin: pravastatin 40 mg, £606*

A decline in CHD mortality of 5% per year has been assumed throughout

Pooled estimates for RR reductions in primary prevention have upper 95% CI approaching unity, and this results in very large upper limits for cost-effectiveness

TABLE 12 *Cost-effectiveness, in terms of cost per life-year gained, of dietary interventions*

Dietary intervention	Estimate	Cost (£) per life-year gained (95% CI)	
		Discounted	Undiscounted
Mediterranean diet	Gross	221 (149–1463)	150 (100–999)
	Net	26 (18–174)	18 (12–119)
Dietary fish	Gross	318 (190–1250)	241 (144–947)
	Net	460 (276–1809)	348 (209–1371)
Dietary fish and fish oil*	Gross	444 (267–1749)	337 (202–1325)
	Net	586 (352–2309)	445 (267–1749)

* *22% of the study population were consuming maxepa*

A decline in CHD mortality of 5% per year has been assumed throughout

TABLE 13 *Cost-effectiveness, in terms of cost per life-year gained, of antiplatelet drugs*

Antiplatelet therapy	Estimate	Cost (£) per life-year gained (95% CI)	
		Discounted	Undiscounted
Antiplatelets combined*	Gross	1685 (908–10,213)	1220
	Net	736 (397–4459)	533
Aspirin 300 mg	Gross	32 (17–192)	23
	Net	[–917]† ([–495]–[–5561])	[–665] ([–358]–[–4028])

* *Aspirin 75 mg + dipyridamole 400 mg*

† *[–£], treatment results in net savings to the health service*

A decline in CHD mortality of 5% per year has been assumed throughout

TABLE 14 *Cost-effectiveness, in terms of cost per life-year gained, of bendrofluazide (antihypertensive drug)*

Antihypertensive	Estimate	Cost (£) per life-year gained (95% CI)	
		Discounted	Undiscounted
Bendrofluazide 2.5 mg (patients mean age 56 years)	Gross	68 (42–138)	38 (24–77)
	Net	[–546] ([–340]–[–1104])	[–305] ([–190]–[–618])
Bendrofluazide 2.5 mg (patients mean age 69 years)	Gross	45 (27–183)	29 (17–118)
	Net	[–874]* ([–519]–[–3537])	[–565] ([–335]–[–2288])

* *[–£], treatment results in net savings to the health service*

A decline in CHD mortality of 5% per year has been assumed throughout

TABLE 15 *Cost-effectiveness, in terms of cost per life-year gained, of beta-blockers following myocardial infarction*

Annual total mortality rate	Estimate	Cost (£) per life-year gained (95% CI)	
		Discounted	Undiscounted
Atenolol 50 mg	Gross	128 (94–229)	97 (71–174)
	Net	[–121]* ([–89]–[–217])	[–92] ([–68]–[–165])

* *[–£], treatment results in net savings to the health service*

A decline in CHD mortality of 5% per year has been assumed throughout

Trials of at least 1-year duration were used in making estimates of cost-effectiveness

TABLE 16 *Results adjusted to a baseline total mortality risk of 1.5% per year, approximately equivalent to a combined fatal and non-fatal CHD event rate of 3% per year*

Intervention	Estimate	Cost (£) per life-year gained (95% CI)	
		Discounted	Undiscounted
Statins	Gross	8239 (6225–11,277)	4742 (3574–6503)
	Net	7242 (5471–9912)	4168 (3141–5716)
Antihypertensives			
Bendrofluazide 2.5 mg	Gross	66 (41–134)	38 (24–77)
Patients mean age 56 years	Net	[–578]* ([–360]–[–1167])	[–329] ([–205]–[–667])
Enalapril 20 mg	Gross	5634 (3512–11,388)	3212 (1998–6503)
Patients mean age 56 years	Net	4990 (3111–10,087)	2845 (1770–5760)
Low-cost regimen	Gross	1509 (491–2050)	860 (535–1742)
Patients mean age 56 years†	Net	865 (539–1749)	493 (307–999)
High-cost regimen	Gross	10,955 (6828–22,142)	6245 (3884–12,643)
Patients mean age 56 years‡	Net	10,311 (6427–20,840)	5878 (3656–11,900)
Antiplatelets			
Aspirin 75 mg +	Gross	2798 (1498–17,079)	1618 (864–9901)
dipyridamole 400 mg	Net	2339 (1252–14,275)	1353 (722–8275)
Aspirin 300 mg	Gross	53 (28–322)	30 (16–187)
	Net	[–407] ([–218]–[–2482])	[–235] ([–126]–[–1439])
Beta-blockers			
Atenolol 50 mg	Gross	227 (166–409)	131 (95–237)
	Net	130 (94–234)	75 (54–135)
Diet			
Mediterranean diet	Gross	293 (195–1981)	168 (109–1161)
	Net	179 (119–1206)	102 (66–707)
Dietary fish	Gross	555 (327–2221)	324 (190–1302)
	Net	613 (362–2454)	358 (209–1439)
Dietary fish and fish oil§	Gross	776 (458–3107)	453 (265–1823)
	Net	834 (492–3340)	487 (285–1959)

* *[–£], treatment results in net savings to the health service*
† *Low-cost regimen: 100% bendrofluazide 2.5 mg, 50% atenolol 100 mg, 20% enalapril 20 mg; annual cost £46*
‡ *High cost regimen = 100% enalapril 20 mg, 50% amlodipine 10 mg, 20% doxazosin 4 mg; annual cost £332*
§ *22% of the study population were consuming maxepa*

TABLE 17 *Cost-effectiveness for a range of CHD prevention therapies, ranked by cost per life-year gained (central estimate)*

Therapy	**Gross discounted cost (£) per life-year gained (95% CI)**
Bendrofluazide 2.5 mg only (patients mean age 69 years)	45 (30–180)
Aspirin 300 mg daily	50 (30–320)
Bendrofluazide 2.5 mg only (patients mean age 56 years)	70 (40–130)
Atenolol 50 mg	230 (170–410)
Mediterranean diet	290 (200–1980)
Fish diet, advice only	560 (330–2220)
Fish diet plus 20 mg maxepa	780 (460–3110)
Antihypertensive, low-cost combined regimen* (patients mean age 56 years)	1510 (940–3050)
Aspirin 75 mg + dipyridamole 400 mg	2800 (1500–17,080)
Simvastatin 27 mg	8240 (6220–11,280)

* *See* Table 16 *for details*

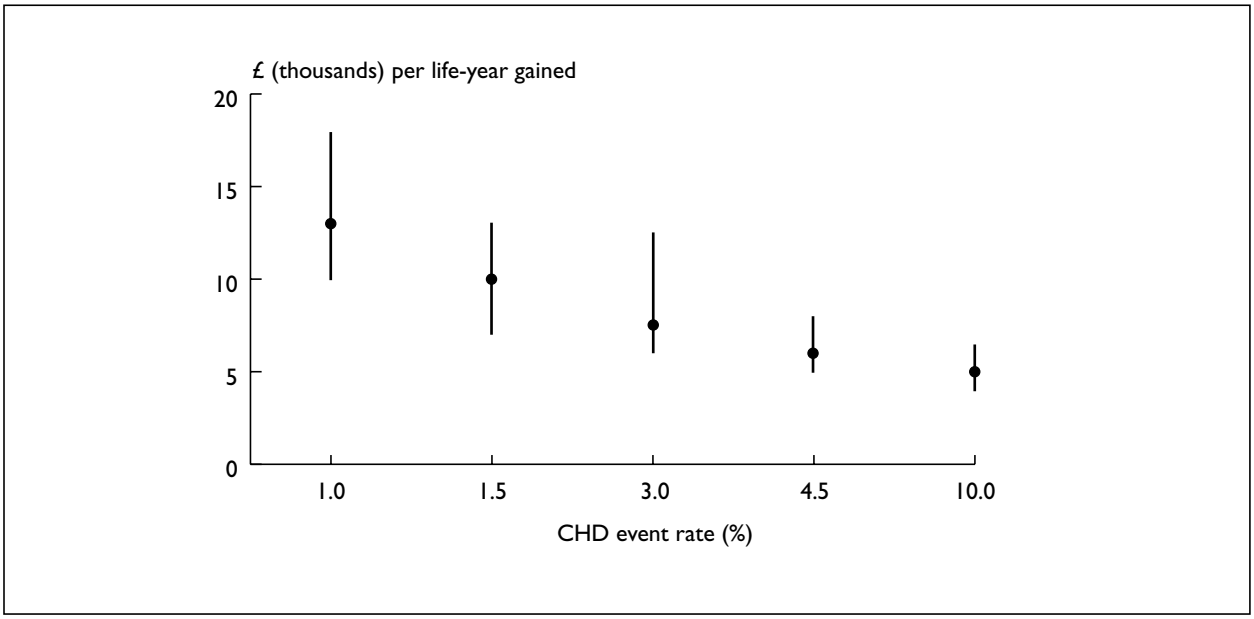

FIGURE 4 *Cost per life-year gained with statins by initial CHD risk (●, mean; bars indicate 95% CI)*

Chapter 4
Discussion

Main findings

The net cost per life-year gained with statins of about £8000 (for patients with an annual combined fatal and non-fatal CHD event risk of about 3%) compares favourably with several other interventions currently provided by the NHS, including those in the management of CHD. The cost per life-year gained increases markedly when treatment is offered to people at much lower risk, for example in primary prevention.

There is evidence that statins are clinically effective at levels of combined fatal and non-fatal CHD risk ranging from 1.3% to 4% per year. At the lower levels of risk, much of the benefit is confined not to avoiding deaths but to reducing revascularisations and acute non-fatal myocardial infarction. In Britain, tobacco smoking rates are much higher than in the USA or Australia and it is clear that more cost-effective smoking cessation advice in primary care prevention is required, rather than the prescribing of statins to those who fail to stop smoking, as has been recommended by the WOSCOPS investigators.[60]

At higher levels of risk in secondary prevention, it is clear that the benefits of statins are additional to the treatment gains that can be achieved with optimal use of aspirin, antihypertensives and beta-blockers. It is less clear from the trials whether optimal smoking cessation advice and advice about other lifestyle factors such as diet and exercise were offered. It seems likely that even if patients have received optimal drug and lifestyle advice, they still stand to benefit from statin treatment. If the different statins are equally efficacious and safe – which on current knowledge seems to be true – then the use of the drugs having the lowest cost per percentage reduction in cholesterol would appear to be preferable.

It is important for the NHS to ensure that as many people as possible are receiving the more cost-effective therapies and current evidence suggests that this is not happening. If more people at increased CHD risk were appropriately treated with aspirin and anti-hypertensive drugs, and were helped to stop smoking and change their diet, then a large population (possibly over half) would have their CHD risk sufficiently reduced to make statin treatment relatively cost-ineffective.[61] However, limiting the widespread provision of statin therapy for secondary prevention through encouraging the use of other more cost-effective treatments is not supported by the trial evidence, which shows that statins have effects that are additive to those of the other therapies.

Limitations of this review

Set against these results must be a consideration of the quality of the evidence for the various CHD therapies. Particular attention is drawn to the trials on diet modification. The DART and the Mediterranean diet trials did show significant reduction in CHD in comparison with placebo, but replication of these trials has not been attempted.[16,17] In addition, the evidence on compliance with dietary therapies in general suggests that significant changes in behaviour are difficult to achieve. This contrasts starkly with the quality of evidence for statin therapy. There are five major trials of statins (4S, WOSCOPS, CARE, LIPID, AFCAPS/TexCAPS)[12–14,36,37] which demonstrate significant clinical benefit in terms of reduced cholesterol, reduced all-cause and CHD mortality and reduced CHD events. Therefore, the benefits from statin therapy are more certain than those from dietary therapies.

A further limitation of the work presented is that the costs do not include the cost of contacting and screening the appropriate population for any of these therapies. Given the estimates by Haq and colleagues of the size of the population able to benefit from statin therapy, the total cost is likely to be significant, and careful consideration should be given to the most cost-effective method of implementing any CHD prevention strategy.[11,62]

The review relies entirely on trial and meta-analysis estimates of absolute risk in estimating cost-effectiveness of treatments. The true cost-effectiveness of treatments as used in routine

clinical practice may be different for a number of reasons. Firstly, people recruited to RCTs tend to be at lower risk of clinical events because of the exclusion criteria and self-selection bias. This effect can be marked, as was found in the thrombosis prevention trial[41] which had an event rate 62% of that predicted. Event rates in the MRC mild hypertension trial were closer to those observed in normotensive than hypertensive men in the general population.[63] Secondly, there are various inefficiencies in routine clinical practice that concern coverage, accuracy of diagnosis, and compliance – both professional and patient – which conspire to reduce the efficacy of treatment estimated in trials. Therefore, in routine practice, the effects of treatment will tend to be lower because of these inefficiencies but the NNT will tend to be smaller because of the higher absolute risks experienced outside trials. It is possible that these effects will cancel each other out, and if so, the data from trials and meta-analyses will provide reasonably accurate cost-effectiveness estimates. Further research to model the effects of selection bias and inefficiencies on application of trial findings in routine practice is feasible and required.

Cholesterol screening

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, of whom most 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 CHD to be used in isolation. Finally, cholesterol lowering with statins 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 the level of cholesterol by itself 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 are demonstrated by use of a risk assessment instrument to have a significant risk of a CHD event or who have 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.

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 healthcare resources. It is of concern, therefore, that people who might benefit from these interventions following myocardial infarction are not being treated. A recent survey of hospitals in the UK showed that secondary prevention in patients at high risk of CHD mortality because of a history of a CABG, PTCA, or acute myocardial infarction was highly variable and that many risk factors remained unmanaged.[64] 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 most cost-effective are used in practice. Statins should be used in addition to optimal prescribing of these other more cost-effective treatments. It seems unlikely that use of these other treatments, in the context of secondary prevention, would lower an individual's CHD risk to below some arbitrarily defined threshold below which statins could be deemed cost-ineffective.

Targeted use of statins

The level of CHD risk above which it is decided that the use of statins is sufficiently cost-effective 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. A recent statement by the Standing Medical Advisory Committee 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.[65] The implications of this advice for the drug budget locally and nationally will depend on the degree to which lower priced statins are prescribed, the use of lower starting doses, titration of dose, rates of case identification and compliance with treatment. If the decision to use statins were based on a threshold of 3% annual coronary event risk, about 3.4% of people aged 35 to 69 years in England (about 700,000 people) would be eligible for treatment

with statins, in addition to those who have had a CHD event.[62]

If statins were used to treat people with CHD event rates below 3%, many more people would have to be treated for much less health gain than in secondary prevention. However, the trial evidence would support treatment at lower levels, and certainly down to annual CHD event rates of around 1.5%. At this threshold, almost 20% of people aged 35 to 69 years would require primary prevention treatment, which, in addition to the 5% of the population who would benefit from secondary prevention with statins, would result in almost 5 million people requiring treatment.

Cost of statins

The cost of statins is a major cause of concern to the NHS. Costs of statins vary quite markedly and there is the potential for greater cost-effectiveness through the use of lower doses or of cheaper statins, neither of which has been tested in clinical event trials. As shown in *Table 11,* use of atorvastatin 10 mg daily for secondary prevention results in a cost-effectiveness of £2188 (net, discounted). Atorvastatin is very potent and half of this dose would result in a 20% reduction in LDL cholesterol which should be sufficient to achieve reductions in CHD events. If a suitable 5 mg tablet was marketed at half of the price of the 10 mg tablet, the cost-effectiveness would fall to about £1000 per life-year gained and would be equivalent to many other treatments. Interestingly, statins purchased in India are much less expensive – about £67 per year (i.e. about a seventh of UK prices), at which price their cost-effectiveness is in line with other secondary prevention treatments.[66] As the price of drugs is agreed by the Department of Health, there may be a case for further examining the prices of statins, given the very large potential market for these drugs in primary prevention. Once patents expire, it is likely that statins of proven clinical efficacy will be available at much lower prices.

CHD scoring systems

Various scoring systems derived from the Framingham prediction equations are available to help to estimate an individual's CHD event risk. These include the Sheffield tables,[62,67] the New Zealand tables,[68] the joint British guidelines,[69] and the Vallance risk estimator.[70] The most recently developed methods not only calculate risk from an individual's risk factors but also assess the likely effect of modifying risk factors for each patient. This should make it possible for patients to make informed decisions on the basis of individualised and valid estimates of their risk and trade-offs with benefits of different interventions.[70]

However, all of these methods have weaknesses. They do not take into account the increased risk associated with certain ethnic groups (e.g. South Asians) or low socio-economic class. The Framingham risk equations aimed to produce the best prediction of risk but did not use the most readily obtainable or modifiable risk factors: for example, physical inactivity does not feature as a risk factor. The estimates of absolute risk obtained are likely to be inaccurate because they are based on rates in the USA in the 1980s, but rates have fallen dramatically – by at least half – in both the USA and Britain. Worryingly, the Framingham risk equation markedly over-estimates event rates when applied to a large representative sample of British men.[71] It is quite likely that these differences are explained by the way in which risk factors are measured and categorised. Furthermore, as CHD risk is much greater in the north than the south of Britain, and is higher in socially disadvantaged people, simple computer packages and charts are unlikely to provide absolute risk estimation of sufficient accuracy to define thresholds for treatment. Indeed, by using average risk prediction unadjusted for social or ethnic differences, these equations seriously disadvantage poorer people and those from ethnic minorities who will be at higher than predicted absolute risk, and thereby denied effective treatment because they fall below the threshold.

The risk equations also persist in giving undue emphasis to blood cholesterol, or more recently the HDL cholesterol:total cholesterol ratio. The predictive value of blood cholesterol is low (see *Figures 1* and *2*, page 2), and in the WOSCOPs trial,[54] hypercholesterolaemia (defined as LDL cholesterol of 4–6 mmol/litre) without any other risk factors was associated with an annual CHD event rate of below 1%, even in men aged 55–64 years. Smoking, hypertension and a family history of heart disease were all much more important predictors of future CHD events. Blood cholesterol levels in the UK are high and the increased relative risk of CHD appears to be constant per unit increase in blood cholesterol over a very wide range,[72] suggesting that there is no threshold level of blood cholesterol (or HDL cholesterol:total cholesterol ratio) above which treatment is beneficial.

While the identification of individual risk and application of a treatment threshold provides an explicit means of rationing healthcare resources, there is no scientific evidence that supports the level chosen. The revised Sheffield tables now provide both 1.5% and 3.0% annual CHD event levels, aimed to guide the use of aspirin and antihypertensives. As the cost of statins falls, it would presumably be logical for the CHD risk threshold for treatment to be lowered. Periodic resetting of the threshold levels would require computer packages to be adjusted, policy makers and general practitioners to be informed of the changes, and statins to be offered to patients who might previously have been told they did not need them.

One component generally missing from these risk identification methods is the view of the patient. It is possible that some patients will prefer to make lifestyle changes rather than accept lifelong drug treatment. Further research is needed to evaluate patient preferences for different treatment options, and the cost, use, accuracy and impact of currently available computerised risk packages in primary care.

Chapter 5

Further research

This review has highlighted the need for a range of further research. The major areas demanding attention are as follows.

The effectiveness of statins for broader clinical indications

Owing to trial recruitment policies, little is known of the efficacy of statins among older people who are at highest risk of CHD. Trials in people over the age of 75 years are needed and at least one is underway in the west of Scotland.

Evidence about the effectiveness of statins for the treatment of women is sparse. Available data provide reasonable support for the efficacy of statins among women who have already suffered a cardiovascular event, but their role in primary prevention among women is not clear.

Although statins appear to reduce the risk of stroke in people with other forms of cardiovascular disease, their value in people with transient ischaemic attacks and stroke is not known.

Side-effects of statins

There is a need for continued surveillance for long-term adverse consequences of statins.

Efficacy of different types of statin

Although the evidence presented here appears to support the notion of a class effect from statins, little is known of the effects of the newer statins on clinical outcomes. This may have important implications for the choice of statin in further trials to extend clinical indications, as referred to above.

Responsiveness to statins

Although the statins are effective in secondary prevention, identifying people who stand to benefit from their use would be of great value in providing a further means of targeting treatment and improving cost-effectiveness. Predictive factors would include genetic markers, physiological characteristics and lifestyles. It may be possible to use individual patient meta-analyses to perform some of the relevant sub-group analyses to develop predictive hypotheses.

Efficacy of dietary interventions

Both the oily fish diet and the Mediterranean diet stand out as potentially important dietary changes that require further testing in high risk populations. Small-scale replications are underway but given the apparent scale of benefit in the original studies[16,17] and the relatively low cost of these interventions, a high priority should be given to large-scale trials.

Validation and evaluation of CHD risk scoring systems

Research to validate CHD risk scoring systems among cohorts of the contemporary British population would be of value. At present it is not clear whether existing systems accurately predict absolute risk, or whether their predictive performance is equally good among socio-economic, ethnic and geographic subgroups. The effects of risk scoring systems on professional and patient behaviour, risk factor distributions, and outcomes requires careful evaluation. The HTA programme has recently started commissioning work in this area. It is likely that effects will vary greatly between professionals and different types of patients, and a complex programme of work, rather than isolated projects, will be required.

Patient preferences

Patient preferences for life-long drug treatment or for lifestyle modification have been under-explored. A programme of work examining the determinants of patient preferences, their impact on compliance with drug and other health behavioural interventions, and the relative costs to patients of different approaches to reducing risk is urgently required.

Chapter 6
Conclusions

There is a wide range of therapies with varying levels of evidence for efficacy, effectiveness and cost-effectiveness for the prevention of CHD. In this report we have presented an attempt to compare these therapies using a common analytical technique, to inform the current discussion on the best approach for CHD prevention.

The results indicate that statins are a cost-effective therapy for CHD prevention, compared with a range of currently provided interventions. However, they also indicate that many pre-existing therapies are equally if not more cost-effective, with the implication that significant efforts should be made to ensure that these therapies – when indicated – have been implemented before undertaking the significant additional expenditures associated with the use of statins for CHD prevention. In secondary prevention of CHD there is no doubt that statins provide benefit over and above that obtained from the use of pre-existing treatments, such as aspirin.

The wide confidence intervals around some of the estimates of cost-effectiveness of dietary interventions reflect the relatively few data available. Attempts to replicate the results of trials such as the DART[16] study and the Mediterranean diet trial[17] would be valuable, not only to improve the precision of the estimates of cost-effectiveness, but also to corroborate the findings.

There is a need to distinguish population strategies from clinical strategies for the **primary** prevention of CHD. Pressing primary care clinicians into providing advice on diet to a large proportion of their patients is of limited value,[73] whereas providing advice on cessation of tobacco smoking is most cost-effective. Additional benefits would be obtained from improved detection and control of high blood pressure, although the evidence required to develop new initiatives is lacking.[74] The effectiveness of statins in primary prevention is not in doubt, but their cost-effectiveness in comparison with other approaches to CHD prevention is poor. Reduction in the cost of statins to the level of many antihypertensive drugs – and indeed to the level at which they are marketed in some countries[66] – would change the cost-effectiveness picture dramatically.

In public health terms, the major approaches to the primary prevention of CHD remain the fiscal and legislative control of tobacco, the reduction of hidden saturated fats and calories in the diet, encouraging and extending facilities available for physical activity throughout life, and the reduction of poverty.

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Appendix 1

Reasons for exclusion of statin trials identified by search

Trial not yet completed

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No untreated/placebo comparison group

Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anti-coagulation on obstructive changes in saphenous-vein coronary artery bypass grafts. *New Engl J Med* 1997;**336**:153–62.

Non-randomised comparison

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Appendix 2

Search strategies

Search strategy for MEDLINE for cardiovascular RCTs and cholesterol lowering

1. randomized controlled trial.pt.
2. randomized controlled trials/
3. random-allocation.sh.
4. double-blind-method.sh.
5. single-blind-method.sh.
6. 1 or 2 or 3 or 4 or 5
7. clinical trials.pt.
8. clinical trials.sh.
9. clin$ near trial$.ti.
10. clin$ near trial$.ab.
11. placebo.sh.
12. placebo.tw.
13. random.tw.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. limit 14 to human
16. coronary disease.sh.
17. cerebrovascular disorders.sh.
18. 16 or 17
19. 15 and 18
20. cholesterol.tw
21. lipid lowering.tw.
22. statin*.tw.
23. simvastatin.tw.
24. pravastatin.tw.
25. lovastatin.tw.
26. fluvastatin.tw.
27. HMG*.tw.
28. co-reductase inhibitor*.tw.

Search strategy for MEDLINE for systematic reviews of cholesterol lowering with statins

1. (meta-analysis or review literature).sh.
2. meta-anal$.tw.
3. metaanal$.tw.
4. (systematic$ adj4 (overview$ or review$)).tw.
5. meta-analysis.pt.
6. case report.sh.
7. letter.pt.
8. historical article.pt.
9. review of reported cases.pt.
10. review, multicase.pt.
11. 6 or 7 or 8 or 9 or 10
12. 1 or 2 or 3 or 4 or 5
13. 12 not 11
14. limit 13 to human
15. coronary disease.sh.
16. cerebrovascular disorders.sh.
17. 16 or 17
18. 15 and 18
19. cholesterol.tw
20. LDL-cholesterol.tw.
21. HDL-cholesterol.tw.
22. lipid lowering.tw.
23. statin*.tw.
24. simvastatin.tw.
25. pravastatin.tw.
26. lovastatin.tw.
27. fluvastatin.tw.
28. hydroxymethylglutaryl*.tw.
29. HMG*.tw.
30. co-reductase inhibitor*.tw.

Search of the Cochrane CENTRAL trials register

A simple search of the Cochrane CENTRAL trials register was conducted:

Heart*
Statin*
Cholesterol*
simvastatin
pravastatin
lovastatin
fluvastatin
hydroxymethylglutaryl*
HMG*

Other searches

In addition, reference lists of published papers and meta-analyses were checked for references.

Trials concerned with cholesterol lowering with other drugs and diet relied on an earlier meta-analysis conducted for the *Effective Health Care Cholesterol: Screening and Treatment* 1993:**1**(3);1–8 and published as:

Sheldon TA, Song F, Davey Smith G, Freemantle N. Mason J, Long A. Cholesterol screening and cholesterol lowering treatment. *Qual Health Care* 1993;**2**:134–7.

Appendix 3

Data from trials of statins and other cholesterol lowering drugs

TABLE 18 *Pravastatin – primary prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
WOSCOPS (Shepherd, *et al.*, 1995[13])	3.8	Primary Cholesterol ≥ 6.5 mmol/litre	Pravastatin 40 mg/placebo	4.9	M (55)	3302/3293	106/135	41/61	6/4	143/204	40/47	51/80†		7.03	20
KAPS (Salonen *et al.*, 1995[75])	3.0	Primary LDL cholesterol > 4.0 mmol/litre	Pravastatin 40 mg/placebo	3	M (57)	224/223	3/5	2/1	0/1	3/6	2/3	4/4	0/1	6.7	19
Multinational pravastatin study (PMSG, 1993[76])	3.8	Primary ≥ 2 CVD risk factors	Pravastatin 20 mg/placebo	1.5	MF (55)	530/532	0/3	0/3	0/0	1/8	0/4	0/3	–	6.7	19

* *Per 1000 person-years*
† *Either CABG or PTCA*

PMSG, Pravastatin Multinational Study Group for Cardiac Risk Patients; CVD, cardiovascular disease

TABLE 19 *Pravastatin – secondary prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
CARE (Sacks, *et al.*, 1996[14])	11.5	Post-MI Cholesterol > 6.2 mmol/litre	Pravastatin 40 mg/placebo	5	MF (59)	2081/2078	180/196	96/119	10/6†	135/173	44/72†	156/207	172/219	5.40	20
PLAC I (Furberg, *et al.*, 1995[77])	5.0	CHD	Pravastatin 40 mg/placebo	3	MF (57)	206/202	4/6	3/3	0/0	7/16	0/2	–	–	6.0	20
PLAC II (Byington, *et al.*, 1995[39])‡	8.8	CHD	Pravastatin 40 mg (73%), 20 mg (27%)/ placebo)	3	MF (63)	75/76	3/5	2/2	0/1	2/8	1/2	–	–	6.05	21
REGRESS (de Groot, *et al.*, 1995[78])	5.7	CHD	Pravastatin 40 mg/placebo	2	MF (56)	450/435	5/8	3/5	0/0	7/12	3/5	24/22	20/47	6.02	20
HARP (Sacks, *et al.*, 1994)[78a]	8.5	CHD Cholesterol < 6.5 mmol/litre	Pravastatin 40 mg/placebo	2.5	MF (58)	44/47	1/1	1/1	–	2/0	–	1/1	1/2	5.5	28
Kobashigawa, *et al.*, 1995[79]	–	Post-transplantation	Pravastatin 40 mg/placebo	1.0	MF (52)	47/50	3/10	0/0	0/0	0/0	0/0	0/0	0/0	4.5	26
LIPID (LIPID Study Group, 1998[36])	13.8	Post-MI	Pravastatin 40 mg/placebo	6	MF (31–75§)	4512/4502	498/633	287/373	–	–	–	–	–	5.60	18

* *per 1000 person-years*
† *Data provided by Hebert stroke meta-analysis*[79a]
‡ *The pooled analysis of regression trials reported by Byington et al., 1995*[39] *has event numbers that do not tally with the original reports*
§ *Range*

TABLE 20 *Simvastatin – secondary prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
MAAS Investigators, 1994[80]	5.0	CHD	Simvastatin 20 mg/placebo	4	MF (55)	204/200	4/11	4/4	0/0	9/3	1/2	8/16	15/22	6.35	23
4S (4S Group, 1994[81])	15.7	CVD Diabetes	Simvastatin 40 mg (37%), 20 mg (63%)/ placebo	5.4	MF (60)	2221/2223	182/256	111/189	14/12	134/207	61/90†	252/383‡		6.74	25
CIS (Bestehorn, *et al.*, 1997[82])	7.0	CHD Cholesterol 5.3–9.0 mmol/litre	Simvastatin 40 mg/placebo	2.3	M (50)	129/125	1/4	1/2	0/0	1/5	0/0	5/4‡		6.2	28
Tomei, *et al.*, 1993[83]	8.3	Hyperlipidaemia	Simvastatin 20 mg/placebo	4	MF (11–96§)	28/30	1/1	1/1	0/0	–	–	–	–	NA	–

* *per 1000 person-years*
† *Data provided by Hebert stroke meta-analysis*[79a]
‡ *Either CABG or PTCA*
§ *Range*

TABLE 21 *Lovastatin – prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
AFCAPS/ TexCAPS (Downs, *et al.*, 1998[37])	0.9	Primary	Lovastatin 20–40 mg/ placebo	5.2	MF	3301/3304	–	–	–	–	–	–		5.71	18
EXCEL (Bradford, *et al.*, 1991[84])	2.0	Primary	Lovastatin 20–80 mg/ placebo	0.9	MF (56)	6582/1663	33/3	28/3	–	–	–	–	–	6.7	24
Sahni, *et al.*, 1991[85†]	26.5	Secondary	Lovastatin 20–40 mg/usual	2	MF (60)	79/78	4/5	2/4	–	–	–	–	–	5.4	12.8
Brown, *et al.*, 1990[86]	4.10	CHD	Lovastatin 40 mg + colestipol/ placebo +/– colestipol	2.5	M (47)	46/52	1/0	1/0	0/0	1/0	1/6	0/0	1/3	7.12	37
Weintraub, *et al.*, 1994[87]	10.0	CHD	Lovastatin 80 mg/placebo	0.5	MF (62)	203/201	3/1	3/1	0/0	5/14	0/1[‡]	36/38[§]		5.3	32 (LDL)
ACAPS (Probstfield, *et al.*, 1995;[88] Furberg, *et al.*, 1994[89])[91] ‖	4.4	CHD	Lovastatin 20–40 mg/ placebo/ warfarin	3.0	MF (62)	460/459	1/8	0/4	0/2	5/5	0/3	–		6.1	17
CCAIT (Waters, *et al.*, 1994[90])	3.0	CHD	Lovastatin 20–80 mg/ placebo	2.0	MF (53)	165/166	2/2	2/1	0/0	5/6	1/0	0/0[§]		6.5	21
MARS (Blankenhorn, *et al.*, 1993[91])	3.7	CHD	Lovastatin 80 mg/placebo	2.0	MF (58)	134/136	2/1	1/1	0/0	–	0/3[91]	–		6.0	32

* *per 1000 person-years*
† *2-year follow-up data: R Sahni, personal communication, 1993*
‡ *Not specified; allocated to non-fatal*
§ *Either CABG or PTCA*
‖ *Duplicate publication*
[91] *Data provided by Hebert stroke meta-analysis*[79a]

TABLE 22 *Other drugs – prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
Sprecher, *et al.*, 1994[92]	8.90	CHD LDL cholesterol ≥ 4.14 mmol/litre	Fluvastatin 10–20 mg/placebo +/– cholestyramine	0.5	MF (54)	150/74	1/0	1/0	0/0	0/0	0/0	0/0	0/0	7.55	13
CLASI/CLASII (Azen, *et al.*, 1996[93])	10.5	CHD	Colestipol + niacin/placebo	7	M (54)	80/82	2/6	2/6	–	7/19	–	23/25†		6.3	26
Ryan & Jain, 1972[94]	0	Primary Cholesterol ≥ 6.5 mmol/litre	Colestipol/ cholestyramine/ placebo	1	MF (54)	15/15/15	0/1/0	0/1/0	0/0/0	0/0/0	0/0/0	0/0/0	–	7.5	14/14
Ryan, *et al.*, 1974[95]	6.9	Primary Cholesterol ≥ 6.5 mmol/litre	Colestipol/placebo	3	MF (57)	44/48	1/1	1/1	0/0	0/1	0/0	0/0	–	7.6	15
Ruoff, 1978[96]	10.5	CHD	Colestipol/placebo	5	MF (49)	21/19	0/1	0/1	0/0	0/0	0/0	0/0	–	7.7	19
Gundersen *et al.*, 1976[97]	66.7	Primary Cholesterol ≥ 6.7 mmol/litre	Colestipol/placebo	0.5	MF (53)	36/30	0/1	0/1	0/0	0/0	0/0	0/0	–	7.6	15
Marmorston, *et al.*, 1962[98]	110.4	Secondary	Oestrogen/placebo	2.5	M (50–70‡)	285/147	70/38	62/35	–	–	–	–	–	NA	–
Stamler, *et al.*, 1963[99]	78.8	Secondary	Oestrogen/placebo	5	M (< 50)	156/119	37/40	34/39	–	–	–	–	–	6.4	3
McCaughan, 1981[100]	72.7	Secondary	Probucol/placebo	1	M (50)	88/30	2/3	2/2	–	–	–	–	–	7.9	8

* *per 1000 person-years*
† *Either CABG or PTCA*
‡ *Range*

continued

TABLE 22 contd *Other drugs – prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
Harrold, *et al.*, 1969[101]	63.5	Diabetics	Clofibrate/placebo	1	MF (NA)	30/33	0/3	0/2	–	–	–	–	–	NA	–
Carlson & Rosenhamer, 1988[102]	62.1	Secondary	Clofibrate-niacin/ placebo	5	MF (60)	279/276	61/82	47/73	–	–	–	–	–	6.4	13
Schock, 1968[103]	50.3	Secondary	Various drugs/ placebo	3.2	M (51)	427/143	81/27	71/23	–	–	–	–	–	6.2	6.3
			niacin/placebo			77/143	15/27	13/23	–	–	–	–	–	6.3	13.2
Newcastle-upon-Tyne Study, 1971[104]	48.9	Secondary	Clofibrate/corn oil	5	MF (55)	244/253	31/51	25/44	–	–	–	–	–	6.5	9.8
Oliver & Boyd, 1961[105]	48.8	Secondary	Oestrogen/lactose	5	M (35–64‡)	50/50	17/12	13/10	–	–	–	–	–	6.1	12.4
Acheson & Hutchinson, 1972[106]	21.9	Secondary	Clofibrate/corn oil	6	MF (NA)	47/48	23/20	13/5	–	–	–	–	–	7.5	8.5
STARS (Watts, *et al.*, 1992[107])	34.4	Secondary	Cholestyramine/ diet/usual	3	M (51)	30/30/30	0/1/3	0/1/3	–	–	–	–	–	7.2	23.8/11.1
CDP (Canner, *et al.*, 1986;[108] CDP Research Group, 1975[109])	42.0	Secondary	Niacin + clofibrate/ placebo	6.2	M (30–64‡)	2222/2789	555/723	478/632	–	–	–	–	–	6.5	8.1

* *per 1000 person-years*
‡ *Range*

continued

TABLE 22 contd *Other drugs – prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
CDP (Canner, *et al.*, 1986;[108] CDP Research Group, 1975[109])	35.9	Secondary	Dextrothyroxine/ placebo	3	M (30–64‡)	1083/2715	160/339	119/274	–	–	–	–	–	6.5	11
CDP (Canner, *et al.*, 1986;[108] CDP Research Group, 1975[109])	32.9	Secondary	Oestrogen 5 mg/placebo	1.5	M (30–64‡)	1119/2788	91/193	67/133	–	–	–	–	–	6.5	NA
CDP (Canner, *et al.*, 1986;[108] CDP Research Group, 1975[109])	34.5	Secondary	Oestrogen 2.5 mg/placebo	4.7	M (30–64‡)	1101/2789	219/525	162/410	–	–	–	–	–	6.5	NA
Research Committee of the Scottish Society of Physicians, 1971[110]	27.3	Secondary	Clofibrate/olive oil	6	MF (52)	350/367	42/48	34/35	–	–	–	–	–	7.0	16
Dorr, *et al.*, 1978[111]	14.5	Primary	Colestipol/placebo	1.9	MF (54)	1149/1129	37/48	19/31	–	–	–	–	–	7.9	9.4
NHLBI (Brensike, *et al.*, 1984[112])	18.2	Secondary	Cholestyramine + diet/diet	5	NA (46)	71/72	5/7	5/6	–	–	–	–	–	8.4	16.3

* *per 1000 person-years*
‡ *Range*

continued

TABLE 22 contd *Other drugs – prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
POSCH (Buchwald, *et al.*, 1990[113])	11.8	Secondary	Ileal surgery/ control	9.7	MF (51)	421/417	49/62	32/44	–	–	–	–	–	6.5	22.5
Frick, *et al.*, 1993[114]	5.1	Secondary	Colestipol + niacin + diet/diet + placebo	2	M (49)	311/317	19/12	17/8	–	–	–	–	–	7.0	8.5
LRCPPT, 1984 (Lipid Research Clinics Program, 1984[115,116])	3.2	Primary	Cholestyramine/ placebo	7.4	M (48)	1906/1900	68/71	32/44	–	–	–	–	–	7.2	8.5
Frick, *et al.*, 1987[116a]	1.9	Primary	Gemfibrozil/ placebo	5	M (47)	2051/2030	44/43	14/19	–	–	–	–	–	7.0	10.1
WHO, 1978[117]	2.8	Primary	Clofibrate/olive oil	5.3	M (46)	5331/5296	236/181	91/77	–	–	–	–	–	6.9	9
SCOR (Kane, *et al.*, 1990[118])	0	Familial hyper-cholesterolaemia	Various drugs + diet/diet	2	MF (41)	48/49	0/1	0/0	–	–	–	–	–	9.6	24.5
FATS (Brown, *et al.*, 1990[86])	0	Secondary	Various drugs + diet/diet	2.5	M (47)	94/52	1/0	1/0	–	–	–	–	–	7.0	24.9
Gross & Figueredo, 1973[119]	0	Secondary	Colestipol/placebo	1	MF (57)	23/29	1/2	1/0	–	–	–	–	–	7.7	9.6
Rifkind, *et al.*, 1967;[120§] Begg, 1972[121]	7.6	PAD	Clofibrate/placebo	1.5	NA (55)	76/79	4/10	4/9	0/1	3/10	5/4	–	–	6.45	15

* *per 1000 person-years*
§ *Stroke events do not tally with those reported in the review article by Begg*[121]
PAD, peripheral artery disease

continued

TABLE 22 contd *Other drugs – prevention data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
Cullen, *et al.*, 1974[122]	NA	Diabetes	Clofibrate/placebo	2.0	MF (51)	20/20	1/2	–	–	–	–	–	–	NA	–
VA Study Group (atherosclerosis), 1973[123]	10.1	Stroke/TIA	Clofibrate/placebo	4.5	M (< 70)	268/264	22/30	11/12	5/7	8/9	37/23	–	–	6.2	6
Cohn, *et al.*, 1975[124]	NA	CHD	Clofibrate/placebo	1.0	NA (49)	32/33	1/1	–	–	–	–	–	–	6.7	3
BECAIT (de Faire, *et al.*, 1997[125])	0	CHD	Bezafibrate/ placebo	5.0	MF (42, < 45)	47/45	2/0	2/0	0/0	1/4	0/0	1/5	0/3	6.9	9
Italian I (Belcaro, 1993, unpublished)	2.7	Diabetes	Bezafibrate/placebo	4	MF (11–96‡)	185/182	1/2	1/2	0/0	–	–	–	–	NA	–
Italian II (unpublished)	1.4	Hyperlipidaemia	Bezafibrate/placebo	4	MF (11–96‡)	178/181	0/1	0/1	0/1	–	–	–	–	NA	–
VA Study Group (oestrogens), 1966[126]	29.7	Stroke	Oestrogens/placebo	5	M (60)	289/283	114/94	33/42	32/29	10/8	43/37	–	–	NA	–

* *per 1000 person-years*
‡ *Range*
TIA, transient ischaemic attack

Appendix 4

Data from trials on multiple risk factor interventions

TABLE 23 *Multiple risk factors – data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
SCRIP (Haskel, *et al.*, 1994[127])	4.8	CHD	Multiple risk factor/ usual care	4.0	MF (56)	145/155	3/3	2/3	0/0	4/10	0/0	6/14	13/17	6.0	16
Agewall, *et al.*, 1994[128]	15.4	Hypertension	Multiple risk factor/ usual care	3.0	M (66)	253/255	14/21	12/13	0/0	18/22	5/17	–	–	6.6	5
WHO (industry) (Rose, *et al.*, 1980 & 1983;[129,130] WHO, 1983[131])	2.2	Primary	Multiple risk factor/ usual care	6	M (49)	30,489/ 26,971	1325/1186	428/398	–	–	–	–	–	5.5	0
Wilhelmsen, *et al.*, 1986[132]	3.9	Primary	Diet + drugs + smoking/usual care	11.8	M (51)	10,000/ 20,018	1293/2636	462/923	–	–	–	–	–	6.5	0.2
Oslo Study (Hjermann, *et al.*, 1981; [133] Holme, *et al.*, 1985[134])	4.5	Primary	Diet + smoking/ usual care	5	M (45)	604/629	16/24	5/10	–	–	–	–	–	8.5	6
MRFIT Research Group, 1976 & 1990[135,136]	2.8	Primary	Diet + smoking + exercise + drugs/ usual care	6	M (46)	6428/6438	265/260	115/124	–	–	–	–	–	6.6	2
Miettinen, *et al.*, 1985;[137] Naukkarinen, *et al.*, 1989[138]	0.3	Primary	Diet + smoking + exercise + drugs/ usual care	5	M (48)	612/610	10/5	4/1	–	–	–	–	–	7.1	6.3
HDFP (HDFP Cooperative Group, 1977 & 1979[139,140])	5.9	Hypertension	Diet + smoking + exercise + BP drugs/usual care	5	MF (51)	5485/5455	349/419	131/148	–	–	–	–	–	NA	–

* *per 1000 person-years*

continued

TABLE 23 contd *Multiple risk factors – data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
John Hopkins Study (Morisky, *et al.*, 1980 & 1983;[141,142] Levine, *et al.*, 1987[143])	32.0	Hypertension	Diet + BP drugs/ usual care	5	MF (54)	350/50	35/11	23/8	–	–	–	–	–	NA	–
CELL (Lindholm, *et al.*, 1995[144])	3.1	Primary	Diet + exercise + drugs/usual care	1	MF (49)	339/320	2/1	2/1	–	–	–	–	–	6.8	2.2
OXCHECK (OXCHECK Study Group, 1991 & 1994[145,146])	1.2	Primary	Diet + smoking + exercise + drugs/ usual care	3	MF (50)	8307/2783	146/40	52/13	–	–	–	–	–	M 6.1 F 6.2	1.6 4.5

* *per 1000 person-years*
BP, blood pressure

Appendix 5

Data from trials on dietary cholesterol lowering interventions

TABLE 24 *Dietary interventions – data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
Morrison, 1951[147†]	8.7	CHD	Low cholesterol + low fat/usual	3.0	MF (32–70‡)	50/50	7/15	6/13	0/2	–	–	–	–	8.06	29
Rose, *et al.*, 1965[148§]	20.3	Post-MI	Corn + olive oil/ usual	2.0	MF (55)	54/26	8/1	8/1	0/0	–	–	–	–	6.7	3.6
MRC, 1965[149]	56.0	Post-MI	Low fat diet/usual	3.0	M (< 65)	123/129	20/24	17/20	0/0	43/44	–	–	–	6.8	6.6
MRC, 1968[150]	29.1	Post-MI	Soya bean/usual	4.8	M (< 60)	199/194	28/31	25/25	0/0	25/25	–	–	–	7.0	14.3
Dayton, *et al.*, 1969[151]	32.4	Residents, Veterans Association homes	Low fat/usual	3.7	M (66)	424/422	177/174	41/50	3/9	19/28	–	–	–	6.1	12.7
Woodhill *et al.*, 1978[152]	23.2	Post-MI	Low fat diet/usual	5.0	M (49)	221/237	39/28	35/26	–	–	–	–	–	7.3	4.0
Oslo Diet (Leren, 1966[153])	56.0	Post-MI	Low fat/usual	5.0	M (56)	206/202	41/55	37/50	–	42/76	–	–	–	7.7	14.4
DART-fat (Burr, *et al.*, 1989[16,154])	50.6	Post-MI	Low fat/usual	2.0	M (57)	1018/1015	111/113	97/97	4/3	35/47	–	–	–	6.5	3.5
DART-fish (Burr, *et al.*, 1989[16,154])	57.0	Post-MI	Oily fish/usual	2.0	M (57)	1015/1018	94/130	78/116	–	49/33	–	–	–	?	0
DART-fibre (Burr, *et al.*, 1989[16,154])	41.8	Post-MI	Cereal fibre/usual	2.0	M (57)	1017/1016	123/101	109/85	–	41/41	–	–	–	?	0

* *per 1000 person-years*
† *Alternate allocation to groups; by 12 years 38% survival in clofibrate group vs. 0% in controls; cholesterol level reduced by 29% relative to baseline in clofibrate group*
‡ *Range*
§ *Randomised three ways but data pooled*

continued

TABLE 24 contd *Dietary interventions – data sheet: RCTs of cholesterol lowering*

Trials	CHD risk: control group*	Predominant patient group	Interventions: treatment/ control	Follow-up (years)	Sex (mean age)	No. treated/ no. controls	No. of deaths (treated/controls)			No. of non-fatal events (treated/controls)				Total baseline cholesterol	
							Total	CHD	Stroke	MI	Stroke	CABG	PTCA	mmol/ litre	% reduction
Frantz, *et al.*, 1989[155]	15.7 M 10.2 F	Residents, mental hospital	Low fat/usual	1.05	M (43) F (48)	2197/2196 2344/2320	158/153 111/95	22/24	–	40/23	–	–	–	5.4	13.8
STARS (Watts, *et al.* 1992[107])	34.4	CHD	Low fat/usual	3.0	M (49)	30/30	1/3	1/3	0/0	2/6	0/0	–	–	7.2	11.1
Singh, *et al.*, 1992[156]	127.5	Post-MI	Fruit + nut/ usual	1	MF (51)	204/202	28/51	25/45	–	44/94	–	–	–	5.9	7.2
Schuler, *et al.*, 1992[157]	17.5	Angina	Low fat diet/ usual	1	MF (54)	56/57	2/1	2/1	0/0	0/3	0/0	0/1	2/3	6.05	10

* *per 1000 person-years*

Appendix 6

Meta-analysis of statin trials

TABLE 25 *Statin trials: meta-analysis data*

Trial	No. patients included		Total mortality		CHD deaths		MI non-fatal		Revascularisation		Non-fatal stroke	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
CARE (Sacks, *et al.*, 1996[14])	2081	2078	180	196	96	119	135	173	291	391	44	72
PLAC I (Furberg, *et al.*, 1995[77])	206	202	4	6	3	3	7	16	0	0	0	2
PLAC II (Byington, *et al.*, 1995[39])	75	76	3	5	2	2	2	8	0	0	1	2
REGRESS (de Groot, *et al.*, 1995[78])	450	435	5	8	3	5	7	12	44	69	3	5
HARP (Sacks, *et al.*, 1994)	44	47	1	1	1	1	2	0	2	3	–	–
Kobashigawa *et al.*, 1995[79]	47	50	3	10	–	–	–	–	–	–	0	0
WOSCOPS (Shepherd, *et al.*, 1995[13])	3302	3293	106	135	41	61	143	204	51	80	40	47
KAPS (Salonen *et al.*, 1975[75])	224	223	3	5	2	1	3	6	4	5	2	3
PMSG, 1993[76]	530	532	0	3	0	3	1	8	0	3	0	4
LIPID (LIPID Study Group, 1998[36])	4512	4502	498	633	287	373	–	–	–	–	–	–
MAAS (MAAS Investigators, 1994[80])	204	200	4	11	4	4	9	3	23	38	1	2
4S (4S Group, 1994[81])	2221	2223	182	256	111	189	134	207	252	383	61	90
CIS (Bestehorn, *et al.*, 1997[82])	129	125	1	4	1	2	1	5	5	4	0	0
Italian IV[83] (unpublished data)	28	30	1	1	1	1	–	–	–	–	–	–
Sahni, *et al.*, 1991[85]	79	78	4	5	2	4	–	–	–	–	–	–
EXCEL (Bradford, *et al.*, 1991[84])	6582	1663	33	3	28	3	–	–	–	–	–	–
Weintraub, *et al.*, 1994[87]	203	201	3	1	3	1	5	14	36	38	0	1
ACAPS (Probstfield, *et al.*, 1995[88])	460	459	1	8	0	6	5	5	–	–	0	3
CCAIT (Waters, *et al.*, 1994[90])	165	166	2	2	2	1	5	6	0	0	1	0
MARS (Blankenhorn, *et al.*, 1993[91])	134	136	2	1	1	1	–	–	–	–	0	3
Brown, *et al.*, 1990[86]	46	52	1	0	1	0	1	0	1	3	1	6
AFCAPS/TexCAPS (Downs, *et al.*, 1998[37])	3304	3301	80	70	11	15	46	80	106	157	–	–
Sprecher, *et al.*, 1994[92]	150	74	1	0	1	0	–	–	–	–	0	0

Appendix 7

Meta-analysis results for statins and non-statin cholesterol lowering interventions

TABLE 26 *End-point summary for statins*[*]*: log of OR, fixed model*

End-point	OR	95% CI	*p*, association	*p*, homogeneity	No. of studies	No. of patients
All trials[†]						
Total mortality	0.782	0.719–0.850	< 0.001	0.341	23	45,322
CHD deaths	0.722	0.646–0.806	< 0.001	0.782	23	45,322
MI non-fatal	0.662	0.589–0.744	< 0.001	0.224	15	27,159
Revascularisation	0.658	0.599–0.724	< 0.001	0.964	15	26,338
Composite end-point	0.643	0.551–0.752	< 0.001	0.950	18	27,757
Sub-group: pravastatin						
Total mortality	0.783	0.709–0.863	< 0.001	0.721	10	22,909
CHD deaths	0.754	0.663–0.858	< 0.001	0.974	10	22,909
MI non-fatal	0.690	0.592–0.804	< 0.001	0.323	8	13,798
Revascularisation	0.674	0.586–0.775	< 0.001	0.951	8	13,798
Sub-group: simvastatin						
Total mortality	0.669	0.550–0.813	< 0.001	0.550	4	5160
CHD deaths	0.579	0.457–0.733	< 0.001	0.840	4	5160
MI non-fatal	0.646	0.518–0.806	< 0.001	0.040	3	5102
Revascularisation	0.615	0.523–0.724	< 0.001	0.546	3	5102
Sub-group: lovastatin						
Total mortality	1.074	0.809–1.427	0.622	0.308	8	17,029
CHD deaths	1.022	0.600–1.741	0.937	0.398	8	17,029
MI non-fatal	0.580	0.422–0.798	< 0.001	0.549	4	8259
Revascularisation	0.706	0.565–0.882	0.002	0.662	4	7438
Sub-group: secondary						
Total mortality	0.757	0.691–0.831	< 0.001	0.575	19	23,819
CHD deaths	0.717	0.638–0.806	< 0.001	0.805	19	23,819
MI non-fatal	0.668	0.575–0.775	< 0.001	0.154	13	13,959
Revascularisation	0.660	0.592–0.735	< 0.001	0.914	13	13,138
Composite end-point	0.612	0.484–0.775	< 0.001	0.963	16	14,557
Sub-group: primary						
Total mortality	0.902	0.741–1.099	0.306	0.146	42	1503
CHD deaths	0.759	0.543–1.061	0.106	0.286	42	1503
MI non-fatal	0.653	0.541–0.788	< 0.001	0.394	2	13,200
Revascularisation	0.653	0.532–0.801	< 0.001	0.817	2	13,200
Composite end-point	0.669	0.543–0.823	< 0.001	0.208	2	13,200

[*] *No excluded trials; statistic of heterogeneity = Q Cochran*
[†] *All trials = primary and secondary*

TABLE 27 *End-point summary for non-statin cholesterol lowering interventions: log of OR, fixed model*

End-point	OR	95% CI	*p*, association	*p*, homogeneity	No. of studies	No. of patients
Sub-group: oestrogens						
Total mortality	1.070	0.791–1.178	0.171	0.193	6	9176
CHD deaths	0.980	0.869–1.105	0.738	0.122	6	9176
MI non-fatal	1.217	0.494–2.999	0.670	NA	1	572
Revascularisation	–	–	–	–	0	–
Sub-group: clofibrate						
Total mortality	0.970	0.899–1.046	0.428	0.013	11	18,357
CHD deaths	0.927	0.848–1.014	0.099	0.018	9	18,252
MI non-fatal	0.612	0.294–1.274	0.189	0.206	2	687
Revascularisation	–	–	–	–	0	–
Sub-group: colestipol						
Total mortality	0.422	0.131–1.366	0.150	0.815	4	360
CHD deaths	0.422	0.131–1.366	0.150	0.815	4	360
MI non-fatal	0.379	0.173–0.829	0.015	0.797	2	254
Revascularisation	0.943	0.586–1.517	0.809	–	1	162
Sub-group: bezafibrate						
Total mortality	0.766	0.132–4.432	0.766	0.408	3	818
CHD deaths	0.766	0.132–4.432	0.766	0.408	3	818
MI non-fatal	0.282	0.040–1.986	0.203	–	1	92
Revascularisation	0.120	0.016–0.919	0.041	–	1	92
Other drugs						
Total mortality	1.023	0.912–1.148	0.696	0.376	15	16,865
CHD deaths	0.953	0.829–1.097	0.505	0.311	15	16,865
MI non-fatal	–	–	–	–	0	–
Revascularisation	–	–	–	–	0	–
Sub-group: diet						
Total mortality	0.972	0.897–1.054	0.498	0.011	15	18,292
CHD deaths	0.920	0.823–1.027	0.138	0.020	15	18,292
MI non-fatal	0.795	0.700–0.904	< 0.001	< 0.001	12	17,654
Revascularisation	0.539	0.112–2.600	0.441	–	1	113
Sub-group: multiple risk factor interventions						
Total mortality	0.968	0.927–1.010	0.134	0.057	11	132,185
CHD deaths	1.304	1.203–1.413	< 0.001	< 0.001	11	132,185
MI non-fatal	0.719	0.426–1.214	0.217	0.331	2	808
Revascularisation	0.655	0.388–1.107	0.114	–	1	300

ND, no data

Appendix 8

Meta-analysis of trials of statins to examine effects in women

TABLE 28 *Summary of results of meta-analysis of trials on women*

Trial	Sample size		Maximum no. of events		CHD, fatal/ non-fatal		Breast cancer		Gynaecological cancer		Options	
	T+	T–	T+	T–	T+	T–	T+	T–	T+	T–	Order	Group
4S	407	420	88	142	60	91	3	6	6	6	1	1
Pravastatin pooled	56	58	0	4	0	4	ND	ND	ND	ND	2	1
CARE	286	290	46	80	19	34	0	1	12	1	3	1
LIPID	755	753	91	98	ND	ND	5	7	5	7	4	1
AFCAPS/TexCAPS	499	498	7	13	ND	ND	13	9	ND	ND	5	1

T+, intervention; T–, control

TABLE 29 *Maximum no. of events*: log of RR, fixed model*

Trial	Risk difference	Variance	Weight (%)	RR	95% CI
4S	–0.445	0.014	0.4352	0.640	0.510–0.804
Pravastatin pooled	–2.797	4.201	0.0014	0.061	0.001–3.385
CARE	–0.536	0.027	0.2168	0.584	0.423–0.807
LIPID	–0.076	0.018	0.3185	0.926	0.710–1.209
AFCAPS/TexCAPS	–0.604	0.209	0.0281	0.546	0.223–1.339

* *If < 1, the number of events is taken to be 0; a pseudocount method is used with a constant = 0.25*

TABLE 30 *Cumulative analysis (heterogeneity by Q Cochran test)*

Trial	RR	95% CI	*p*, association	*p*, homogeneity
4S	0.640	0.510–0.804	< 0.001	1.000
Pravastatin pooled	0.635	0.506–0.798	< 0.001	0.252
CARE	0.618	0.513–0.744	< 0.001	0.476
LIPID	0.706	0.606–0.822	< 0.001	0.059
AFCAPS/TexCAPS	0.701	0.603–0.814	< 0.001	0.101

TABLE 31 *End-point summary (all trials)*: log of RR, fixed model*

End-point	RR	95% CI	*p*, association	*p*, homogeneity	No. of studies	No. of patients
Maximum events	0.701	0.603–0.814	< 0.001	0.101	5	4022
CHD, fatal/non-fatal	0.647	0.500–0.838	< 0.001	0.435	3	1517
Breast cancer	1.191	0.665–2.132	0.557	0.060	4	3908
Gynaecological cancer	1.228	0.583–2.589	0.589	0.054	3	2911

* *No excluded trials; statistic of heterogeneity: Q Cochran*

Appendix 9

Meta-analysis of trials of statins to examine effects on older people

TABLE 32 *Summary of results of meta-analysis of trials on older people*

	Sample size		Maximum outcome		Primary events		Options	
Trial	**T+**	**T–**	**T+**	**T–**	**T+**	**T–**	**Order**	**Group**
CARE	1054	1075	213	291	89	122	1	1
Pravastatin pooled	125	101	2	11	2	11	2	1
WOSCOPS	1603	1551	117	152	117	152	3	1
4S	518	503	204	271	133	195	4	1
AFCAPS/TexCAPS	1713	1712	ND	ND	78	112	5	1

TABLE 33 *Primary events: log of RR, fixed model*

Trial	Risk difference	Variance	Weight (%)	RR	95% CI
CARE	–0.295	0.018	0.1937	0.744	0.574–0.965
Pravastatin pooled	–1.917	0.573	0.0059	0.147	0.033–0.648
WOSCOPS	–0.294	0.014	0.2454	0.745	0.591–0.938
4S	–0.411	0.009	0.3896	0.662	0.551–0.795
AFCAPS/TexCAPS	–0.361	0.021	0.1652	0.696	0.525–0.922

TABLE 34 *Cumulative analysis (heterogeneity by Q Cochran test)*

Trial	RR	95% CI	*p*, association	*p*, homogeneity
CARE	0.744	0.574–0.965	0.026	1.000
Pravastatin pooled	0.709	0.549–0.916	0.008	0.035
WOSCOPS	0.729	0.614–0.865	< 0.001	0.104
4S	0.697	0.615–0.790	< 0.001	0.165
AFCAPS/TexCAPS	0.697	0.621–0.781	< 0.001	0.278

TABLE 35 *End-point summary (all trials)* log of RR, fixed model*

End-point	RR	95% CI	*p*, association	*p*, homogeneity	No. of studies	No. of patients
Maximum outcome	0.734	0.669–0.805	< 0.001	0.205	4	6530
Primary events	0.697	0.621–0.781	< 0.001	0.278	5	9955

* *No excluded trials; statistic of heterogeneity: Q Cochran*

Appendix 10

Estimating absolute risk reductions

TABLE 36 *Statin data for exploring different total mortality rates*

Variable	Mortality rate: statins combined, trial data	Fixing placebo group mortality rates				
		0.5% total mortality	**1.0% total mortality**	**1.5% total mortality**	**3.0% total mortality**	**6.0% total mortality**
Placebo group risk: all-cause mortality	18.6 per 1000 py	5 per 1000 py	10 per 1000 py	15 per 1000 py	30 per 1000 py	60 per 1000 py
RR for all-cause mortality (95% CI)	0.77 (0.70–0.83)	0.77 (0.70–0.83)	0.77 (0.70–0.83)	0.77 (0.70–0.83)	0.77 (0.70–0.83)	0.77 (0.70–0.83)
Placebo group risk for non-fatal MI	16.5 per 1000 py	4.4 per 1000 py	8.9 per 1000 py	13.3 per 1000 py	26.6 per 1000 py	53.2 per 1000 py
RR for non-fatal MI (95% CI)	0.67 (0.60–0.76)	0.67 (0.60–0.76)	0.67 (0.60–0.76)	0.67 (0.60–0.76)	0.67 (0.60–0.76)	0.67 (0.60–0.76)
Placebo group risk for non-fatal stroke	5.9 per 1000 py	1.6 per 1000 py	3.2 per 1000 py	4.8 per 1000 py	9.5 per 1000 py	19.2 per 1000 py
RR for non-fatal stroke	0.64 (0.53–0.79)	0.64 (0.53–0.79)	0.64 (0.53–0.79)	0.64 (0.53–0.79)	0.64 (0.53–0.79)	0.64 (0.53–0.79)
Placebo group risk for CABG/PTCA	26.1 per 1000 py	7.0 per 1000 py	14.0 per 1000 py	21.1 per 1000 py	42.1 per 1000 py	84.2 per 1000 py
RR for CABG/PTCA	0.66 (0.60–0.79)	0.66 (0.66–0.79)	0.66 (0.60–0.79)	0.66 (0.60–0.79)	0.66 (0.60–0.79)	0.66 (0.60–0.79)
Sex of participants	M	M	M	M	M	M
Mean age of participants	56 years	55 years	55 years	55 years	55 years	55 years
Mean duration of trials	3.74 years	3.74 years	3.74 years	3.74 years	3.74 years	3.74 years
Name of drug	Simvastatin	Simvastatin	Simvastatin	Simvastatin	Simvastatin	Simvastatin
Mean daily dose	27.2 mg	27.2 mg	27.2 mg	27.2 mg	27.2 mg	27.2 mg

py, patient-years

TABLE 37 *Data for further runs of beta-blockers at a fixed placebo group total mortality risk of 1.5% (equivalent to a 3% CHD event rate)*

Variable	Beta-blockers (trial data)	Beta-blockers: 1.5% total mortality
Placebo group risk: all-cause mortality	68 per 1000 py	15 per 1000 py
RR for all-cause mortality (95% CI)	0.77 (0.69–0.87)	0.77 (0.69–0.87)
Placebo group risk for non-fatal MI	44.9 per 1000 py	9.9 per 1000 py
RR for non-fatal MI (95% CI)	0.74 (0.66–0.83)	0.74 (0.66–0.83)
Placebo group risk for non-fatal stroke	NA	NA
RR for non-fatal stroke	NA	NA
Placebo group risk for CABG/PTCA	NA	NA
RR for CABG/PTCA	NA	NA
Sex of participants	M	M
Mean age of participants	55 years	55 years
Mean duration of trials	2 years	2 years
Name of drug	Atenolol	Atenolol
Dose	50 mg daily	50 mg daily

TABLE 38 *Data for further runs of antihypertensives at a fixed placebo group total mortality risk of 1.5% (equivalent to a 3% CHD event rate)*

Variable	Antihypertensives: middle-aged persons (trial data)	Antihypertensives: 1.5% total mortality
Placebo group risk: all-cause mortality	14 per 1000 py	15 per 1000 py
RR for all-cause mortality (95% CI)	0.88 (0.81–0.94)	0.88 (0.81–0.94)
Placebo group risk for non-fatal MI	4.7 per 1000 py	5.0 per 1000 py
RR for non-fatal MI (95% CI)	0.85 (0.75–0.96)	0.85 (0.75–0.96)
Placebo group risk for non-fatal stroke	5.2 per 1000 py	5.6 per 1000 py
RR for non-fatal stroke	0.64 (0.56–0.73)	0.64 (0.56–0.73)
Placebo group risk for CABG/PTCA	NA	NA
RR for CABG/PTCA	NA	NA
Sex of participants	52% F	52% F
Mean age of participants	56 years	56 years
Mean duration of trials	4.9 years	4.9 years
Name of drug	Bendrofluazide	Bendrofluazide
Dose	2.5 mg daily	2.5 mg daily

TABLE 39 *Data for further runs for middle-aged persons with hypertension at a fixed placebo group total mortality risk of 1.5% (equivalent to a 3% CHD event rate) and for different drugs*

Variable	Middle-aged persons: ACE inhibitor	Middle-aged persons: antihypertensives combined*
Placebo group risk: all-cause mortality	15 per 1000 py	15 per 1000 py
RR for all-cause mortality (95% CI)	0.88 (0.81–0.94)	0.88 (0.81–0.94)
Placebo group risk for non-fatal MI	5.0 per 1000 py	5.0 per 1000 py
RR for non-fatal MI (95% CI)	0.85 (0.75–0.96)	0.85 (0.75–0.96)
Placebo group risk for non-fatal stroke	5.6 per 1000 py	5.6 per 1000 py
RR for non-fatal stroke	0.64 (0.56–0.73)	0.64 (0.56–0.73)
Placebo group risk for CABG/PTCA	NA	NA
RR for CABG/PTCA	NA	NA
Sex of participants	52% F	52% F
Mean age of participants	55 years	55 years
Mean duration of trials	4.9 years	4.9 years
Name of drug	Enalapril	Bendrofluazide 2.5 mg + atenolol 50 mg + enalapril 2.5 mg
Dose	5 mg daily	Bendrofluazide 100%; atenolol 50%; enalapril 20%

* *Bendrofluazide + atenolol + ACE inhibitor*

TABLE 40 *Data for further runs for elderly persons with hypertension, using real trial data and changing the drugs*

Variable	Elderly persons: ACE inhibitor	Elderly: antihypertensives combined*
Placebo group risk: all-cause mortality	33.1 per 1000 py	33.1 per 1000 py
RR for all-cause mortality (95% CI)	0.88 (0.80–0.97)	0.88 (0.80–0.97)
Placebo group risk for non-fatal MI	11.8 per 1000 py	11.8 per 1000 py
RR for non-fatal MI (95% CI)	0.85 (0.73–0.99)	0.85 (0.73–0.99)
Placebo group risk for non-fatal stroke	11.9 per 1000 py	11.9 per 1000 py
RR for non-fatal stroke	0.65 (0.55–0.76)	0.65 (0.55–0.76)
Placebo group risk for CABG/PTCA	NA	NA
RR for CABG/PTCA	NA	NA
Sex of participants	51% F	51% F
Mean age of participants	68.5 years	68.5 years
Mean duration of trials	4.1 years	4.1 years
Name of drug	Enalapril	Bendrofluazide 2.5 mg + atenolol 50 mg + enalapril 2.5 mg
Dose	5 mg daily	Bendrofluazide: 100%; atenolol 50%; enalapril 20%

* *Bendrofluazide + atenolol + ACE inhibitor*

TABLE 41 *Data for further runs for antiplatelet drugs at a fixed placebo group total mortality risk of 1.5% (equivalent to a 3% CHD event rate)*

Variable	Trial data	Combined drugs	1.5% total mortality (aspirin)	1.5% total mortality (combined drugs)
Placebo group risk: all-cause mortality	52 per 1000 py	52 per 1000 py	15 per 1000 py	15 per 1000 py
RR for all-cause mortality (95% CI)	0.88 (0.78–0.98)	0.88 (0.78–0.98)	0.88 (0.78–0.98)	0.88 (0.78–0.98)
Placebo group risk for non-fatal MI	32.5 per 1000 py	32.5 per 1000 py	9.4 per 1000 py	9.4 per 1000 py
RR for non-fatal MI (95% CI)	0.69 (0.57–0.81)	0.69 (0.57–0.81)	0.69 (0.57–0.81)	0.69 (0.57–0.81)
Placebo group risk for non-fatal stroke	7.5 per 1000 py	7.5 per 1000 py	2.2 per 1000 py	2.2 per 1000 py
RR for non-fatal stroke	0.61 (0.39–0.83)	0.61 (0.39–0.83)	0.61 (0.39–0.83)	0.61 (0.39–0.83)
Placebo group risk for CABG/PTCA	NA	NA	NA	NA
RR for CABG/PTCA	NA	NA	NA	NA
Sex of participants	M	M	M	M
Mean age of participants	60 years	60 years	55 years	55 years
Mean duration of trials	2 years	2 years	2 years	2 years
Name of drug	Aspirin	Aspirin + dipyridamole	Aspirin	Aspirin + dipyridamole
Dose	300 mg daily	Aspirin 75 mg + dipyridamole 400 mg	300 mg daily	Aspirin 75 mg + dipyridamole 400 mg

TABLE 42 *Data for further runs for dietary interventions at a fixed placebo group total mortality risk of 1.5% (equivalent to a 3% CHD event rate)*

Variable	DART-fish		Mediterranean diet	
	Trial data	1.5% total mortality	Trial data	1.5% total mortality
Placebo group risk: all-cause mortality	63.9 per 1000 py	15 per 1000 py	33.7 per 1000 py	15 per 1000 py
RR for all-cause mortality (95% CI)	0.73 (0.56–0.93)	0.73 (0.56–0.93)	0.40 (0.18–0.90)	0.40 (0.18–0.90)
Placebo group risk for non-fatal MI	16.2 per 1000 py	3.8 per 1000 py	28.6 per 1000 py	12.7 per 1000 py
RR for non-fatal MI (95% CI)	1.49 (0.97–2.29)	1.49 (0.97–2.29)	0.30 (0.11–0.79)	0.30 (0.11–0.79)
Placebo group risk for non-fatal stroke	NA	NA	NA	NA
RR for non-fatal stroke	NA	NA	NA	NA
Placebo group risk for CABG/PTCA	NA	NA	NA	NA
RR for CABG/PTCA	NA	NA	NA	NA
Sex of participants	M	M	M	M
Mean age of participants	56.7 years	55 years	56.7 years	55 years
Mean duration of trials	2 years	2 years	2 years	2 years
Dietary intervention	Oily fish + maxepa	Oily fish + maxepa	Diet advice	Diet advice
Treatment	Maxepa 20 mg per week, £57/year	Maxepa 20 mg per week, £57/year	£52/year	£52/year

Appendix 11

Inputs used for economic modelling exercise

TABLE 43 *Inputs for statins for primary and secondary prevention: low, intermediate and high cost statins*[*]

Input variable	Primary low	Primary intermediate	Primary high	Secondary low	Secondary intermediate	Secondary high
Placebo group risk[†]	8.1	8.1	8.1	22.2	22.2	22.2
RR for all cause mortality	0.77	0.77	0.77	0.79	0.79	0.79
Placebo group risk for non-fatal MIs[†]	12.384	12.384	12.384	19.695	19.695	19.695
RR for non-fatal MIs	0.68	0.68	0.68	0.7	0.7	0.7
Placebo group risk for non-fatal stroke[†]	3.067	3.067	3.067	8.091	8.091	8.091
RR for non-fatal stroke	0.82	0.82	0.82	0.63	0.63	0.63
Placebo group risk for PTCA/CABG combined[†]	4.999	4.999	4.999	43.371	43.371	43.371
RR for PTCA/CABG	0.64	0.64	0.64	0.7	0.7	0.7
Mean age of participants	55 years	55 years	55 years	56 years	56 years	56 years
Mean duration of trials	4.35 years	4.35 years	4.35 years	3.54 years	3.54 years	3.54 years
Name of drug used	Low cost statin	Intermediate cost statin	High cost statin	Low cost statin	Intermediate cost statin	High cost statin
Average daily dose of drug used	10 mg atorvastatin	27.2 mg simvastatin	40 mg pravastatin	10 mg atorvastatin	27.2 mg simvastatin	40 mg pravastatin
Annual cost of drug	£246.11	£500.18	£605.90	£246.11	£500.18	£605.90
All-causes mortality decline	5%	5%	5%	5%	5%	5%

[*] *Taken as annual costs as follows: low cost statin: atorvastatin 10 mg, £246; intermediate cost statin: simvastatin 27 mg, £500; high cost statin: pravastatin 40 mg, £606*

[†] *Rates are per 1000 py*

TABLE 44 *Inputs for statins of intermediate cost, varying baseline mortality risk*

Input variable	All statins	All statins:				
		0.5% baseline mortality risk	1% baseline mortality risk	1.5% baseline mortality risk	3% baseline mortality risk	6% baseline mortality risk
Placebo group risk*	18.6	5.0	10.0	15.0	30.0	60.0
RR for all cause mortality	0.77	0.77	0.77	0.77	0.77	0.77
Placebo group risk for non-fatal MIs*	16.5	4.4	8.9	13.3	26.6	53.2
RR for non-fatal MIs	0.67	0.67	0.67	0.67	0.67	0.67
Placebo group risk for non-fatal stroke*	5.9	1.6	3.2	4.8	9.5	19.2
RR for non-fatal stroke	0.64	0.64	0.64	0.64	0.64	0.64
Placebo group risk for PTCA/CABG combined*	26.1	7	14	21.1	42.1	84.2
RR for PTCA/CABG	0.66	0.66	0.66	0.66	0.66	0.66
Mean age of participants	56 years	55 years	55 years	55 years	55 years	55 years
Duration of trial	3.74 years	3.74 years	3.74 years	3.74 years	3.74 years	3.74 years
Name of drug used	Simvastatin	Simvastatin	Simvastatin	Simvastatin	Simvastatin	Simvastatin
Average daily dose of drug used	27.2 mg	27.2 mg	27.2 mg	27.2 mg	27.2 mg	27.2 mg
Annual cost of drug	£500.18	£500.18	£500.18	£500.18	£500.18	£500.18
All-causes mortality decline	5%	5%	5%	5%	5%	5%

* *Rates are per 1000 py*

TABLE 45 *Inputs for beta-blockers (short and longer trial follow-up) and antiplatelet drugs*

Input variable	Beta-blockers	Beta-blockers: longer follow-up	Aspirin 1200 mg	Aspirin 300 mg	Antiplatelets combined
Placebo group risk*	68.0	65.7	52.0	52.0	52.0
RR for all cause mortality	0.77	0.77	0.88	0.88	0.88
Placebo group risk for non-fatal MIs*	47.8	44.9	32.5	32.5	32.5
RR for non-fatal MIs	0.74	0.74	0.69	0.69	0.69
Placebo group risk for non-fatal stroke*	–	–	7.5	7.5	7.5
RR for non-fatal stroke	–	–	0.61	0.61	0.61
Placebo group risk for PTCA/CABG combined*	–	–	–	–	–
RR for PTCA/CABG	–	–	–	–	–
Mean age of participants	55 years	55 years	60 years	60 years	60 years
Mean duration of trials	1.9 years	2 years	2 years	2 years	2 years
Name of drug used	Atenolol	Atenolol	Aspirin	Dispersible aspirin	Dipyrimadole 400 mg + aspirin 75 mg
Average daily dose of drug used	50 mg	50 mg	1200 mg	300 mg	–
Annual cost of drug	£13.82	£13.82	£6.57	£1.64	£87.05
All-causes mortality decline	15%	15%	15%	15%	15%

* *Rates are per 1000 py*

TABLE 46 *Inputs for antihypertensive drugs (trials in middle-aged and elderly persons): bendrofluazide and enalapril*

Input variable	Bendrofluazide: middle-aged patients	Bendrofluazide: elderly patients	Enalapril: middle-aged patients	Enalapril: elderly patients
Placebo group risk*	14.0	33.1	14.0	33.1
RR for all cause mortality	0.88	0.88	0.88	0.88
Placebo group risk for non-fatal MIs*	4.7	11.8	4.7	11.8
RR for non-fatal MIs	0.85	0.85	0.85	0.85
Placebo group risk for non-fatal stroke*	5.2	11.9	5.2	11.9
RR for non-fatal stroke	0.64	0.65	0.64	0.65
Placebo group risk for PTCA/CABG combined*	–	–	–	–
RR for PTCA/CABG	–	–	–	–
Mean age of participants	56 years	69 years	56 years	69 years
Duration of trial	4.9 years	4.1 years	4.9 years	4.1 years
Name of drug used	Bendrofluazide	Bendrofluazide	Enalapril	Enalapril
Average daily dose of drug used	2.5 mg	2.5 mg	20 mg	20 mg
Annual cost of drug	£2.01	£2.01	£170.77	£170.77
All-causes mortality decline	5%	5%	5%	5%

* *Rates are per 1000 py*

TABLE 47 *Inputs for antihypertensive drugs (trials in middle-aged and elderly persons): combination regimens 1 and 2*

Input variable	Regimen 1: middle-aged patients	Regimen 1: elderly patients	Regimen 2: middle-aged patients	Regimen 2: elderly patients
Placebo group risk*	14.0	33.1	14.0	33.1
RR for all cause mortality	0.88	0.88	0.88	0.88
Placebo group risk for non-fatal MIs*	4.7	11.8	4.7	11.8
RR for non-fatal MIs	0.85	0.85	0.85	0.85
Placebo group risk for non-fatal stroke*	5.2	11.9	5.2	11.9
RR for non-fatal stroke	0.64	0.65	0.64	0.65
Placebo group risk for PTCA/ CABG combined*	–	–	–	–
RR for PTCA/CABG	–	–	–	–
Mean age of participants	56 years	69 years	56 years	69 years
Duration of trial	4.9 years	4.1 years	4.9 years	4.1 years
Name of drug used	100% on bendrofluazide 2.5 mg, 50% on atenolol 100 mg and 20% on enalapril 20 mg	100% on bendrofluazide 2.5 mg, 50% on atenolol 100 mg and 20% on enalapril 20 mg	100% on enalapril 20 mg, 50% on amlodepine 10 mg and 20% on doxazosin 4 mg	100% on enalapril 20 mg, 50% on amlodepine 10 mg and 20% on doxazosin 4 mg
Average daily dose of drug used	–	–	–	–
Annual cost of drug	£45.74	£45.74	£332.02	£332.02
All-causes mortality decline	5%	5%	5%	5%

* *Rates are per 1000 py*

TABLE 48 *Inputs for dietary interventions*

Input variable	Mediterranean diet	DART-oily fish	DART-oily fish or maxepa
Placebo group risk*	33.7	63.9	63.9
RR for all cause mortality	0.4	0.73	0.73
Placebo group risk for non-fatal MIs*	28.6	16.2	16.2
RR for non-fatal MIs	0.3	1.49	1.49
Placebo group risk for non-fatal stroke*	–	–	–
RR for non-fatal stroke	–	0.66	–
Placebo group risk for PTCA/ CABG combined*	–	–	–
RR for PTCA/CABG	–	–	–
Mean age of participants	54 years	57 years	57 years
Duration of trial	2.25 years	2 years	2 years
Dietary intervention	Mediterranean diet	Oily fish	Oily fish or maxepa
Treatment	Total trial costs: 1-hour long session with dietician/cardiologist and researcher proxied by cost of additional outpatient appointment at £92. Four subsequent visits by dietician at £6.48 per visit. Cost of food not included.	Total trial costs: one home visit by general practitioner (£30) and eight visits by dietician at £6.48 per visit.	22% of patients take maxepa 10 tablets of 1 g per week. 200 g costs £28.57. Assume all patients get dietary advice at £36.48 and maxepa.
Annual cost of drug	£52.41	£40.92	£57.26
All-causes mortality decline	10%	10%	10%

* *Rates are per 1000 py*

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This report was identified as a priority by the Pharmaceutical Panel.

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