TRENT DEVELOPMENT AND EVALUATION COMMITTEE
CLINICAL COMMENTARY

Statin Therapy / HMG Co-A Reductase Inhibitor Treatment in the Prevention of Coronary Heart Disease

The Trent Development and Evaluation Committee considered the statement on HMG Co-A reductase inhibitor treatment in the prevention of coronary heart disease at its first meeting on 22 January 1997. Dr D M Pickin and Dr J N Payne presented the findings to the Committee. The evidence that statins reduce blood cholesterol levels and increase life expectancy of those at risk of coronary heart disease was convincing.

The Committee endorsed the following recommendations:

1 **Secondary Prevention**
That statins be used in the treatment of patients with pre-existing coronary heart disease. Whilst there were less data for women, it was concluded that cost-effectiveness for women was likely to be of the same order as that for men.

2 **Primary Prevention**
That statins be available for the treatment of those who were found to have a high risk of suffering from coronary heart disease. A 4.5% risk of annual coronary event or above is high.

The Committee did not review the other arrangements which need to be in place for the effective use of statins, nor the other treatments which might promote the health of those who are at risk or suffer from coronary heart disease.

Professor Sir David Hull
Chairman Trent DEC
27 February 1997

December 1996

STATIN THERAPY / HMG CO-A REDUCTASE INHIBITOR TREATMENT IN THE PREVENTION OF CORONARY HEART DISEASE

DM Pickin
JN Payne
IU Haq
CJ McCabe
SE Ward
PR Jackson
WW Yeo
LE Ramsay

Trent Institute for Health Services Research
Universities of Leicester, Nottingham and Sheffield

GUIDANCE NOTE FOR PURCHASERS 96/04

Published by the Trent Institute for Health Services Research

ISBN 1900733064

Referencing information:

Pickin DM, Payne JN, Haq IU, McCabe CJ, Ward SE, Jackson PR, Yeo WW, Ramsay LE. *Statin Therapy / HMG Co-A Reductase Inhibitor Treatment in the Prevention of Coronary Heart Disease.* Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 1996. Guidance Note for Purchasers : 96/04.

Further copies of this document are available (price £6.00) from:-

Suzy Paisley
Information Officer
Trent Institute for Health Services Research
Regent Court
30 Regent Street
SHEFFIELD S1 4DA

Tel 0114 222 5420
Fax 0114 272 4095
E-mail scharrlib@sheffield.ac.uk

Please make cheques payable to "The University of Sheffield"

AUTHORS

Dr D M Pickin is an MRC Research Fellow in the Medical Care Research Unit, ScHARR, University of Sheffield.

Dr J N Payne is Acting Director of Policy and Public Health, Sheffield Health.

DR I U Haq is a Research Fellow in the Department of Medicine and Pharmacology at the Royal Hallamshire Hospital, Sheffield.

Mr C J McCabe is a Lecturer in Health Economics at ScHARR, University of Sheffield.

Ms S E Ward is a Senior OR Analyst at ScHARR, University of Sheffield.

Dr P R Jackson is an Honorary Consultant Physician and Senior Lecturer in Clinical Pharmacology and Therapeutics in the Department of Medicine and Pharmacology at the Royal Hallamshire Hospital, Sheffield.

Dr W W Yeo is a Consultant Physician and Senior Lecturer in Clinical Pharmacology and Therapeutics in the Department of Medicine and Pharmacology at the Royal Hallamshire Hospital, Sheffield.

Professor L E Ramsay is a Consultant Physician and Professor of Clinical Pharmacology and Therapeutics in the Department of Medicine and Pharmacology at the Royal Hallamshire Hospital, Sheffield.

ACKNOWLEDGEMENTS

The Authors would like to acknowledge the assistance of:
(i) the support team of the ScHARR Working Group on Acute Purchasing, with the production of the document: Mr A Brennan, Miss S P Holmes, Ms N J Howson and Ms S F Paisley; and
(ii) Ms R Eve and Dr P Hodgkin, from the Framework for Appropriate Care Throughout Sheffield (FACTS) project, who wrote Appendix C.

ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Institute:

- provides advice and support to NHS staff on undertaking Health Services Research (HSR);
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Akehurst currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within the University of Sheffield in conjunction with the School of Health and Related Research (ScHARR).

FOREWORD

Individuals or small groups in each District Health Authority in Trent have historically considered evidence on the likely effectiveness of new procedures or therapies in conjunction with their cost, making judgements on whether these should be supported. Since all or most Health Authorities face the same issues, there tends to be repetition in analysis and this can be wasteful of scarce professional expertise.

There are national attempts to remedy this situation by providing information on the effectiveness of interventions and these are welcomed. There remains, however, a significant gap between the results of research undertaken and their incorporation into contracts.

Following a request from purchasers, a network has been established in the Trent Region to allow purchasers to share research knowledge about the effectiveness of acute service interventions and to determine collectively their purchasing stance.

ScHARR, which houses the Sheffield Unit of the Trent Institute for Health Services Research, facilitates a Working Group on Acute Purchasing. A list of interventions for consideration is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic and is assisted, as necessary, by a support team from ScHARR which provides help including literature searching, health economics and modelling. A seminar is then led by the consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes.

CONTENTS

LIST OF TABLES AND FIGURES

Page

EXECUTIVE SUMMARY

Introduction

This Guidance Note for Purchasers examines the evidence for effectiveness and cost-effectiveness of cholesterol lowering treatment with statin drugs in the prevention of coronary heart disease (CHD) in patients with and without pre-existing CHD.

The statins are a class of drug (HMG Co-A reductase inhibitor), which lower cholesterol and reduce the risk of CHD.

Statin Treatment in Secondary Prevention of Coronary Heart Disease: Effectiveness and Cost-effectiveness

In patients with pre-existing CHD (secondary prevention), there is strong evidence of effectiveness obtained from a large well designed randomised controlled trial: the 4S study. In these patients, simvastatin reduced deaths from CHD, major coronary events and all cause mortality.

The cost per life year gained for men (average age 58 years) has been estimated using data from the 4S study. For lifelong treatment the cost per life year gained is estimated at £5,100. If potential NHS savings from the treatment can be realised, the net cost per life year gained is estimated at £4,252

These figures are similar to costs per life year gained of other interventions currently in use.

Statin Treatment in Primary Prevention of Coronary Heart Disease: Effectiveness and Cost-effectiveness

In patients without pre-existing CHD (primary prevention), there is also strong evidence of effectiveness from a large well designed randomised controlled trial: the West of Scotland Coronary Prevention Study (WOSCOPS). In these patients, pravastatin reduced deaths from CHD and major coronary events. (There was less strong evidence of a reduction in all cause mortality).

The cost per life year gained for men (average age 55 years) has been estimated using data from the WOSCOPS study. For lifelong treatment the cost per life year gained is estimated at £18,200. If potential NHS savings from the treatment can be realised, the net cost per life year gained is estimated at £17,600.

These figures are more expensive than most interventions currently in use.

Benefits from cholesterol lowering treatment are higher in patients at higher risk of CHD. Therefore, cost-effectiveness will be higher in primary prevention patients at a higher risk of CHD than those in the WOSCOPS trial.

Four treatment thresholds have been considered:

- secondary prevention;
- primary prevention at a 4.5% annual coronary event risk;
- primary prevention at a 3% annual coronary event risk;
- primary prevention at a 1.5% annual coronary event risk (similar to patients in the WOSCOPS trial).

Costs per life year gained have been estimated for all these treatment thresholds, with primary prevention at the 4.5% threshold having a similar cost per life year to secondary prevention, and primary prevention at the 3.0% threshold having a cost per life year between the levels found in the 4S and WOSCOPS trials.

Population Implications of Statin Treatment Policies

The number of people who might benefit from statin treatment is very large. The dataset from the Health Survey for England has been re-analysed to calculate the number in a typical district. The implications of treating patients at each treatment threshold have been estimated. Numbers treated, drug costs, potential savings and mortality and morbidity prevented have been calculated and are shown in a summary matrix. The implications for a typical district of a policy to treat patients above each threshold vary from 9,300 patients at an annual cost of £5.2 million for secondary prevention only, to 48,100 patients at an annual cost of £34 million for secondary and primary prevention at the 1.5% threshold and above.

Conclusions

Options for purchasers are discussed and recommendations for purchasing strategies are made in the document. It is concluded that the scale and cost-effectiveness of secondary prevention (and primary prevention at the higher risk levels) make it a higher funding priority than primary prevention in patients with a 1.5% annual coronary event risk.

1. INTRODUCTION

1.1 Use of Statins

The statins are a class of cholesterol lowering drugs which work by inhibiting an enzyme (HMG Co-A reductase) involved in the production of cholesterol.

A raised serum cholesterol is a common problem strongly associated with an increased morbidity and mortality from coronary heart disease (CHD).[1] Diets to lower cholesterol have been designed, but either have very little effect on serum cholesterol and CHD risk, or are very restrictive and poorly tolerated.[2]

Many trials of cholesterol lowering drugs have been undertaken. Apart from the statin drugs, these trials have shown reductions in cholesterol and reductions in CHD (mortality and morbidity), but no reduction in overall (all cause) mortality in the treatment groups. This appears to be because of an increase in non-cardiovascular mortality in patients receiving these (non-statin) cholesterol lowering drugs. A meta-analysis of these trials [3] demonstrated that (non-statin) cholesterol lowering drugs achieve a reduction in all cause mortality only among patients with a high initial overall risk of death from CHD. It is estimated that a net benefit is only achieved in people with over a 3% chance of dying from CHD over the next year.

Statins are an important advance in cholesterol lowering treatment because they have been shown to be safe, well-tolerated and effective. They lower cholesterol and reduce both morbidity and mortality from CHD, without increasing non-cardiovascular mortality.[4,5]

1.2 Questions Addressed by this Review

- Does treatment with statin drugs, in patients with established CHD and a cholesterol level above a treatment threshold, lead to a reduction in morbidity and mortality from CHD and an overall reduction in mortality?

- Does treatment with statin drugs, in patients without established CHD but with a cholesterol level above a treatment threshold, lead to a reduction in morbidity and mortality from CHD and an overall reduction in mortality?

- How many people might benefit from treatment with these drugs?

- How cost-effective are statins in the prevention of CHD?

- What are the possible cost and benefit implications for a population of introducing treatment with statins?

- What strategies can purchasers follow to ensure that this treatment is made available to those who need it most, in a co-ordinated, rational and affordable way?

2. USE OF STATINS IN CORONARY HEART DISEASE: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Evidence of Effectiveness

2.1.1 Secondary Prevention of CHD: The 4S Study [4,6]

This was a randomised, double-blind, placebo controlled trial with a median follow up of 5.4 years. The objectives of the study were to determine:

- whether simvastatin treatment is safe;
- whether simvastatin treatment improves survival; and
- whether simvastatin treatment decreases atherosclerotic events in patients with CHD.

The setting was 94 clinical centres in Scandinavia. The subjects were 4,444 patients (3,617 men and 827 women) aged 35 to 70 years (mean age: men 58, women 60.5 years), with serum cholesterol levels of 5.5 mmol/litre or above who were allocated to receive either simvastatin 10-40 mg daily (mean dose 27.4mg) or placebo.

Simvastatin decreased cholesterol by 25%. Intention to treat analysis showed:

- a reduction in major coronary events ($P<0.001$, Relative Risk Reduction (RRR) 30%, Number Needed to Treat (NNT) 15); and
- a reduction in all cause mortality ($P<0.001$, RRR 28.8%, NNT 30).

The results did not differ for age. Risk reduction in women was confined to fewer major coronary events.

2.1.2 Primary Prevention of CHD: The West of Scotland Coronary Prevention Study[5,7]

This was a randomised, double-blind, placebo controlled trial with a mean follow up of 4.9 years. The objective of the study was to evaluate the effectiveness of pravastatin in preventing coronary events in men with moderate hypercholesterolemia and no history of myocardial infarction (MI).

The setting was coronary screening clinics in the West of Scotland. The subjects were 6,595 men aged 45 to 64 (mean age 55 years) with a serum cholesterol of 6.5 mmol/litre or above[a] who were allocated to receive either pravastatin, 40mg each evening, or placebo. Lipid-lowering dietary advice was also given.

Pravastatin decreased cholesterol by 20%. Intention to treat analysis showed:

- a reduction in definite non-fatal MIs and deaths from CHD (the combined primary end point) (P<0.001, RRR 31% NNT 42); and
- a reduction in definite MIs (P<0.001, RRR 31% NNT 53). There was no significant decrease in deaths definitely from CHD (P=0.13). The reduction in all cause mortality was of borderline significance (P=0.05, RRR 22%, NNT 113).

2.2 Conclusion on Direction of Evidence and its Quality

On the basis of these well designed Randomised Controlled Trials, there is strong evidence that:

- Simvastatin reduces coronary events, coronary mortality and all cause mortality when used in secondary prevention of CHD.
- Subgroup analysis showed that the reduction in coronary events and coronary mortality occurred in both men and women and that all cause mortality was reduced in men. There were fewer women in the study and subgroup analysis of all cause mortality did not show a significant result. There was a non-significant trend towards an increased all cause mortality in the simvastatin treated women.
- Pravastatin reduces coronary events and (with less strong evidence) all cause mortality in primary prevention of CHD in men.

Using the US Task Force on Preventive Health Care rating scale,[8] this amounts to grade A evidence of effectiveness: there is good evidence that the procedure (treatment with statins) is effective.

The NNTs (to prevent one death) of 30 patients for 5.4 years for secondary prevention and 113 patients for 4.9 years for primary prevention show that statins produce greater survival benefits when used in secondary prevention of CHD.

---

[a] and Low Density Lipoprotein (LDL) cholesterol of 4.0mmol/litre or above.

Whilst these trials have shown the statins to be safe over five to six years, little is known about their long-term effects. More evidence about the balance between benefits and risks will emerge from further large trials[9] and an overview of such trials.[10]

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 Scale of the Problem

3.1.1 How Many People Might Benefit from Statin Treatment?

Haq et al.[11] have assessed the possible need for statins for primary and secondary prevention of CHD in a population using data from the Health Survey for England.[12]

(i) Secondary Prevention of CHD

The Health Survey for England dataset was obtained by courtesy of the Essex Data Archive. These data were re-analysed to find the proportion of people aged 35 to 69 who would meet the criteria for the 4S study, i.e. patients with an MI or angina and cholesterol greater than 5.5 mmol/litre.

Since patients with other forms of atherosclerotic vascular disease, such as, peripheral vascular disease or symptomatic carotid disease, have a risk of coronary events at least equal to that of patients with stable angina, they should logically benefit equally (in terms of reduction in risk of *coronary* events) from treatment with statins.[13] Therefore, analysis of the data attempted to include these patients, although this was only possible for patients who reported a stroke.

The results of this analysis are shown in Figure 1. They show that 4.8% of 35 to 69 year olds in England might benefit from treatment with a statin. The proportion is higher in men than in women and increases with age, (16.2% of 65 to 69 year old men might benefit.) This means that approximately 930,000 men and women aged 35-69 in England might benefit from treatment with statins for secondary prevention of CHD. Choosing to treat all these people would cost over £0.5 billion per annum in drug costs alone.

(ii) Primary Prevention of CHD

The Health Survey for England data were also analysed to determine the proportion of 35 to 69 year olds who might benefit from treatment with statins for primary prevention of CHD.

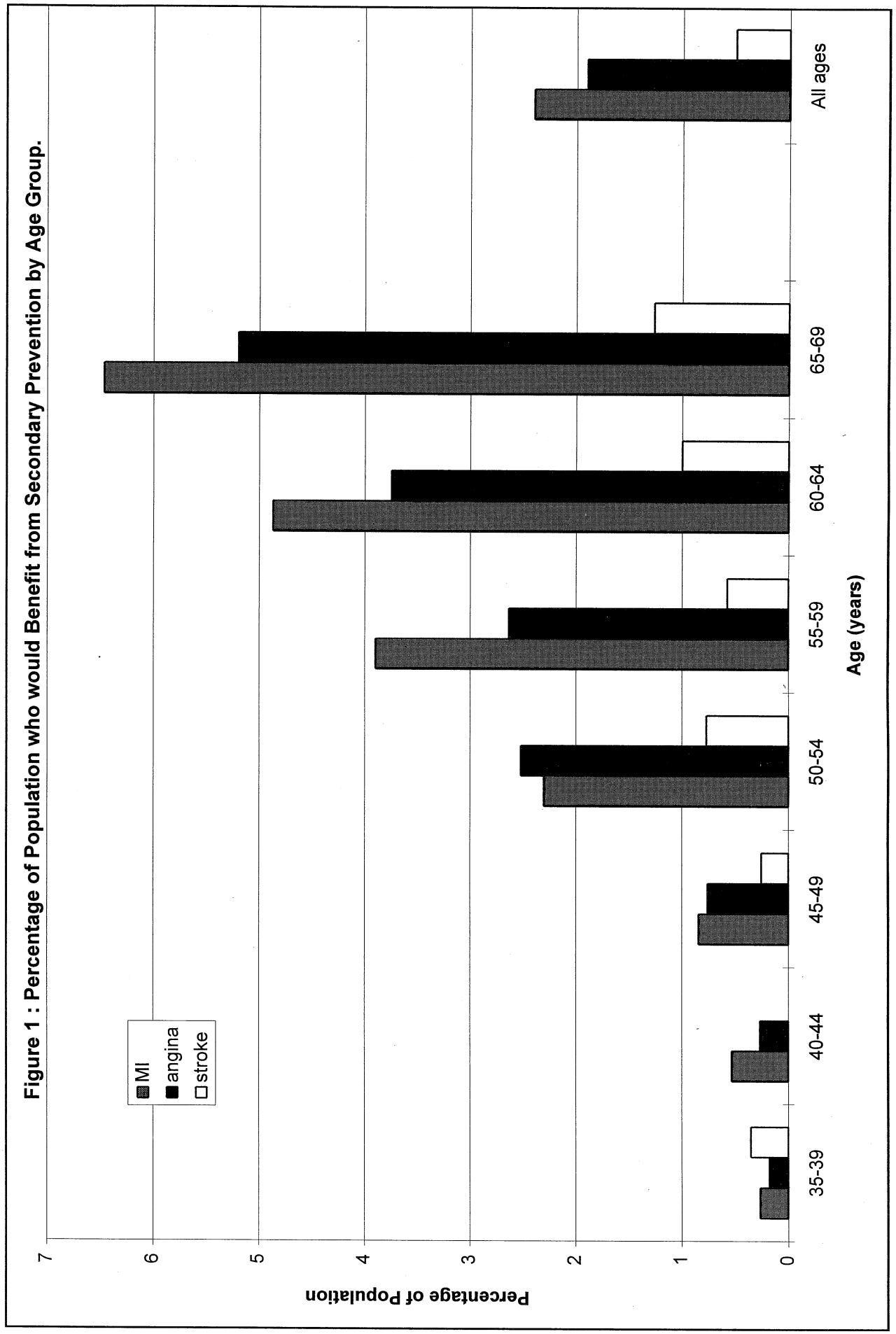


Figure 1 : Percentage of Population who would Benefit from Secondary Prevention by Age Group.
MI
angina
stroke
Percentage of Population
0
1
2
3
4
5
6
7
35-39
40-44
45-49
50-54
55-59
60-64
65-69
All ages
Age (years)

Using data on coronary risk factors in the survey, and a method of calculating coronary risk derived from the Framingham population,[14] the proportions of people without CHD but with an annual risk of coronary events of 4.5%, 3% and 1.5% (and with cholesterol greater than 5.5mmol/litre) were estimated. These risk thresholds were chosen because they represented similar risks of coronary events to:

- 4.5%: patients post MI (shown to benefit in the 4S trial);
- 1.5%: patients without pre-existing CHD shown to benefit in the West of Scotland Coronary Prevention Study (WOSCOPS);
- 3.0%: patients with angina. (A useful intermediary figure).

We would expect all patients above these thresholds with raised cholesterol to benefit from statin treatment, with the higher risk patients benefiting more from treatment.

The analysis showed that, in addition to the 4.8% of 35 to 69 year olds in England, who might benefit from treatment with a statin for secondary prevention:

- for a treatment threshold of 4.5% annual coronary event risk, 0.3% would require treatment with statins for primary prevention;
- for a treatment threshold of 3% annual coronary event risk, 3.4% would require treatment; and
- for a treatment threshold of 1.5% annual coronary event risk, 19.6% would require treatment.

(The figures for 3% threshold include patients above the 4.5% threshold, and the figures for the 1.5% threshold include patients above the 3% and 4.5% thresholds.)

Figure 2 illustrates the implication of choosing a 3% annual coronary event risk threshold. When primary and secondary prevention patients are combined, 8.2% of 35-69 year olds, approximately 1.6 million people in England, would require treatment. This would cost more than £0.8 billion per annum in drug costs alone.

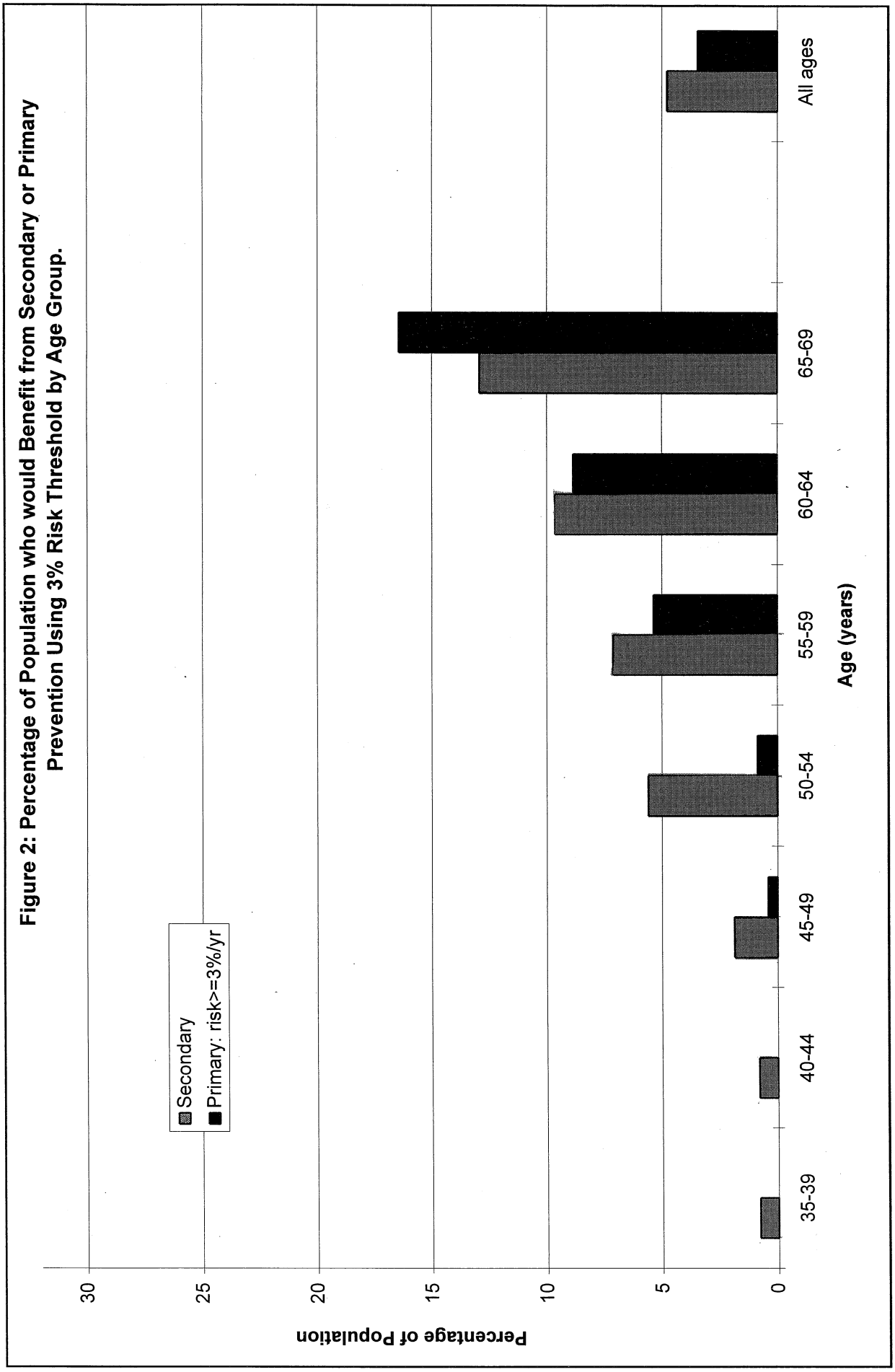


Figure 2: Percentage of Population who would Benefit from Secondary or Primary Prevention Using 3% Risk Threshold by Age Group.
Secondary
Primary: risk>=3%/yr
Percentage of Population
0
5
10
15
20
25
30
35-39
40-44
45-49
50-54
55-59
60-64
65-69
All ages
Age (years)

3.2 Evidence of Cost-effectiveness

3.2.1 Are Statins Cost-effective?

The issue of cost-effectiveness is particularly important to address in the case of the statins given the potential scale of the resource implications.

The analysis presented below is limited by the fact that the costing data used were not collected during the 4S and WOSCOPS trials. Therefore, cost estimates had to be obtained from other studies.[15]

A current life table method has been used to attempt to estimate the cost per life year gained as a result of statin treatment in a cohort of patients of the same average age as those in the 4S and WOSCOPS trials. No attempt has been made to estimate the cost-effectiveness of statin treatment in preventing non-fatal events, although, clearly, there is a value to preventing, for example, an MI even if survival is not prolonged.

3.2.2 Methods

(i) Calculation of Life Years Gained

The survival curves for placebo and statin treated patients are known for the duration of the 4S and WOSCOPS trials. In order to calculate life years gained (LYG) as a result of statin treatment, it is necessary to estimate the survival curves in these groups beyond the end of the trials.

The life table method has been used to estimate survival after the end of the trials under two sets of assumptions.

The life table method

The life table method involves the construction of a table which calculates the mortality experience of a cohort of people. The cohorts used were 1,000 men on simvastatin at the same average age as patients in the 4S trial and 1,000 men on pravastatin at the same

average age as patients in the WOSCOPS trial. For each cohort, the number of people dying in each year is calculated by multiplying the number of people alive at the beginning of the year by the probability of dying in that year. The number surviving that year is then entered into the next row of the table and multiplied by next year's probability of dying to calculate the number of people dying in the second year. This process continues until all the people in the cohort have died.

Life tables were created for the men in the trials on placebo and those on treatment. Probabilities of dying were calculated using general population male age-specific mortality rates provided by the Government Actuary Department. For the placebo group, age-specific mortality rates were assumed to remain for life at the same proportion of the England and Wales population mortality rates (1992-94) as they had been for the duration of the trial. For the treatment groups, the mortality rates were calculated using the relative risks for all cause mortality found in each trial. The relative risks used for each treatment threshold are given in Appendix A.

Summing the number of people alive at the start of each year (minus half the deaths in that year) produces the number of life years lived by each cohort. The difference between the number of life years lived by the treatment cohort and the placebo cohort is the number of life years gained by the treatment.

The total number of LYG, and, therefore, the cost-effectiveness of statin treatment, is heavily dependent upon the assumptions made about the difference between the placebo and statin groups after the end of the trial period. Two scenarios have been constructed to identify the probable range of the cost-effectiveness of statin treatment.

In *Scenario 1* patients are treated for life and the relative risk of dying between the statin group and the placebo group remains constant (at the level found in the trial) for the rest of the patients' lives.

In *Scenario 2* patients are treated for five years (approximately the trial periods) and the relative risk of dying reverts from the level found in the trial to one (i.e. the same in both patient groups) immediately after the first five years.

There is no evidence to suggest that survival beyond the trial period would be better than that observed in the trial, so the estimate of LYG is unlikely to be greater than that in scenario 1. Scenario 2 is an unrealistic one, in that patients are unlikely to have their treatment stopped at five years, if their risk factors for CHD remain. The benefit from treatment for five years only will be lower than that from life-long treatment and (under our assumption of constant relative risk with lifelong treatment) the cost-effectiveness of treatment for five years will be lower. However, it could be said to represent a minimum estimate[b] of cost-effectiveness of statin treatment in this cohort and, since there is trial evidence of these relative risks with five years treatment, it relies on fewer assumptions than scenario 1.

It is reasonable, therefore, to assume that the LYG lies between the two scenarios, with scenario 1 being a more realistic treatment scenario.

Since all the patients in the WOSCOPS trial were men, and the number of women in the 4S trial was too small for conclusions on the effect of statin treatment on total mortality in women to be made, estimates of cost per life year gained have been made for men only.

(ii) Calculation of Drug Costs

The life table method allows the calculation of the number of life years lived and, therefore, the number of patients on treatment, in any given year in each of the two scenarios. This allows the total number of treatment years required in each scenario to be calculated. The total drug costs are calculated as the number of treatment years multiplied by the annual drug cost per patient.

The drug costs used are taken from the British National Formulary and are based on the average dose used in each trial. In the 4S study it was simvastatin 27.4 mg daily (at £1.52 per day or £555 per year). In the WOSCOPS study it was pravastatin 40 mg daily (at £2.22 per day or £810 per year).

[b] The worst case scenario for cost-effectiveness would be that treatment is continued for life with no benefit from statins after the 5 year trial period. This is a very pessimistic scenario, for which we have not estimated cost per life year gained.

(iii) Calculation of Possible Savings

Both trials showed reductions in events e.g. major coronaries, coronary artery bypass grafts (CABGs) and angioplasties. Therefore, a corresponding reduction in hospital admissions for these events/procedures is to be expected, with an associated reduction in resource use. The cost savings associated with the event reductions observed in the statin trials have been estimated using UK data [15] (the Newcastle study) - see Appendix B.

Costings have been applied to the events as reported in the WOSCOPs trial. For the 4S study, events were reported in more detail in a follow-up paper and it is these events that have been used for the costings.[16]

Rates of CABG per head of population are higher (approximately double) in Scandinavia than in the UK.[17] For this reason, in calculating possible savings, it has been estimated that half the CABGs and angioplasties prevented in the 4S trial would be prevented in the UK. This adjustment was not necessary for the UK based WOSCOPS trial.

The cost savings have been calculated using the costs reported in the Newcastle study,[15] adjusted by the proportion that CABG costs have increased in the years since the Newcastle study reported.

Only secondary care costs have been used. Potentially, primary care accounts for a significant proportion of the total cost of statin treatment and the savings that might accrue. However, data on the primary care implications were not reported by either of the trials and no attempt has been made to estimate these costs and savings.

(iv) Discounting of Costs and Benefits

Costs and benefits occurring in the future may be valued less than those occurring in the present. Therefore, the cost-effectiveness results have been calculated using a 6% p.a. discount rate for drug costs, potential savings and LYG, and have also been calculated without discounting. (Six percent is the Treasury recommended discount rate for public expenditure).

(v) Calculation of Gross and Net Cost per Life Year Gained

The ratio of total costs, both gross (drug costs) and net (drug costs minus potential savings) to total LYG gives the cost per life year gained.

These have been calculated for men in the 4S and WOSCOPS trials. For each study, results are given as gross and net cost per LYG, discounted and undiscounted, for treatment scenarios 1 and 2.

(vi) Estimate of Cost-effectiveness of Primary Prevention in Patients with 4.5% and 3% Annual Risk of Coronary Events.

The estimates of cost per life year gained from the 4S and WOSCOPS trials can be used to compare the cost-effectiveness of statin treatment in secondary prevention (4S result) and in primary prevention at a treatment threshold of 1.5% annual coronary event risk (WOSCOPS result). There is no direct trial evidence of primary prevention in patients at a 4.5% annual risk of coronary events. Since benefit depends on initial risk, it is argued that these patients will experience similar benefits to secondary prevention patients, who also have a 4.5% annual risk of coronary events. Since costs (and savings) will be similar, the cost per life year gained is likely to be similar to the 4S result.

There is no direct trial evidence of primary prevention in patients at a 3% annual risk of coronary event. To estimate the cost-effectiveness of this treatment, it is assumed that treatment with simvastatin, at the same dose as that used in the 4S trial, produces the same relative risk reduction as found in the 4S trial (all persons). This relative risk for all cause mortality is also the average of the relative risks for men in the 4S and WOSCOPS trials. Since these patients are at lower risk of coronary events (and, therefore, coronary mortality and total mortality) and have a higher relative risk of dying, the absolute benefits will be smaller, and the cost per life year gained more expensive.

In calculating the cost per life year gained, the mortality rate in the placebo group was estimated. This was achieved by assuming that the ratio of coronary deaths to major coronary events is the same as that found in the 4S trial and that the non-coronary mortality remains the same as that found in the 4S trial.

Clearly, the estimates of cost-effectiveness for primary prevention at the 4.5% annual coronary event treatment threshold and, particularly, at the 3.0% threshold, rely on more assumptions than the estimates of cost-effectiveness of secondary prevention and primary prevention at the 1.5% threshold, which are more firmly based on trial data.

The assumptions made for all the calculations are given in Appendix A.

3.2.3 Results

The estimates of cost per life year gained in scenarios 1 and 2, gross and net, discounted and undiscounted are given below for secondary prevention and primary prevention at the three treatment thresholds.

Table 1: Secondary Prevention (and Primary Prevention at a 4.5% Annual Coronary Event Risk)

COST PER LIFE YEAR GAINED	GROSS UNDISCOUNTED	GROSS DISCOUNTED AT 6%	NET UNDISCOUNTED	NET DISCOUNTED AT 6%
SCENARIO 1	£3,200	£5,100	£2,600	£4,300
SCENARIO 2	£5,200	£8,200	£4,300	£6,800

Based on 4S trial results, used to estimate the cost per life year gained in men (average age 58) treated with simvastatin.

Table 2: Primary Prevention at a 1.5% Annual Coronary Event Risk

COST PER LIFE YEAR GAINED	GROSS UNDISCOUNTED	GROSS DISCOUNTED AT 6%	NET UNDISCOUNTED	NET DISCOUNTED AT 6%
SCENARIO 1	£9,000	£18,000	£8,600	£17,600
SCENARIO 2	£20,800	£39,200	£20,000	£37,700

Based on WOSCOPS trial results, used to estimate the cost per life year gained in men (average age 55) treated with pravastatin.

Table 3: Primary Prevention at a 3% Annual Coronary Event Risk

COST PER LIFE YEAR GAINED	GROSS UNDISCOUNTED	GROSS DISCOUNTED AT 6%	NET UNDISCOUNTED	NET DISCOUNTED AT 6%
SCENARIO 1	£4,100	£7,400	£3,700	£6,700
SCENARIO 2	£7,800	£13,500	£7,100	£12,300

Based on 4S trial results (including coronary death:major coronary event ratio), used to estimate the cost per life year gained in men (average age 58) treated with simvastatin.

(i) Cost Per Life Saved

The cost per life saved of treatment with statins was calculated by dividing the number of deaths (all cause, all persons) prevented, by the cost (gross and net) of treatment. The results are given in Table 4:

Table 4: Cost Per Life Saved

COST PER LIFE SAVED	GROSS COST	NET COST
SECONDARY PREVENTION	£90,000	£75,000
PRIMARY PREVENTION 4.5% ANNUAL CORONARY EVENT RISK	£90,000	£75,000
PRIMARY PREVENTION 3% ANNUAL CORONARY EVENT RISK	£131,000	£120,000
PRIMARY PREVENTION 1.5% ANNUAL CORONARY EVENT RISK	£447,000	£430,000

The cost per life saved calculated from the 4S trial (£75,000 to £90,000) is much cheaper than that calculated from the WOSCOPS trial (£430,000 to £447,000), although much of this is due to the higher cost of the drug. If simvastatin 27.4mg had been used in the WOSCOPS trial, and the same benefits achieved, the cost per life saved would be £294,000 to £306,000.

The cost per life saved estimated for primary prevention at a 3% annual coronary event rate is between the 4S and WOSCOPS results (£120,000 to £131,000).

3.2.4 Comparison with other Estimates of Cost-effectiveness of Statin Treatment.

The cost per life year gained for secondary prevention treatment with simvastatin has been estimated previously at £23,100 to £32,440[18] and more recently at £6,000 (in men aged 55-64 who have had an MI, with cholesterol greater than 7.2) to £361,000 (in women aged 45-54, with angina and a cholesterol level of 5.5-6.0 mmol/litre).[19] In this latter study, by Pharoah and Hollingworth, a wide range of costs per life year are given, depending on age, sex and cholesterol level. The costs per life year are based on 10 years' treatment, and on reductions in all cause mortality calculated from reductions in relative risk of coronary deaths. The placebo mortality rates are calculated from the general population age-specific mortality rates, adjusted to calculate the age-specific coronary mortality rates.

The costs per life year, which have been calculated, are cheaper than these estimates. The general principle was to stick as closely as possible to data from the 4S and WOSCOPS trials. Hence, either lifelong treatment has been assumed, which is felt to be a more likely treatment scenario, or the five year treatment period of the trials. The relative risks for all cause mortality found in the trials, which have been used, are lower than those calculated by Pharoah and Hollingworth for 58 year old men. The placebo mortality rates used were those found in the trials, assumed to continue at the same proportion of the normal male population for life. Simple cohorts of men at average age 58 (and 55) as found in the 4S and WOSCOPS trial were considered. Such cohorts will have a higher placebo mortality rate than cohorts of men all of the same age. The assumptions made in the calculations are given in Appendix A.

Longer duration of treatment, higher placebo mortality rates, and (most importantly) lower relative risks for all cause mortality, will all lead to higher estimates of benefits and, hence, lower estimates of cost per life year gained. In the absence of any trial evidence of a reduction in all cause mortality in women on statin treatment, the estimates of cost per life year gained have been confined to men.

It is hoped that the treatment categories considered, which are based on risk of coronary events not age or sex, will be practical, useful and acceptable to clinicians.

The estimates of cost per life saved are comparable to previous estimates of £85,000 to £136,000 [20, 21] for treatment with simvastatin, although the estimate of cost per life saved for primary prevention at a 1.5% annual coronary event risk, is considerably higher at £430,000 to £447,000.

3.2.5 Comparison with other Treatments

A recent Health of the Nation publication gave the cost per life year gained for other interventions for CHD. [22]

Table 5 : Cost Per Life Year Gained for Other Interventions for CHD

INTERVENTION	COST PER LIFE YEAR GAINED
Blood Pressure Reduction for under 65s	<£1,000 for first line drugs £5,000 for alpha blockers
Thrombolytics for MI	£3,000
Counselling for Physical Activity	£3,000

The results can also be compared (with considerable caution) to other cost per life year valuations of treatments from the Department of Health Register of Cost-Effectiveness Studies 1994 as set out in Table 6.

Table 6: Published Cost Per Life Year Valuations for Selected Interventions

INTERVENTION	COST PER LIFE YEAR 1991
Opportunistic lipid screening in General Practice	£3,671
Nicotine gum compared to physician advice against cigarette smoking in primary care: men aged 35-39	£3,934
Coronary care unit provision for people experiencing MI	£4,974
Breast cancer screening for women aged 45 to 65	£8,417
Formal screening for cervical cancer	£9,070
Intensive care treatment for patients with multiple trauma	£9,977
Use of neonatal intensive care unit: BW 500 to 999g	£11,400
Kidney transplant with immunosuppressive therapy	£17,400
Haemodialysis	£27,000

3.2.6 Conclusion on Cost-effectiveness

The estimated cost per life year saved in men of average age 58 for secondary prevention of CHD with simvastatin (4S data) is £5,100 (gross discounted). If potential savings can be realised, it is £4,300. These estimates are similar to costs per life year gained of many other treatments currently in use (e.g. coronary care unit provision for people experiencing MI, £4,974 per LYG, 1991 figures). For this group of patients simvastatin can be considered to represent good value for money.

In primary prevention in men of average age 55 with a 1.5% annual coronary event risk, (WOSCOPS trial data), treatment with pravastatin represents much poorer value for money. This is to be expected given the larger NNT to prevent one death, and the higher cost of treatment with pravastatin 40mg compared with simvastatin 27.4mg. Using the more optimistic (and realistic) scenario 1, the cost per LYG is £18,200 (gross discounted) or £17,600 (net discounted). An example of an intervention currently in use producing LYG in this price range is renal transplant with immunosupressive therapy (£17,400 per LYG, 1991

figures). Using the more pessimistic scenario 2, the cost per LYG is £39,100 (gross discounted) or £37,700 (net discounted), which is beyond the level that most purchasers would consider to be affordable.

Treatment with pravastatin (40mg daily) produced a 20% fall in cholesterol in the WOSCOPS patients. Treatment with simvastatin produced a 25% fall in cholesterol in the 4S patients. If it is assumed that at least a 20% fall in cholesterol could be achieved in the WOSCOPS patients by treatment with simvastatin (27.4mg daily), producing the same trial mortality benefits, the cost per life year would fall (due to the lower cost of treatment).

These assumptions lead to an estimate of cost per life year gained of £12,500 (gross discounted) or £11,800 (net discounted) for primary prevention at 1.5 % risk level. These figures are similar to those for the use of neonatal intensive care units (£11,400 per LYG, 1991 figures).

At higher treatment thresholds, primary prevention with statins will be more cost-effective. Since benefits of treatment with cholesterol lowering drugs are dependent on CHD risk, it might be expected that at a threshold of 4.5% CHD event risk, the cost per LYG would be similar to that seen in the secondary prevention patients with MI. Similarly, at a threshold of 3% CHD event risk, the cost per LYG might be expected to be similar to that seen in the secondary prevention patients without MI. However, no trial has been reported on such patients and, therefore, the estimates of cost per LYG in these groups rely more on assumptions.

The estimated cost per life year gained for primary prevention in men of average age 58 with a 3% annual coronary event rate is £7,400 (gross discounted) or £6,700 (net discounted). This figure is closer to the estimate for secondary prevention than for primary prevention at the 1.5% level. An example of an intervention with a similar estimated cost per life year gained is breast cancer screening for women aged 45 to 65 (£8,417 per LYG, 1991 figures).

3.3 Population Cost and Benefit Implications of Adopting Intervention

3.3.1 What are the Cost and Benefit Implications for a Population of Statin Treatment?

The population implications of treating with statins at different treatment thresholds are given in the tables below.

The numbers treated are calculated by multiplying the proportions of 35-69 year olds benefiting from treatment (given in Section 3.1.1) by the population of England. (The proportion in Section 3.1.1 for primary prevention above the 3% threshold includes the proportion above the 4.5% threshold, and the proportion for primary prevention above the 1.5% threshold includes the proportions above the 3% and 4.5% thresholds. For these tables the additional numbers in each treatment group have been calculated.)

The drug costs of treating this number of patients are calculated by multiplying the numbers treated by the annual drug cost per person (£555 for simvastatin, £811 for pravastatin).

The events prevented (deaths all cause, major coronary events, CABGs/angioplasties) per 5.4 years (4S) and 4.9 years (WOSCOPS) are calculated by dividing the numbers treated by the NNT to prevent one event found in the trial. The events prevented per year are calculated by dividing this figure by 5.4 (4S) or 4.9 (WOSCOPS).

Major coronary events (MCEs) include deaths from coronary heart disease and non fatal coronary events.

The NNT for CABGs/angioplasties from the 4S trial has been adjusted to the UK CABG rate. The annual potential savings are calculated using the same method described in the calculation of net cost per life year gained. The net cost is the drug cost minus the potential savings.

The figures for a typical district are based on a hypothetical district that is 1% of the English population.

Table 7 shows the population implications of treating patients with existing coronary heart disease with simvastatin 27.4mg daily.

Table 7: Secondary Prevention Only

	ENGLAND	TYPICAL DISTRICT
NUMBERS TREATED	930,000	9,300
ANNUAL DRUG COST (£m)	516	5.16
EVENTS PREVENTED PER YEAR:		
DEATHS (ALL CAUSE)	5,700	57
MCEs	14,800	148
CABGs/ANGIOPLASTIES	5,100	51
ANNUAL POTENTIAL SAVINGS (£m)	85	0.85
ANNUAL NET COST (£m)	431	4.31

Table 8 shows the *additional* or *marginal* implications of extending treatment to primary prevention at the treatment threshold of 4.5% coronary event rate. Again, treatment is with simvastatin 27.4mg daily and the NNTs are from the 4S trial.

The marginal costs of extending statin treatment to this group of patients is £32.5 million per year, with marginal benefits of 360 deaths, 930 major coronary events and 5,100 CABGs/angioplasties prevented per year. Economists would say that it is efficient to extend the provision of statin therapy to the point where the value of the marginal benefits is exactly equal to the marginal or additional costs.

Table 8: Primary Prevention 4.5% Threshold

	ENGLAND	TYPICAL DISTRICT
NUMBERS TREATED	58,500	585
ANNUAL DRUG COST (£m)	32.5	0.325
EVENTS PREVENTED PER YEAR:		
DEATHS (ALL CAUSE)	360	4
MCEs	930	9
CABGs/ANGIOPLASTIES	319	3
ANNUAL POTENTIAL SAVINGS (£m)	5.32	0.053
ANNUAL NET COST (£m)	27.2	0.272

Table 9 shows the *additional* implications of extending treatment to primary prevention at the treatment threshold of 3% coronary event rate. Treatment is with simvastatin 27.4mg daily. The NNTs are calculated using the same assumptions as in the calculation of the cost per life year gained at the 3% treatment thresholds.

Table 9: Primary Prevention 3% Threshold

	ENGLAND	TYPICAL DISTRICT
NUMBERS TREATED	605,000	6,100
ANNUAL DRUG COST (£m)	336	3.36
EVENTS PREVENTED PER YEAR:		
DEATHS (ALL CAUSE)	2,600	26
MCEs	6,200	62
CABGs/ANGIOPLASTIES	1,900	19
ANNUAL POTENTIAL SAVINGS (£m)	28.7	0.29
ANNUAL NET COST (£m)	307	3.07

Table 10 shows the *additional* implications of extending treatment to primary prevention at the treatment threshold of 1.5% coronary event rate. Treatment is with pravastatin 40mg daily. The NNTs are from the WOSCOPS trial.

Table 10: Primary Prevention 1.5% Threshold

	ENGLAND	TYPICAL DISTRICT
NUMBERS TREATED	3,200,000	32,000
ANNUAL DRUG COST (£m)	2,610	26.1
EVENTS PREVENTED PER YEAR:		
DEATHS (ALL CAUSE)	5,800	58
MCEs	16,100	161
CABGs/ANGIOPLASTIES	5,800	58
ANNUAL POTENTIAL SAVINGS (£m)	95	0.95
ANNUAL NET COST (£m)	2,510	25.1

The above costs are based on pravastatin 40mg daily at £811 per year. Clearly, if the same benefits could be achieved with simvastatin 27.4mg daily at £555 per year, the costs of treatment would be proportionately lower.

In Tables 11 and 12 the costs and benefits are summed to give the total cost and benefit implications of each treatment policy for England and for a typical district health authority (1% of the England population).

Table 11: Overall Implications of Each Policy: England

	NUMBERS TREATED	ANNUAL DRUG COST (£m)	ANNUAL NET COST (£m)	ANNUAL DEATHS (ALL CAUSE) PREVENTED	ANNUAL MAJOR CORONARY EVENTS PREVENTED	ANNUAL CABGs/ ANGIOPLASTIES PREVENTED
SECONDARY PREVENTION PLUS	930,000	516	431	5,700	14,800	5,100
PRIMARY PREVENTION AT:						
4.5%	990,000	549	459	6,100	15,700	5,400
3.0%	1,590,000	885	766	8,600	21,900	7,291
1.5%	4,810,000	3,490	3,280	14,500	37,900	13,100

(Numbers in rows are cumulative totals)

Table 12: Overall Implications of Each Policy: Typical Health District

	NUMBERS TREATED	ANNUAL DRUG COST (£m)	ANNUAL NET COST (£m)	ANNUAL DEATHS (ALL CAUSE) PREVENTED	ANNUAL MAJOR CORONARY EVENTS PREVENTED	ANNUAL CABGs/ ANGIOPLASTIES PREVENTED
SECONDARY PREVENTION PLUS	9,300	5.16	4.32	57	148	51
PRIMARY PREVENTION AT:						
4.5%	9,900	5.49	4.59	61	157	54
3.0%	15,900	8.85	7.66	86	219	72
1.5%	48,100	34	32	145	379	131

(Numbers in rows are cumulative totals)

3.3.2 Current Expenditure

Expenditure on lipid lowering drugs reached £40 million in 1993.

In 1995 the National Audit Office estimated that the total NHS expenditure on CHD was £1,000 million. [17] The cost of all dispensed prescriptions from the Prescriptions Pricing Authority (PPA) in England in 1994/95 was £3,889 million. The costs of the four policy options represent a significant proportion of this cost as shown below:

Table 13: Percentage of Current Prescribing Costs

POLICY	STATIN DRUG COST AS A % OF ALL DISPENSED PRESCRIPTIONS 94/95	STATIN NET COST AS A % OF ALL DISPENSED PRESCRIPTIONS 94/95
SECONDARY PREVENTION ONLY	13	10
PRIMARY PREVENTION AT		
4.5%	14	11
3.0%	23	18
1.5%	89	81

4. OPTIONS FOR PURCHASERS AND PROVIDERS

Several possible options were presented and discussed at the Trent Institute Working Group on Acute Purchasing in April 1996. During discussion the following points were made:

4.1 General Principles

It was agreed that populations at highest risk of CHD would benefit most from statins and that steps should be taken to ensure that they were considered a priority for implementation. In particular, it was felt important that areas with high CHD morbidity and mortality (such as areas of deprivation) should not fall foul of the "inverse care law", with a low use of statin drugs in a population most in need.

4.1.1 Treatment of Men or Women

Whilst it was recognised that the evidence on primary prevention came from a trial on men only, and that strong evidence of prolongation of life in the secondary prevention trial was only seen amongst men, the option of treating men only was not supported. Women had been shown to benefit equally in terms of reduction of CHD morbidity in secondary prevention, and it was agreed that treatment should be based on CHD risk, not gender.

4.2 Treatment Policies

Various options were considered:

4.2.1 Secondary Prevention of CHD

There was strong agreement that there was good evidence of effectiveness of statin treatment in patients with existing CHD (MI or angina) and cholesterol levels greater than 5.5 mmol/litre. It was also agreed that there was evidence of acceptable cost-effectiveness and that there was a good case for purchasers to fund statin treatment for these patients.

A strong case was also made for those patients with other cardiovascular disease (stroke; transient ischaemic attack (TIA) caused by carotid disease; or peripheral vascular disease) and cholesterol levels greater than 5.5 mmol/litre, since the underlying disease process is similar and they share a similar risk of CHD. Again, there was general agreement that purchasers should consider funding statin treatment for these patients.

4.2.2 Primary Prevention of CHD

There was agreement that there was good evidence of effectiveness of statin treatment in men without existing CHD but with cholesterol levels greater than 6.5 mmol/litre[c]. Such men have an annual coronary event risk of approximately 1.5%.

There was general agreement that decisions to treat with statins in primary prevention should be based on overall CHD risk rather than cholesterol level alone.

Three levels of risk of CHD were considered as possible thresholds for treatment: 1.5% annual coronary event risk, 3.0% annual coronary event risk and 4.5% annual coronary event risk.

Whilst there was agreement that statins would be effective in these groups, there were concerns about cost-effectiveness, particularly at the 1.5% risk level.

There was no consensus on which threshold should be funded by purchasers, but there was general agreement that primary prevention would be much more effective and cost-effective at the higher risk thresholds. The costs per life year gained at the 4.5% and 3.0% treatment thresholds were more in keeping with those of currently used interventions than the cost per life year gained at the 1.5% treatment threshold.

The population implications of each policy showed that there was a very large task ahead in implementing even secondary prevention alone (9,300 patients to treat in a typical district, with drug costs of £5.2 million per annum).

[c] and Low Density Lipoprotein (LDL) cholesterol of 4.0mmol/litre or above

As the threshold for primary prevention was lowered, the scale of the implementation task became much larger, and the benefits more expensive. Primary prevention at the 4.5% threshold would add only another 600 patients to be treated in a typical district at a drug cost of £330,000 per year. Primary prevention at the 3.0% threshold would add an extra 6,000 patients at a drug cost of £3.4 million per year. Primary prevention at the 1.5% threshold would add very substantially to the size of the implementation task: an extra 32,200 patients at £26.1 million per year.

The implications for a typical district of the four treatment policies (secondary prevention only; secondary plus primary prevention at 4.5% threshold; secondary plus primary prevention at 3.0% threshold; secondary plus primary prevention 1.5% threshold) are shown in Figure 3 (numbers treated), Figure 4 (annual drug and net costs), and Figure 5 (annual deaths and Major Coronary Events prevented).

In view of the above, it was agreed that, after secondary prevention, priority should be given to implementing primary prevention at a threshold of 4.5 %.

Health authorities and other purchasers would need to consider whether, and how, they would implement and afford this treatment, which, for these two groups (secondary prevention and primary prevention at 4.5% risk) is potentially needed on a very large scale.

They would also need to decide whether they would then implement primary prevention at the 3% level, given the cost per life year gained of around £7,000 and, if so, how they would afford the even larger scale and cost.

It was felt unlikely that purchasers would be able to fund primary prevention at the 1.5% level, given the cost per life year gained of around £18,000 (although this might be lower if simvastatin were used) and the very large scale and cost.

Concern was expressed about where purchasers would find the funds necessary for the implementation of statin treatment. Options include:

- identifying other, less cost-effective treatments (particularly preventative interventions for coronary heart disease) from which resources could be diverted into statin treatment;
- lobbying for a reduction in the cost of the drugs;

- lobbying for extra central funding for this treatment;
- reducing the numbers to be treated by some other method other than the annual coronary event risks considered above (e.g. by age, sex, smokers).

No consensus (other than a rejection of a 'men only' policy) was reached on this difficult matter.

There was discussion about the likelihood of potential NHS savings from this treatment being realised. Given the possible scale and cost of implementing statin treatment, this was felt to be very important, although there was some concern that spare capacity rather than real savings would result. One important point is that targets for CABGs might need to be revised downwards, if a statin treatment programme were fully implemented.

It was agreed that purchasers could use the information in this report to calculate the implications of various policy decisions on their resident populations (in terms of numbers to treat, costs and benefits).

In addition, it was agreed that the development of a toolkit or 'ready reckoner' which helped health authorities to do this, using as much as possible of their own demographic, mortality/morbidity, and health service cost data, would be beneficial.

It was also agreed that health authority policy decisions would need to be supported by clear guidance to clinicians, particularly GPs, using experience gained by the Framework for Appropriate Care Throughout Sheffield (FACTS) project (see Appendix C). Without such an implementation strategy, uptake of statins would be likely to be haphazard and uncoordinated.[d] In this context it should be noted that the 'Sheffield Tables'[13] for the identification of patients at 4.5% annual coronary event risk have been amended to allow identification of patients at 3.0% annual coronary event risk.

[d] Compare with the introduction and management of antihypertensive treatment. See for example:
Payne JN, Milner PC, Saul C, Bowns IR, Hannay DR, Ramsay LE,. Local confidential inquiry into avoidable factors in deaths from stroke and hypertensive disease. *BMJ* 1993;**307**(6911):1027-30

Figure 3: Implications for a Typical District: Numbers Treated

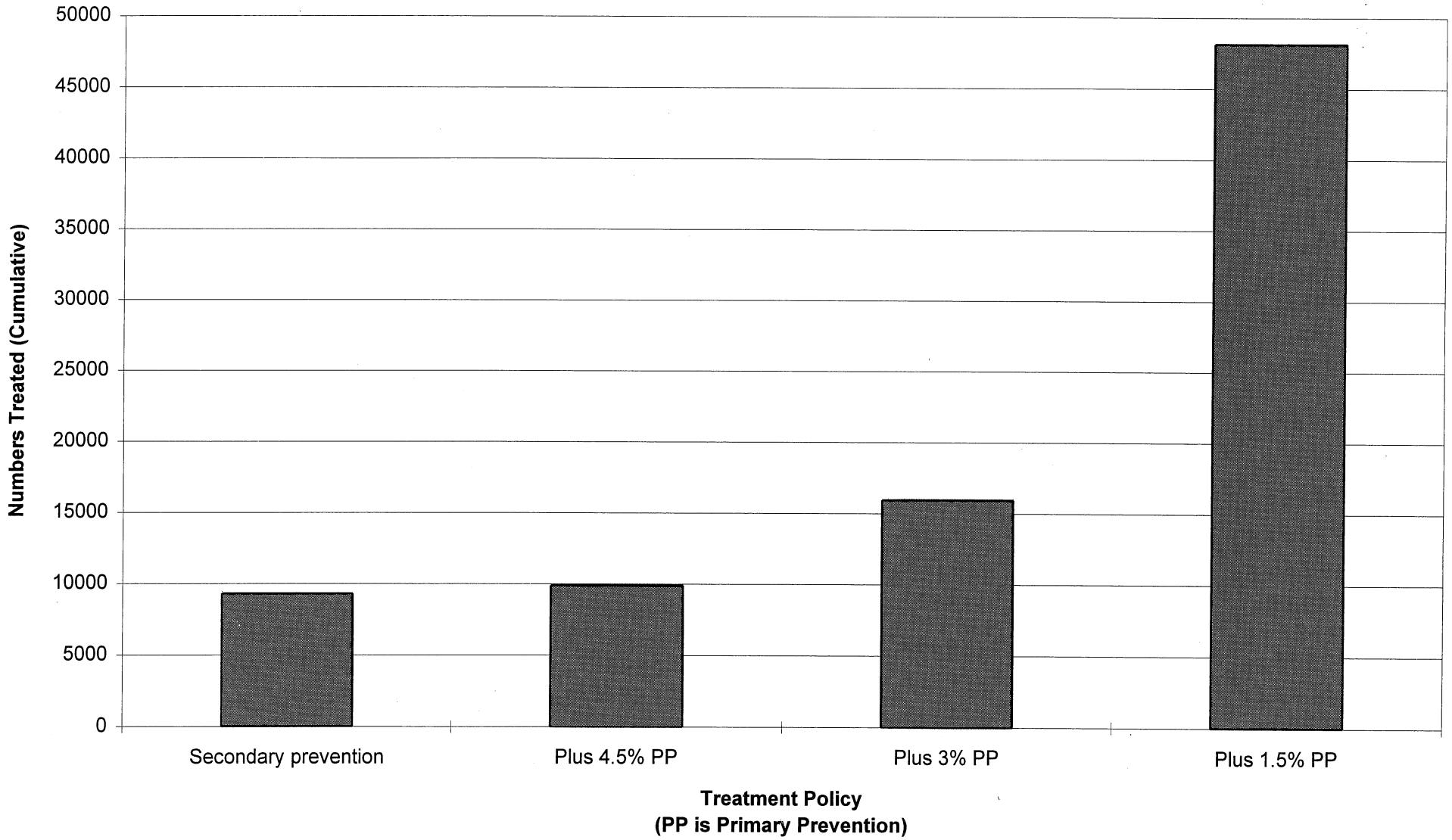


Figure 4: Implications for a Typical District: Annual Drug and Net Costs

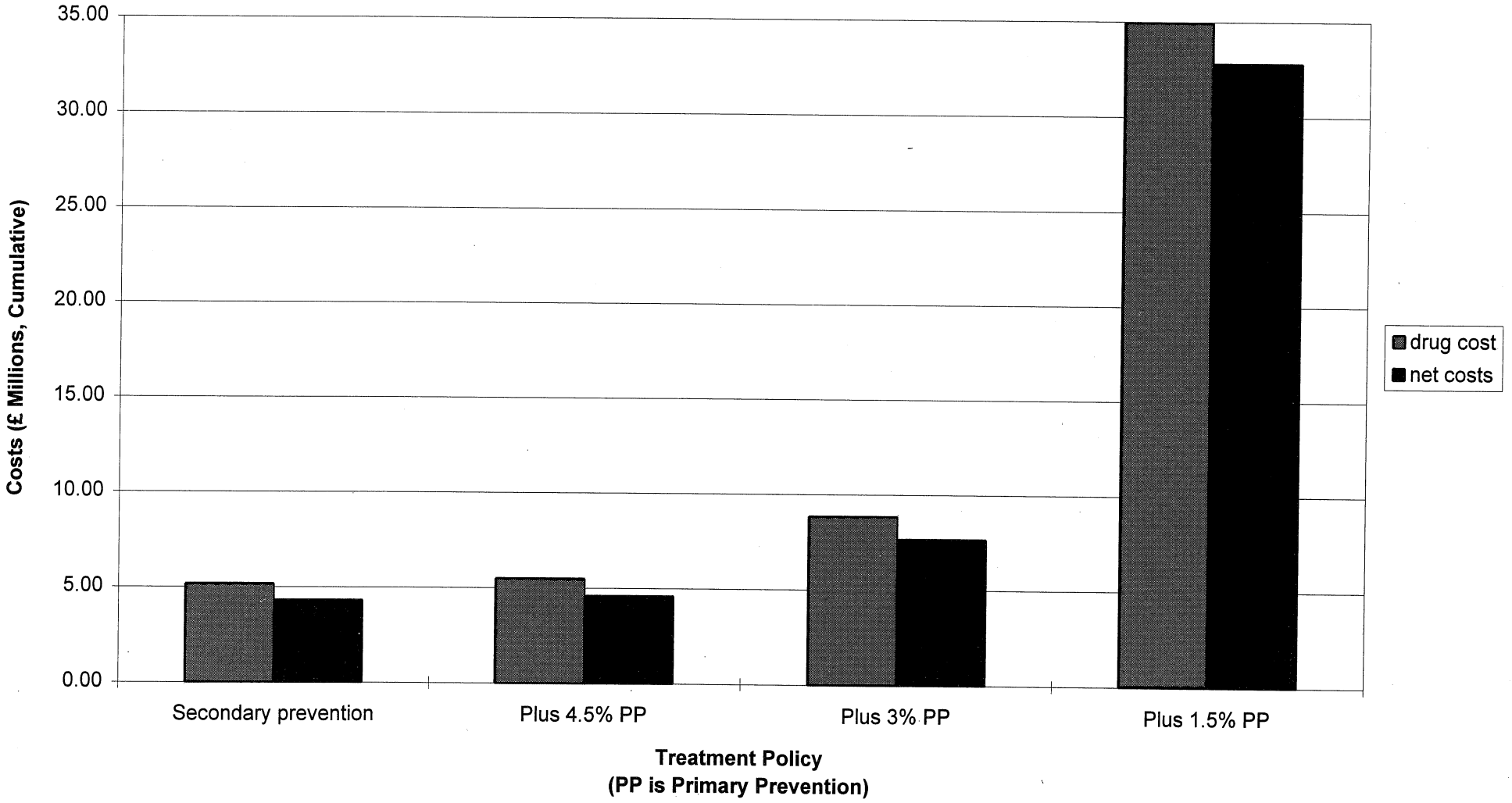
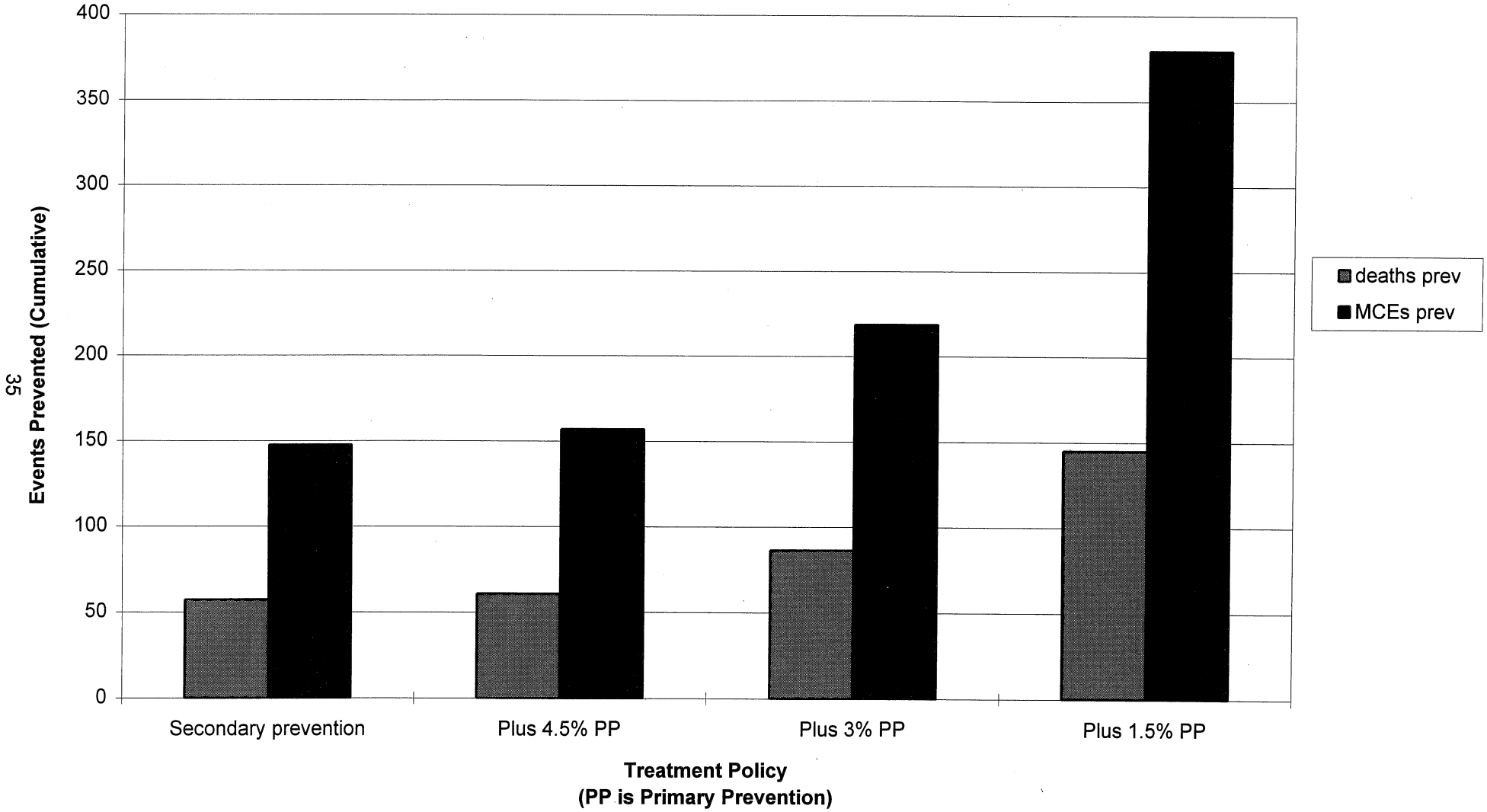


Figure 5: Implications for a Typical District: Annual Deaths and Major Coronary Events (MCEs) Prevented



5. DISCUSSION AND CONCLUSIONS

After discussion at the Trent seminar it was agreed to recommend that:

- Purchasers should develop local strategies for the use of statins in the prevention of coronary heart disease.

- Purchasers should be aware of the potentially very large scale prescribing of these drugs when developing their strategies.

- Health authorities need to plan how they will manage the process of disseminating statin treatment into the NHS and the consequences their introduction might have for other services, including secondary sector cardiac services. The potential scale of activity is large and there is a need to avoid uncontrolled implementation of statin treatment, especially in primary prevention.

- Purchaser strategies for the introduction of statin treatment should include mechanisms for monitoring and realising potential savings that will arise from the use of statin drugs.

- Purchasers should consider immediately developing a strategy for implementing the use of statins in secondary prevention of CHD, since the estimated cost per life year gained appears competitive in this group of patients. There appears to be a strong case for supporting funding of statins in this group, although authorities will need to consider local circumstances and weigh up the potential benefits of funding such a programme against benefits from alternative uses of those resources.

- Purchasers should develop a strategy for primary prevention of CHD with statins. Again, local circumstances will need to be considered.

- Primary prevention at an annual coronary event risk of 4.5% or above should be the priority in any primary prevention programme with statin drugs. The risk of coronary events in these patients is similar to the secondary prevention group (post MI) and the cost-effectiveness is also likely to be similar.

- Authorities will need to consider local circumstances and weigh up the potential benefits of funding a programme of primary prevention, at an annual coronary event risk of 3% or above, against benefits from alternative uses of those resources. Primary prevention at an annual coronary event risk of 3% or above is less cost-effective than secondary prevention and primary prevention at a 4.5% event risk. However, the cost per life year gained (at around £7,000) is similar to that of some currently funded interventions. The scale of implementation in this group would be another 3% of 35-69 year olds, in addition to the 5% for secondary prevention and primary prevention at the higher treatment threshold.

- Decisions about implementation at 1.5% annual coronary event risk should be made after consideration of the likely local population implications (scale, costs and benefits) using data from this report. Implementation in these groups should be considered lower priority than secondary prevention and primary prevention at 4.5% annual coronary event risk. The figures for cost per life year gained and (particularly) scale in this report suggest that purchasers would be reluctant to fund primary prevention at the 1.5% level.

- A toolkit/ready reckoner should be developed to help purchasers quantify population implications of treatment policies using as much local data as possible. Consideration should be given as to who would be best suited to undertake this project and what funding arrangements would be necessary.

- The cost of statin drugs used should be monitored, since the cost-effectiveness of statins is dependent on this. The cost of the drugs should also be included as an adjustable item in the toolkit/ready reckoner mentioned above.

- Purchaser policies on statin prescribing should be supported by implementation strategies which use the experience of the Framework for Appropriate Care Throughout Sheffield (FACTS) project, to encourage a logical and consistent uptake throughout the target population.

- Purchaser policies should prioritise areas of high CHD morbidity and mortality, including areas of deprivation.

6. USE OF STATINS IN THE PREVENTION OF CHD: SUMMARY MATRIX

Estimated activity, costs, savings and events prevented p.a. in a typical district (1% of population of England).
Figures for each patient group are in addition to figures for previous patient groups

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Secondary Prevention: Adults with Existing Cardiovascular Disease	35-69 year olds with previous MI, angina stroke, or peripheral vascular disease and serum cholesterol >5.5 mmol/l .	4.8% of 35 - 69 year olds i.e. 9,300. Drug cost: £5.2m.	Reductions in hospital admissions for MIs and other CHD. Reductions in revascularisation procedures (CABGs and angioplasties). Reductions in OP treatment for CHD. Above estimated at £1.2 m.	Adherence to guidelines: Proportion of patients in whom statins are indicated receiving them: (on discharge from hospital, in OP, in primary care). Proportion of patients receiving statin treatment outside the patient criteria (on discharge from hospital, in OP, in primary care). Hospital admissions for CHD. CABG/angioplasty rates. Death rates from CHD. Statin cholesterol management in patients dying from CHD or suffering a CHD event.	57 deaths (all cause) prevented. 148 major coronary events prevented. 51 revascularisation procedures prevented. A projected 3.3 years of life gained per patient (based on men of average age 58 treated for life).	Cost per life saved = £90,000 (£75,000 if savings realised) Based on men average age 58 treated for life Cost per life year gained = Undiscounted £3,600 Discounted £5,100 After taking into account possible savings: Undiscounted £2,600 Discounted £4,300.
Primary Prevention: adults without existing CHD 4.5% annual coronary event risk	35-69 year olds with combination of risk factors giving risk of CHD events of 4.5% per year (including cholesterol >5.5mmol/litre).	0.3% of 35 - 69 year olds i.e. 590. Drug cost: £330,000.	As above. Hospital admission and OP dept. savings estimated at £53,000	As above. Use of Sheffield tables in primary care to inform decisions on cholesterol measurement and treatment with statins. Rates of cholesterol testing and statin prescribing outside purchaser guidelines.	4 deaths (all cause)prevented. 9 major coronary events prevented. 3 revascularisation procedures prevented. A projected 3.3 years of life gained per patient (based on men of average age 58 treated for life).	Cost per life saved = £30,000 (£75,000 if savings realised) Based on men average age 58, treated for life Cost per life year gained = Undiscounted £3,600 Discounted £5,100 After taking into account possible savings: Undiscounted £2,600 Discounted £4,300

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Primary Prevention: adults without existing CHD 3.0% annual coronary event risk	35-69 year olds with combination of risk factors giving risk of CHD events of 3.0 % per year (including cholesterol >5.5mmol/l)	3.4% of 35 - 69 year olds i.e. 6,000. Drug cost: £3.4 m.	As above. Hospital admission and OP dept. savings estimated at £290,000	As above.	26 deaths (all cause) prevented. 62 major coronary events prevented. 19 revascularisation procedures prevented. A projected 3 years of life gained per patient (based on men of average age 58, treated for life)	Marginal cost per life saved = £130,000 (£120,000 if savings realised) Based on men average age 58 treated for life Cost per life year gained = Undiscounted £4,100 Discounted £7,400 After taking into account possible savings: Undiscounted £3,700 Discounted £6,700
Primary Prevention: adults without existing CHD 1.5% annual coronary event risk	35-69 year olds with combination of risk factors giving risk of CHD events of 1.5 % per year (including cholesterol >5.5mmol/l)	19.6% of 35-69 year olds i.e. 32,000. Drug cost: £26.1 m.	As above. Hospital admission and OP dept. savings estimated at £960,000	As above.	58 deaths (all cause) prevented. 161 major coronary events prevented. 58 revascularisation procedures prevented. A projected 2.2 years of life gained per male treated for life (based on men of average age 55 treated for life).	Marginal cost per life saved = £450,000 (£430,000 if savings realised) Based on men average age 58 treated for life Cost per life year gained = Undiscounted £9,000 Discounted £18,200 After taking into account possible savings: Undiscounted £8,600 Discounted £17,600

APPENDIX A: Assumptions Used in the Estimates of Cost-effectiveness and Population Implications.

Secondary Prevention

Estimation of cost per life year gained.

Based on men in 4S study, average age 58.

Simvastatin 27.4mg/day at cost of £1.52 per day (£555 per year).

Relative Risk of death (all causes) = 0.66 (for duration of treatment) i.e. that found for men in 4S study.

Potential savings based on Pederson data[16] = £91 per person per year.

Mortality of men on placebo in 4S trial found to be 1.74 x that found in general population males aged 58 - 64. That ratio assumed to remain constant for life.

Scenario 1: Lifelong treatment.

Scenario 2: Treatment for 5 years.

Population implications

Drug costs and potential savings as above.

Events prevented based on NNTs (all persons) from the 4S trial (5.4 years treatment).

Deaths (all cause):30

Major Coronary Events:12

CABGs/angioplasties 17 (adjusted to 34 for UK CABG rates).

Primary Prevention at 4.5% annual coronary event rate

Same assumptions as used for secondary prevention.

Primary Prevention at 3.0% annual coronary event rate

Estimation of cost per life year gained.

Based on men in 4S study, average age 58.

Simvastatin 27.4mg/day at cost of £1.52 per day (£555 per year).

Relative Risk of death (all causes) = 0.71 (for duration of treatment) i.e. that found for persons in 4S study.

Potential savings based on 4S data with adjustments for lower baseline risks of preventable events= £47 per person per year.

Mortality of men on placebo calculated by assuming ratio of coronary deaths: major coronary events = 0.3 (i.e. that found in 4S trial persons). Non coronary mortality assumed to be equal to that found in 4S trial (persons). These assumptions produced a placebo mortality rate 1.08 x that found in general population males aged 58 - 64.

That ratio assumed to remain constant for life.

Scenario 1: Lifelong treatment.

Scenario 2: Treatment for 5 years.

Population implications

Drug costs and potential savings as above.

Events prevented based on NNTs (all persons) from the 4S trial (5.4 years treatment) adjusted for lower baseline rates:

Deaths (all cause):44

Major Coronary Events:18

CABGs/angioplasties: 29 (adjusted to 59 for UK CABG rates)

Primary Prevention at 1.5% annual coronary event rate

Estimation of cost per life year gained.

Based on men in WOSCOPS study, average age 55.

Pravastatin 40mg/day at cost of £2.22 per day (£811 per year).

Relative Risk of death (all causes) = 0.78 (for duration of treatment) i.e. that found for men in WOSCOPS study.

Potential savings based on WOSCOPS data = £30 per person per year.

Mortality of men on placebo in WOSCOPS trial found to be 0.87 x that found in general population males aged 55 - 60. That ratio assumed to remain constant for life.

Scenario 1: Lifelong treatment.

Scenario 2: Treatment for 5 years.

Population implications

Drug costs and potential savings as above.

Events prevented based on NNTs from the WOSCOPS trial (4.9 years treatment).

Deaths (all cause):112

Major Coronary Events:41

CABGs/angioplasties: 113

APPENDIX B: Costing Assumptions

(a) Inpatient Costs

Cost of Hospital Treatment for Coronary Heart Disease

Surgery	CABG	£ 5,500
	PTCA	£ 3,517
Emergency -	MI	£ 1,887
Emergency -	IHD	£ 1,471

The above costs accounted for over 85% of costs saved. Other minor cost saving resulted from other events including stroke and revascularisation.

Source: York Health Economics Consortium - J Piercy & G Pledger Nov 1991Estimating the Resource Implications of Coronary Heart Disease in Newcastle. Table 7.4

Figures scaled by 1.28. Based on range of Audit Commission figures for CABG of between £2,850 and £8,000. Representative figure taken to be £5,500, which is 28% above the York costs. Other costs are assumed to have risen by the same proportion.

(b) Outpatient costs

Assumed to be additional 5% over and above inpatient costs

Source: York Health Economics Consortium - J Piercy & G Pledger Nov 1991 Estimating the Resource Implications of Coronary Heart Disease in Newcastle Table 7.4.

(c) Primary care costs

Not included in analysis

APPENDIX C: Lessons from the Framework for Appropriate Care Throughout Sheffield (FACTS) project

Possible implementation strategies:

Left to themselves, different GPs will innovate at different rates, for different levels of risk and with different degrees of thoroughness. Given the potential costs and benefits, as outlined in this report, there are great strategic advantages in a more coherent and planned introduction of statins at a district level.

This appendix outlines how such a planned approach might be created. It incorporates the experience of the FACTS project in Sheffield in helping 66 practices in one city prescribe aspirin to several thousand patients at high risk of heart attack and stroke.

Developing a district wide strategy

Developing a district wide strategy for the prescription of statins can be broken down into several stages:

a) Creating a clear and credible district-wide policy stating which groups are to be targeted. If the intention is to motivate GPs then such a policy must:
   - be clear, coherent and consistent with the evidence. The decision as to which patients to target must take account of those groups of patients which practices can easily identify (see below);
   - deal explicitly and fairly with the question of prescribing costs. Policies which simply expect GPs to absorb the very considerable costs of statins into their drug budgets will have little or no effect.

b) Any policy, once formulated, is more likely to be effective if it is supported by a coalition of key players. Ideally this would include:
   - key local Consultants;
   - members of the Local Medical Committee;
   - the Director of Public Health;

- given GPs' likely worries about cost implications, it might also be useful to have the specific endorsement of the Chief Executive of the Health Commission for the policy.

Such coalitions do not necessarily need to include everyone and the experience of the FACTS project shows that coalitions are often best negotiated through a series of meetings with individuals rather than trying to get all 'stakeholders' together for a single, potentially fractious, meeting.

The purpose of the coalition is to ensure support for the overall principles of the policy, and to explore potential problems from the perspectives of different players. It is not to develop guidelines or detailed policies about implementation.

c) Given a clear policy endorsed by local consultants, together with an equitable strategy for dealing with prescribing costs, most GPs will want to participate. In order to do so effectively, practices will need to:
   - identify patients in target groups;
   - pull the notes;
   - exclude those who are known to have normal cholesterol;
   - invite remaining patients for a blood test and preliminary counselling;
   - in the light of the cholesterol result(s), prescribe if appropriate.

d) A whole series of other barriers within practices are likely to arise at this point:
   - workload - few practices have capacity for work that is likely to be seen as 'extra' to the demands of everyday practice;
   - difficulty identifying target patients;
   - lack of computer skills;
   - concerns about clinical aspects of statins, side effects etc.

Health Commissions should seriously consider policies to address these difficulties. For example:

a) Workload:

   Health Commissions need to recognise this problem explicitly. They can help in two ways:
   - providing concrete help - clear simple guidelines about what to do; stickers and prompts for notes; leaflets for patients; postage for letters; resources.

- reducing burdens in other areas - offering implementation of the statin policy as an alternative to providing any other health promotion activity and/or banding information for the year.

b) Identifying target patients:

There are at least three ways to identify target patients:

- use the CHD health promotion data. This will be available for all practices who reached band 2. However, our experience shows that definitions of what constitutes 'CHD' vary almost as widely as the rigour with which practices have, or have not, collected the information.
- use the practice computer to search for all those on particular drugs. For example nitrates could be used to identify all those with angina.
- use the Health Commission database to identify patents who have had a relevant diagnosis in hospital and send each practice a list, meeting the criteria for secondary prevention.

Each of these methods has advantages and disadvantages. These need to be understood by those who draw up the district policy - selecting the right mix will be crucial if the policy is to be successfully implemented.

c) Computer skills:

Although most practices are computerised, the experience of the FACTS project shows that many practices have relatively poor IT skills. If implementation of the strategy requires anything more than routine computer skills, then many practices will need extra help.

d) Concerns about clinical aspects:

Many GPs - and practice nurses - will have clinical questions about the use of statins, cholesterol testing etc. These need addressing both through continuing medical education (CME) meetings and, if possible, with printed material.

Strategies to avoid over prescription:

One concern of health commissions will be to ensure that people outside the target groups do not receive statins. This might be avoided by giving practices 'completion criteria', which would tell them how many people they should have on statins by the end of their implementation process. Such end points could take into account both the demography of each practice and/or the incidence of CHD. Linking 'completion criteria' to cost-free prescribing (i.e. up to this number of new prescriptions for statins will be discounted from the drug budget) would give a strong message to practices about the importance and coherence of the policy, whilst ensuring a cap to statin costs at a district level.

REFERENCES

(1) Cholesterol screening and treatment. *Effective Health Care Bulletin* 1993; 6.

(2) Ramsay LE, Yeo WW, Jackson PR. Dietary reduction of serum cholesterol concentration: time to think again. *British Medical Journal* 1993; 306: 1367-73.

(3) Davey Smith G, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. *British Medical Journal* 1993; 306: 1367-73.

(4) Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383-9.

(5) Shepherd J, Cobbe SM, Ford I et al. for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine.* 1995 Nov 16; 333: 1301-7.

(6) Long-term simvastatin improved survival in coronary heart disease. [Abstract] ACP Journal Club. 1995 May-June; 122(3):67. Abstract of: Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344:1383-9.

(7) Pravastatin reduced nonfatal MI without increasing noncardiovascular death in men with hypercholesterolemia. [Abstract] Evidence Based Medicine. 1996 March - April; 1: 73. Abstract of : Shepherd J, Cobbe SM, Ford I et al. for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine* 1995; 333: 1301-7.

(8) Report of the US Preventive Services Task Force. *Guide to clinical preventive services. An assessment of the effectiveness of 169 interventions.* Baltimore: Williams and Wilkins, 1989.

(9) Collins R, Keech A, Peto R et al. Cholesterol and total mortality: need for larger trials (letter). *British Medical Journal* 1992; 304: 1689.

(10) Cholesterol Treatment Trialists Collaboration. *American Journal of Cardiology.* 1995; 75: 1130-4.

(11) Haq IU, Ramsay LE, Pickin DM et al. Lipid-lowering for prevention of coronary heart disease: what policy now? *Clinical Science* 1996; 91: 399-413.

(12) Bennett N, Dodd T, Flatley J et al. for the Office of Population and Censuses Surveys. *Health Survey for England 1993.* London: HMSO, 1995.

(13) Haq IU, Jackson PR, Yeo WW et al. Sheffield risk and treatment table for cholesterol lowering for primary prevention of coronary heart disease. *Lancet* 1995; 346: 1467-1471.

(14) Anderson KM, Odell PM, Wilson PWF et al. Cardiovascular disease risk profiles. *American Heart Journal* 1991; 121: 293-298.

(15) Piercy J, Pledger G. Estimating the resource implications of coronary heart disease in Newcastle. (Cost effective purchasing Occasional Paper 2) York : University of York - Health Economics Consortium, 1991.

(16) Pedersson TR, Kjekshus J, Berg K et al. Cholesterol lowering and the utilisation of healthcare resources: results of the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1996; 10: 1796-1802.

(17) Audit Commission. *Dear to Our Hearts? Commissioning services for the treatment and prevention of coronary heart disease.* London: HMSO, 1995.

(18) Malik J, Anderson MH. Cost-efficacy of cholesterol lowering: implications of the Scandinavian simvastatin survival study. *European Heart Journal* 1995; 16: 463.

(19) Pharoah PDP, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. *British Medical Journal* 1996; 312: 1443-8.

(20) Davey Smith G, Pekkanen J. The Scandinavian simvastatin survival study (4S). *Lancet* 1994; 344: 1766.

(21) Grodos D, Tonglet R. The Scandinavian simvastatin survival study (4S). *Lancet* 1994; 344: 1768.

(22) Health of the Nation. *Assessing the options in the CHD and Stroke key area. Target-effectiveness and cost-effectiveness of interventions to reduce CHD and Stroke Mortality.* Department of Health, 1995.

Other papers published by the Trent Institute for Health Services Research are listed below:-

Guidance Notes for Purchasers

96/01	Working Group on Acute Purchasing: The use of DNase in Cystic Fibrosis (1996) by JN Payne, S Dixon, NJ Cooper and CJ McCabe.	£6.00
96/02	Working Group on Acute Purchasing: Tertiary Cardiology (1996) by J Tomlinson, J Sutton and CJ McCabe.	£6.00
96/03	Working Group on Acute Purchasing: The use of Cochlear Implantation (1996) by Q Summerfield and J Tomlinson.	£6.00

Discussion Papers

No. 1.	Patients with Minor Injuries : A Literature Review of Options for their Treatment Outside Major Accident and Emergency Departments or Occupational Health Settings (1994) by S Read.	£7.00
96/01	Working Group on Acute Purchasing: The role of Beta Interferon in the Treatment of Multiple Sclerosis (1996) by RG Richards, CJ McCabe, NJ Cooper, SF Paisley, A Brennan and RL Akehurst.	£7.50
96/02	The Mid-level Practitioner: A Review of the Literature on Nurse Practitioner and Physician Assistant Programmes (1996) by P Watson, N Hendey, R Dingwall, E Spencer and P Wilson.	£10.00
96/03	Evaluation of two Pharmaceutical Care Programmes for People with Mental Health Problems Living in the Community (1996) by A Aldridge, R Dingwall and P Watson.	£10.00

Copies of these documents are available from:-

Suzy Paisley
Information Officer
Trent Institute for Health Services Research
Regent Court
30 Regent Street
SHEFFIELD S1 4DA

Tel 0114 222 5420
Fax 0114 272 4095
E-mail scharrlib@sheffield.ac.uk

Please make cheques payable to "The University of Sheffield"